



**Risedronate Sodium
Briefing Document**

**Joint Advisory Committee Meeting of the Reproductive
Health Drugs Committee and the Drug Safety and Risk
Management Advisory Committee**

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1. INTRODUCTION

Warner Chilcott is a leading specialty pharmaceutical company currently focused on the gastroenterology, women's healthcare, dermatology, and urology segments of the North American and Western European pharmaceuticals markets. In October 2009, Warner Chilcott acquired from the Procter & Gamble Company the risedronate sodium (risedronate) bisphosphonate (BP) products Actonel[®] and Actonel[®] with Calcium. Warner Chilcott also acquired the rights to develop the next-generation risedronate product, Atelvia[®], which was subsequently approved for sale in the US (October 2010).

Warner Chilcott was notified by the FDA of a joint meeting of the Advisory Committee for Reproductive Health Drugs and the Drug Safety and Risk Management Advisory Committee to discuss the evidence supporting the benefit of long-term BP use in light of safety matters such as osteonecrosis of the jaw, atypical femur fractures, and esophageal cancer and how such safety matters might be associated, if at all, with the long-term use of BPs for the treatment and prevention of osteoporosis. Warner Chilcott was given the opportunity to submit a brief background document for the Advisory Committee meeting and the FDA recommended focusing on the following questions:

- (1) Provide an opinion and discussion of whether your efficacy and safety data support a long-term duration of use (ie, > 3 years) for risedronate*
- (2) Provide an opinion and discussion of whether either restricting the duration of use or implementing a drug holiday may be beneficial for patients requiring long-term treatment*

This meeting package presents information and analysis requested by FDA on the long-term use and safety of risedronate, focusing on osteonecrosis of the jaw, atypical femur fractures, esophageal cancer, and the concept of either restricting the duration of treatment or implementing a drug holiday.

2. OSTEOPOROSIS – DISEASE MORBIDITY

Osteoporosis results from an imbalance in the bone remodeling process, whereby bone resorption, mediated by osteoclasts, outpaces bone formation, mediated by osteoblasts. Osteoporosis causes bones to become more porous, gradually making them weaker and more brittle, leading to low bone mass and an increased risk of fracture. The US Department of Health & Human Services has published the following facts ([US Dept HHS 2004a](#)): 1) Osteoporosis is the most prevalent bone disease in the US, afflicting more than 10 million Americans over the age of 50, 80% of whom are women. 2) An additional 34 million Americans have low bone mass (“osteopenia”) and are at risk of developing osteoporosis and bone fracture. 3) Four of every 10 Caucasian women over the age of 50 will have an osteoporosis-related fracture in their remaining lifetime. 4) By 2020, an estimated 1 in 2 Americans over 50 will have or be at risk of developing osteoporosis of the hip. Bone fractures are severe medical events; the Surgeon General reports that hip fractures account for 300,000 hospitalizations per year, with nearly 20% of elderly hip fracture patients ending up in nursing homes ([US Dept HHS 2004b](#)).

3. BISPHOSPHONATES AND RISEDRONATE APPROVAL HISTORY

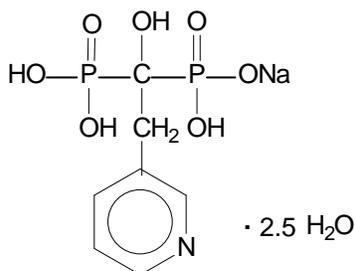
Bisphosphonates (BPs) were first developed in the early 1960s as a potential treatment for bone diseases and they are currently the most frequently prescribed drugs for the treatment of osteoporosis and other diseases characterized by increased bone resorption. In patients with post-menopausal osteoporosis (PMO), BPs reduce osteoclast activity back to the healthy, pre-menopausal levels, thereby decreasing the rate of bone loss. In short, BPs increase bone mass, strengthen bones, and reduce the incidence of fracture, including severe fractures of the hip and spine. BPs approved for the treatment and/or prevention of osteoporosis include alendronate (Fosamax, Fosamax Plus D; Merck), ibandronate (Boniva; Genentech), zoledronic acid (Reclast; Novartis), and risedronate (Actonel, Actonel with Calcium, and Atelvia; Warner Chilcott).

Actonel is approved in more than 90 countries world-wide. Global first approvals, by indication, were as follows: the treatment of Paget's disease of bone (March 1998); the treatment and prevention of PMO and corticosteroid-induced osteoporosis (October 1999); supplemental approval for the reduction of hip fractures (June 2001); and osteoporosis in men (July 2006). In Japan only, independent marketing authorization holders manufacture and market a lower-dose oral risedronate (2.5 mg daily and 17.5 mg weekly) for the treatment of osteoporosis. Actonel is administered orally, can be taken daily, weekly, or monthly, depending on the dosage, and is prescribed to millions of patients every year in the US and throughout the world.

Atelvia is an enteric-coated, delayed-release risedronate formulation currently approved in 3 countries (including the US, October 2010) for the treatment of osteoporosis in post-menopausal women. It is administered orally, once weekly immediately following breakfast.

4. RISEDRONATE CHEMICAL NAME, STRUCTURE, AND AVAILABLE FORMULATIONS

The empirical formula for risedronate sodium hemi-pentahydrate is $C_7H_{10}NO_7P_2Na \cdot 2.5 H_2O$. The chemical name of risedronate sodium is [1-hydroxy-2-(3-pyridinyl)ethylidene]bis[phosphonic acid] monosodium salt. The chemical structure of risedronate sodium hemi-pentahydrate is the following:



Risedronate is available as an immediate-release (IR) formulation (Actonel) and a delayed-release (DR) formulation (Atelvia). Each risedronate sodium IR tablet for oral administration contains the equivalent of 5, 30, 35, 75, or 150 mg of risedronate sodium anhydrous in the form of the hemi-pentahydrate with small amounts of monohydrate. Each risedronate sodium DR tablet for oral administration contains the equivalent of 35 mg of anhydrous risedronate sodium in the form of the hemi-pentahydrate with small amounts of monohydrate.

5. BISPHTHONATE MECHANISM OF ACTION

5.1. Binding Affinity

The primary pharmacological effects of BPs involve 2 key properties: 1) affinity for bone mineral; and 2) inhibitory effects on osteoclasts. Risedronate has an affinity for hydroxyapatite (HAP) in bone and acts as an antiresorptive agent. At the cellular level, risedronate inhibits osteoclasts. The osteoclasts adhere normally to the bone surface, but show evidence of reduced active resorption (eg, lack of ruffled border).

Mineral binding affinities have been shown to differ among the FDA-approved BPs. Risedronate, for example, has a hydrogen bonding angle less than 125 degrees, which does not allow strong HAP bonding, and thus far less bone mineral affinity than other BPs. This difference appears to influence the differential distribution within bone, the biological potency, and the duration of action. A variety of methods used to assess mineral binding affinity show that alendronate and zoledronate bind more strongly to hydroxyapatite than risedronate ([Ebetino et al 2011](#)). The available information on the binding capacity of HAP for risedronate versus other BPs suggests that, even at saturation, less risedronate can be bound to the surface of HAP than for alendronate, ibandronate, and zoledronate ([Nancollas et al 2006](#)).

5.2. Inhibition of Farnesyl Pyrophosphate Synthase

The antiresorptive effects of the FDA-approved BPs (including alendronate, risedronate, ibandronate, and zoledronate) involve their inhibition of the enzyme farnesyl pyrophosphate synthase (FPPS) in osteoclasts. FPPS is a key enzyme in the mevalonate pathway, which generates isoprenoid lipids utilized for the post-translational modification of small GTP-binding proteins that are essential for osteoclast function.

Among the bisphosphonates approved for the treatment of osteoporosis, risedronate is one of the strongest inhibitors of FPPS. The rank order of potency for inhibiting FPPS is zoledronate > risedronate > ibandronate > alendronate, with the more potent heterocyclic bisphosphonates (zoledronate and risedronate) having a more optimal fit than the compounds with an alkyl side chain (alendronate and ibandronate) ([Russell et al 2008](#), [Watts et al 2010](#)).

6. DISCUSSION OF RISEDRONATE EFFICACY AND SAFETY DATA SUPPORTING LONG-TERM DURATION OF USE (IE, > 3 YEARS)

The efficacy and safety of risedronate IR tablets have been assessed in Phase 3 studies in PMO, osteopenia, glucocorticoid-induced osteoporosis (GIO), male osteoporosis, Paget's disease of bone, and pediatric osteogenesis imperfecta (OI).

More than 21,000 men and women aged 37 to 95 years have received placebo or risedronate in over 20 risedronate clinical studies, the majority for up to 3 years (see [Table 1](#)). Extension studies in subjects with PMO increased the duration of exposure to risedronate to 9 years. In addition, the efficacy and safety of risedronate DR tablets have been assessed in one Phase 3 study and two Phase 2 studies in women with PMO.

To more closely reflect the actual population of potential patients, the osteoporosis clinical studies included subjects with pre-existing gastrointestinal disease and concomitant use of non-steroidal anti-inflammatory drugs, proton pump inhibitors, and H₂ antagonists. All subjects

received 500-1000 mg of elemental calcium plus 400 to 800 IU of vitamin D supplementation per day.

Study Number / Phase	Description	Study Design Number of Subjects in ITT Population Duration
RVN008993 Phase 3	Efficacy and safety of 2.5 mg* and 5 mg daily vs. placebo postmenopausal women with PMO with at least 2 vertebral fractures (*2.5 mg dose halted mid-study via amendment) Calcium supplemented, drug-free, follow-up period to assess residual pharmacological effects of 3 years of 5 mg daily treatment	DB, PC, PG study, stratified by number of baseline vertebral fractures 2439 subjects in 3-year study 4 years total (3 years treatment, 1 year drug-free follow-up) Drug-free, follow-up 759 subjects 1-year follow-up
RVE009093 Phase 3	Efficacy and safety of 2.5 mg and 5 mg daily vs. placebo in treatment of OP-related vertebral deformities in females, with at least 2 vertebral fractures	DB, PC, PG study, stratified by number of years since menopause 1222 subjects 3 years (placebo, 5 mg) 2-3 years (2.5 mg)
RON009393 ROE009493 Phase 3	Efficacy and safety of 2.5 mg* and 5 mg daily vs. placebo in increasing lumbar spine BMD in ambulatory females with PM osteopenia (*2.5 mg dose halted via amendment at 9 sites; 4 sites continued 2.5 mg dose)	DB, PC, PG study, stratified by number of years PM RON009393: 643 subjects for 12 or 18 months ROE009493: 541 subjects for 2 years
RHN009193 RHE009293 Phase 3	Efficacy and safety of 2.5 mg and 5 mg daily vs. placebo in reducing hip fractures, and effect on cortical bone at femoral neck in females ≥ 70 years of age	DB, PC, PG study RHN009193: 4889 subjects RHE009293: 4432 subjects 3 years
HMR4003E/3002 Phase 3	5 mg daily, flexible-dosing vs. before-breakfast-dosing, in women with PMO	Single-blind, AC, PG study 730 subjects 6 months
RVE1996077 Year 4/5 extension study Phase 3b	Long-term efficacy and safety of 5 mg daily vs. placebo in treatment of established OP-related vertebral deformities in PM women who had completed study RVE009093	DB, PC, PG, extension study, stratified by number of years since menopause 267 subjects 2 years
RVE1998080 Year 6/7 extension study Phase 3b	Safety and tolerability of 5 mg daily for long-term (7 years) treatment of established OP-related vertebral deformities in PM women who had completed studies RVE009093 and RVE1996077	Open-label, extension study 165 subjects 2 years
RVE2001079 Year 8 extension study Phase 3b	Effects of cessation of long-term (7 years) and short-term (2 years) risedronate therapy on BMD in women with PMO who had sequentially completed studies RVE009093, RVE1996077, and RVE1998080	Drug-free, outpatient, extension study 61 subjects 1 year
RVE2002157 Year 9/10 extension study Phase 3b	Safety and tolerability of restarting 5 mg daily on BMD and BTM in women with PMO who had sequentially completed studies RVE009093, RVE1996077, RVE1998080, RVE2001079	Open-label, extension study 32 subjects 2 years

Table 1: Description of Risedronate Studies

Study Number / Phase	Description	Study Design Number of Subjects in ITT Population Duration
RVN1996052 Phase 3b	Long-term safety and efficacy of 5 mg daily vs. placebo in treatment of women with PMO with established OP-related vertebral deformities, previously enrolled in study RVN008993	DB, PC, PG, extension study 86 subjects 2 years
HMR4003E/3001 Phase 3	5 mg active vs. 35 mg or 50 mg once weekly in women with PMO	DB, AC, PG study 1456 subjects 2 years
2004012 Phase 3	Efficacy and safety of 75 mg 2CDM vs. 5 mg daily in women with PMO	DB, AC, PG, non-inferiority study 1229 subjects 2 years
2005032 Phase 3	Efficacy and safety of 150 mg OAM vs. 5 mg daily in women with PMO	DB, AC, PG, non-inferiority study 1292 subjects 2 years
RBL004494 Phase 3	Efficacy and safety of 2.5 mg and 5 mg daily vs. placebo for the prevention of bone loss in PM ambulatory women	DB, PC, PG study, stratified by center 381 subjects 2 years
RPE002494 Phase 3	Efficacy and safety of 5 mg daily risedronate plus estrogen versus estrogen only for the prevention of bone loss in PM women	DB, PC, PG study 520 subjects 12-18 months
HMR4003B/3001 Phase 3	5 mg daily vs. placebo in prevention of osteoporosis in osteopenic PM women	DB, PG study 170 subjects 2 years
HMR4003F/4001 Phase 4	Efficacy and safety of 35 mg once a week in the prevention of osteoporosis in PM women	DB, PC, PG study 278 subjects 1 year
2001092 Phase 3	Efficacy and safety of 35 mg OAW vs. placebo in men with OP	DB, PC, PG study 284 subjects 2 years
RCP009993 RCT009893 Phase 3	Efficacy and safety of 2.5 mg* and 5 mg daily vs. placebo for the prevention of corticosteroid-induced OP in male and female patients treated with high-dose (≥ 7.5 mg mean daily dose) glucocorticoid-steroids for ≤ 3 months prior to study entry (*2.5 mg dose halted via amendment)	DB, PC, PG study, stratified by sex and menopausal status RCP009993: 224 subjects RCT009893: 285 subjects 1 year
ITT = intent to treat; DB = double-blind; PC = placebo-controlled, AC = active-controlled, PG = parallel-group, PM = post-menopausal, OP = osteoporosis; OAM = once a month; PMO = postmenopausal osteoporosis, OAW = once a week, BMD = bone mineral density, DR = delayed-release, IR = immediate release		

6.1. Efficacy Data from Risedronate Clinical Studies

6.1.1. Fracture and Bone Mineral Density (BMD) Data Supporting Efficacy

The fracture efficacy of Actonel 5 mg daily in the treatment of postmenopausal osteoporosis was demonstrated in 2 large, randomized, placebo-controlled, double-blind studies that enrolled a total of almost 4,000 postmenopausal women under similar protocols. The multinational study (RVE009093) (Actonel 5 mg, N = 408) was conducted primarily in Europe and Australia; a second study was conducted in North America (RVN008993) (Actonel 5 mg, N = 821). Subjects were selected on the basis of radiographic evidence of previous vertebral fracture, and therefore, had established disease. The average number of prevalent vertebral fractures per subject at study entry was 4 in RVE009093 and 2.5 in RVN008993, with a broad range of baseline BMD levels.

The primary endpoint for these studies was the incidence of new and worsening vertebral fractures over a 3-year period. Actonel 5 mg daily significantly reduced the incidence of new-and-worsening vertebral fractures and of new vertebral fractures in both RVE009093 and RVN008993 after 1, 2, and 3 years of treatment. In a subgroup of subjects who had 2 or more vertebral fractures at study entry, the reduction in risk was similar to that observed for the overall study population.

Studies RVE009093 and RVN008993 both included a prospectively planned efficacy endpoint consisting of all radiographically confirmed fractures of skeletal sites accepted as associated with osteoporosis. Fractures at these sites were collectively referred to as osteoporosis-related nonvertebral fractures. Actonel 5 mg daily significantly reduced the incidence of osteoporosis-related nonvertebral fractures over 3 years in RVN008993 (8% versus 5%; relative risk reduction 39%) and reduced the fracture incidence in RVE009093 from 16% to 11%. There was a significant reduction from 11% to 7% when the studies were combined, with a corresponding 36% reduction in relative risk ([Actonel 2010](#)).

Risedronate 5 mg daily significantly increased BMD at the spine, hip, and wrist compared to the effects seen with placebo (RVE009093, RVN008993, ROE009493, RON009393) ([Actonel 2010](#)). In both of the vertebral fracture studies (RVE009093, RVN008993), risedronate 5 mg daily produced increases in lumbar spine BMD that were progressive over the 3 years of treatment, and were statistically significant relative to baseline and to placebo at 6 months and at all later time points.

Risedronate is thus proven to reduce and prevent both vertebral and nonvertebral fractures including hip fractures (composite endpoint). In addition, multiple studies evaluating different dosing regimens of risedronate (both IR and DR) showed a consistent increase in BMD at multiple locations throughout the body.

6.1.2. Long-term Efficacy

[Table 2](#) presents risedronate clinical studies of ≥ 3 years duration.

Core Studies	Extension studies			
Years 0-3 RVE009093 blinded/controlled n = 408; placebo n = 410; 2.5 mg n = 408; 5 mg	Years 4-5 RVE1996077 blinded/controlled n = 130; placebo n = 135; 5 mg	Years 6-7 RVE1998080 uncontrolled n = 164; 5 mg for all 83 former Ris and 81 former placebo	Year 8 RVE2001079 <i>n = 61 off drug</i>	Years 9-10 RVE2002157 uncontrolled n = 32; 5 mg for all
Years 0-3 RVN008993 blinded/controlled n = 820; placebo n = 817; 2.5 mg n = 821; 5 mg	Years 4-5 RVN1996052 blinded/controlled n = 42; placebo n = 44; 5 mg	--	--	--
	Year 4 only RVN008993 Addendum <i>n = 759 off drug</i>	--	--	--
Years 0-3 RHE009293 & RHN009193 blinded/controlled n = 3184; placebo n = 3151; 2.5 mg n = 3162; 5 mg	--	--	--	--

Ris = risedronate.

Risedronate is the only BP that has been studied for 5 years versus placebo. The 3-year, placebo-controlled, multi-national, core study RVE009093, was extended for 2 additional years (via Study 1996077). Subjects in this extension study continued to receive either placebo or risedronate 5 mg daily for a total treatment duration of 5 years. Results from this extension study show that risedronate decreased the incidence of new vertebral fractures by 59% compared with placebo in Years 4/5. This is consistent with the 3-year efficacy data (49% reduction over 3 years). Over 5 years of treatment (data from all subjects enrolled in core Study RVE009093 plus the data from the 2-year extension), the cumulative incidence in new vertebral fractures from Years 1-5 was decreased by 50% versus placebo ($p < 0.001$).

Following completion of the 5-year placebo-controlled study (3 years in Study RVE009093 followed by 2 years in Study 1996077), the subjects were allowed to receive risedronate for 2 years in an open-label study (1998080). The subjects treated with risedronate for up to 7 years did not show a decrease in the degree of fracture protection (Mellström et al 2004). The percent of subjects who had new vertebral fractures during the Year 6/7 extension study was similar for the placebo/risedronate and the risedronate/risedronate groups (6.2% versus 6.0%). The cumulative incidence of new vertebral fractures over the 7-year treatment period showed more subjects in the placebo/risedronate group had new vertebral fractures than the risedronate/risedronate group (32 subjects versus 20). These data are consistent with the vertebral fracture protection of risedronate, as the placebo/ risedronate group was on placebo for the first 5 years of the study.

Subjects who successfully completed the Year 6/7 extension study (RVE1998080) were monitored for 1 year off risedronate to assess the effect of cessation of long-term risedronate therapy on bone mineral density (BMD) and bone turnover markers (BTMs) (see [Section 7.1.2](#)). Subjects who completed the Year 8 study (RVE2001079) were offered the opportunity to participate in an uncontrolled extension study (RVE2002157) for an additional 2 years.

6.2. Safety in Clinical Studies of >3 Years Duration

The safety of long-term use (ie, > 3 years) of risedronate in subjects with postmenopausal osteoporosis has been assessed in extension studies of the 3-year vertebral fracture studies, RVE009093 and RVN008993. In the extension studies of RVE009093, adverse events were similar between the risedronate and placebo groups after 5 years (Study 1996077). Similar percentages of subjects in each treatment group (30.0% placebo; 24.4% 5 mg risedronate) reported serious AEs. Adverse events led to withdrawal for 12.3% of subjects in the placebo group compared to 7.4% of subjects in the 5 mg risedronate group. The incidence of nonvertebral fractures reported as AEs was greater in the placebo group (13.8%) than in the 5 mg risedronate group (10.4%). A retrospective analysis similar to that used for vertebral fractures (using data from all subjects enrolled in the core study, including data from the extension study) revealed a statistically significant 37% reduction ($p=0.022$) in the incidence of nonvertebral fractures in subjects who received 5 mg risedronate versus placebo over 5 years

Study RVE1996077 (Year 4/5 study) was extended for 2 more years (Years 6/7) via the open-label study 1998080, for a total of up to 7 years of risedronate treatment. The subjects who were on placebo for 5 years and then switched to risedronate for Years 6 and 7 ($N = 81$) and those who were on risedronate 5 mg daily for 7 years ($N = 83$) had similar vertebral fracture incidence reported as an AE (3.7% and 3.6%, respectively). More subjects in the placebo/risedronate group had non-vertebral fractures reported as AEs compared to the group that had been on risedronate for 7 years (9.9% and 7.2%, respectively). Overall AEs were similar between the 2 treatment groups after 7 years (85.2%, placebo/risedronate group; 86.7%, risedronate group). Serious AEs were reported more frequently in the risedronate group (31.3%) than in the placebo/risedronate group (25.9%). The overall incidence of serious AEs was highest in the musculoskeletal (7.4%, placebo/risedronate; 9.6%, risedronate) and cardiovascular systems (6.2%, placebo/risedronate; 8.4%, risedronate). The most common individual serious AE was traumatic bone fracture, which occurred more often in the placebo/risedronate subjects (6.2%) than the subjects treated for 7 years with risedronate (4.8%). These data from 7 years of treatment with risedronate provide further support for the long-term use of risedronate.

A biopsy cohort of subjects from the placebo-controlled 3-year vertebral fracture study (RVN008993) was further studied in a 2-year extension study (Study 1996052). Standard histomorphometric analysis continued to show normal histology with no pathological findings and the bone quality appeared to be consistent with that seen in Year 3. This is further discussed in [Section 6.5.2](#).

6.3. Bone Turnover Markers

Various studies have examined BPs and bone metabolism and turnover during long-term administration. The inhibition of bone resorption appears to reach a new steady-state level within days of initiation of treatment, and does not become progressively lower, even when the

compounds are given continuously. This has been clearly shown in rats ([Reitsma et al 1980](#)) and has also been consistently observed in clinical studies ([Table 3](#)). There appears to be no progression of the antiresorptive effect with time; there is a dose-dependent reduction in bone turnover that has been observed in both animals and humans ([Russell et al 2008](#)).

Histomorphometry in rats, dogs, and minipigs showed that risedronate treatment reduces bone turnover (activation frequency, ie, the rate at which bone remodeling sites are activated) and bone resorption at remodeling sites.

Risedronate treatment decreases the elevated rate of bone turnover that is typically seen in postmenopausal osteoporosis. In clinical studies, administration of risedronate to postmenopausal women resulted in decreases in biochemical markers of bone turnover, including urinary deoxypyridinoline/creatinine (a marker of bone resorption) and bone specific alkaline phosphatase (a marker of bone formation)

In risedronate clinical studies with the 5 mg daily dose, decreases in deoxypyridinoline/creatinine were evident within 14 days of treatment. Changes in bone formation markers were observed later than changes in resorption markers, as expected, due to the coupled nature of bone resorption and bone formation; decreases in bone specific alkaline phosphatase of about 20% were evident within 3 months of treatment. Bone turnover markers (BTMs) reached a nadir of about 40% below baseline values by the sixth month of treatment and remained stable with continued treatment for up to 3 years with achievement of a new steady-state, which more nearly approximates the rate of bone turnover seen in premenopausal women.

[Table 3](#) presents 1-year and 2-year BTM data from 4 risedronate clinical studies. These data show that BTM reduction with risedronate treatment is consistent across various dosing regimens and does not change dramatically with a longer duration of therapy.

	NTX/Cr				BAP			
	Year 1		Year 2		Year 1		Year 2	
	N	LS Means						
Risedronate IR Studies								
HMR4003E/3001								
5 mg daily	74	-60.3	69	-50.8	80	-42.4	76	-30.5
35 mg once a week	71	-60.7	71	-52.8	76	-41.0	72	-29.9
50 mg once a week	71	-64.9	54	-61.3	72	-45.7	59	-37.5
2004012								
5 mg daily	511	-53.57	459	-51.77	520	-36.29	463	-30.20
75 mg 2CDM	524	-51.69	459	-48.34	526	-35.32	468	-29.71
2005032								
5 mg daily	537	-51.64	493	-49.45	537	-31.15	494	-25.84
150 mg OAM	553	-48.63	507	-46.62	531	-31.82	507	-25.07
Risedronate DR Study								
2007008								
5 mg IR daily	256	-42.22	242	-49.19	258	-31.90	245	-33.39
35 mg once a week DRFB	253	-47.26	234	-53.93	258	-33.51	235	-36.14

2CDM = 2 consecutive days a month; OAM = once a month; DRFB = delayed release following breakfast.

Studies that directly compare various oral BPs have demonstrated that the amount of BTM reduction is different among the oral BPs. [Table 4](#) presents BTM results from a) Year 1 of a risedronate clinical study comparing 5 mg IR tablet daily to 35 mg DR tablet given once per week (Study 2007008), b) Year 1 results from the FACT study, comparing weekly-dosed alendronate and risedronate ([Rosen et al 2005](#)), and c) results from the MOTION study, comparing weekly-dosed alendronate and monthly-dosed ibandronate ([Emkey et al 2009](#)).

Table 4: Comparison of BTM percent Change from Baseline for Risedronate, Alendronate, and Ibandronate after 1 Year of Treatment						
	Study 2007008 ^{a,c}		FACT Year 1 ^{a,d}		MOTION ^{b,d}	
	5 mg IRBB Ris Daily N = 307	35 mg DRFB Ris Weekly N = 307	70 mg Aln Weekly N = 520	35 mg Ris Weekly N = 533	70 mg Aln Weekly n = 299	150 mg Iban Monthly n = 253
NTX/Cr	-42.2	-47.3	-52.8	-40.3	n/a	n/a
CTX	-44.4	-49.2	-73.8	-54.7	-81.2	-75.5
BAP	-31.9	-33.5	-40.6	-28.1	n/a	n/a
P1NP	n/a	n/a	-63.9	-48.0	-67.7	-68.2

IRBB = immediate release formulation taken at least 30 minutes before breakfast; DRFB = delayed-release formulation taken following breakfast; Ris = risedronate; Aln = alendronate; Iban = ibandronate.
N = number of subjects in the intent -to-treat group; n = number of subjects in the subset with values at Month 12
n/a = analysis not done
a Mean percent change from baseline
b Median percent change from baseline
c Results at Week 52
d Results at Year 1 (LOCF)

In the FACT study, the reduction measured for each BTM after giving 70 mg alendronate weekly was statistically significantly greater than with 35 mg risedronate weekly: 31% (NTX/Cr), 35% (type-1 collagen C-telopeptide [CTX]), and 44% (BAP) greater reductions with alendronate than with risedronate. Additional results from the 1-year extension to the FACT study were consistent with the first year of the study ([Bonnick et al 2006](#)). The reduction in BTMs observed with risedronate treatment in the FACT study was similar to the risedronate clinical study data (Study 2007008).

The authors of the MOTION study concluded that after 1 year of treatment, the reductions in bone turnover were clinically similar between 150 mg ibandronate once-a-month treatment and 70 mg weekly alendronate.

A cross-study comparison of data from the above studies shows that risedronate reduces bone turnover to a lesser extent than these other approved BPs, while maintaining its effectiveness on all fracture types ([Russell et al 2008](#)).

6.4. Overall Post-marketing Exposure

The cumulative post-marketing exposure since the approval of risedronate in 1998 is estimated to be 27.7 million subject years. Warner Chilcott has pharmacovigilance efforts in place for risedronate with ongoing signal detection and continual monitoring of reported events.

Risedronate case reports are retrieved where risedronate was the primary suspect product or co-suspect product with an event. The post-marketing reports in the global safety database include

spontaneous reports received from health care providers (HCPs) and consumers. Consumer reports that were subsequently confirmed by an HCP were re-classified as HCP reports. Data are captured for any post-marketing adverse event reported as having occurred in a subject who received risedronate, irrespective of the causal opinion of the reporter. Currently, all serious reports from clinical studies are entered into this database. Reports received in response to Company-sponsored subject education programs or Internet web sites are considered “solicited” (as per CIOMS V recommendation), and therefore are not included in this assessment unless considered serious and causally-related. The literature is searched on a regular basis and events identified during those searches are included in the safety database when a causal attribution is stated or implied.

Post-marketing safety information for risedronate is presented in the applicable sections below.

6.5. Atypical Fractures

6.5.1. Nonclinical Data

Several specialized studies were conducted to evaluate bone safety and quality in intact and ovariectomized animals given risedronate. The conclusions from these specialized studies are summarized below.

- Risedronate did not impair mineralization (no osteoid accumulation) and did not produce woven bone (ie, the bone formed had normal lamellar structure) in any study, even at the highest doses tested (Study 995.80.00-AH, Study 995.80.00-AR, Study 995.80.00-AA). In the growing rat model (Study 981.82.00-AS), there was no inhibition of mineralization (evidenced by lack of effect on growth plate width) at 5.0 mg/kg/day subcutaneously (the highest dose tested, and equivalent to approximately 500 mg/kg orally). This, together with the lowest effective dose in this model (0.0015 mg/kg/day), gave an inhibition of mineralization-to-antiresorption therapeutic index of >3000.
- Risedronate maintained bone turnover or remodeling as shown by the presence of double tetracycline labels on quantitative bone histomorphometry and had no deleterious effects on bone quality, including bone structure and bone biomechanical strength, in any study, even with long-term administration at high doses (2.5 mg/kg/day orally for 12 months in ovariectomized rats and for 18 months in ovariectomized minipigs). Risedronate either maintained or improved bone structure and bone strength and maintained or improved the positive relationship between bone mass/density and strength (ie, risedronate maintained or improved biomechanical integrity and bone quality) (Study 995.80.00-AH, Study 995.80.00-AR, Study 995.80.00-AA, Study 995.80.00-BK, Study 981.80.00-AC).
- In normal dogs treated with 0.05, 0.1, and 0.5 mg/kg/day for 1 year (0.5, 1 and 5 times the clinical dose for treatment of postmenopausal osteoporosis on a mg/kg basis, respectively), risedronate increased the accumulation of microcracks (sometimes referred to as microdamage) in vertebral bone. The accumulation was non-linearly related to the level of remodeling suppression ([Allen et al 2006](#)). In this study, all dose levels reduced remodeling and increased microcrack accumulation. Despite this, there were no detrimental effects on biomechanical properties, possibly due to off-setting improvements in bone volume and mineralization. Both the 0.1 and 0.5 mg/kg/day doses significantly

increased vertebral bone stiffness. These results are consistent with a previous study that examined just the 0.5 mg/kg/dose given for 1 year to normal dogs ([Mashiba et al 2001](#)).

- At an oral dose equivalent to the clinical dose (0.1 mg/kg/day), risedronate had no significant effect on fracture healing including no effect on the biomechanical strength of the fracture site (Study 995.09.00-FH). Although a 10 times higher dose (1.0 mg/kg/day) caused a slight delay in fracture healing and a decrease in ultimate load, this dose also had no effect on biomechanical strength of the fracture site. Taken in total, these nonclinical studies show that risedronate had no deleterious impact on bone quality (structure and strength) up to 5 times, or higher, the daily clinical dose for the treatment of postmenopausal osteoporosis. There is no mineralization defect, there is no over suppression of bone turnover, strength is maintained or improved, and induced fractures heal normally with risedronate treatment in normal intact animals and ovariectomized animal models of bone loss. Further, risedronate did not induce any spontaneous fractures when dosed chronically to intact dogs (up to 2 mg/kg/day orally for 2 years or 64 mg/kg given once monthly for 1 year).

6.5.2. Bone Biopsy Data from Clinical Studies

In the placebo-controlled study (Study 1996052, a 2-year extension of the 3-year core study, RVN008993) paired iliac crest biopsies were examined at 5 years (placebo, N=12; risedronate, N=13). Standard histomorphometric analysis continued to show normal histology with no pathological findings and the bone quality appeared to be consistent with that seen in Year 3. Double tetracycline label was reported in all biopsies taken from subjects treated with risedronate for 5 years ([Ste-Marie et al 2004](#)).

Additionally, biopsies from high-risk subjects, whose pretreatment bone turnover was higher than premenopausal normative median, were also examined using micro-computed tomography (micro-CT) ([Borah et al 2006](#)), by quantitative back-scattered electron imaging (qBEI) ([Zoehrer et al 2006](#)), and by Fourier Transform Infrared (FTIR) imaging ([Durchschlag et al 2006](#)). These analyses showed neither hyper-mineralized bone nor any changes that would imply a decline in bone quality. The mineralization data from the micro-CT study suggest that bone turnover in postmenopausal women on long-term risedronate treatment (up to 5 years) was comparable to bone turnover in premenopausal women. The results also indicate that the degree and distribution of mineralization were comparable between the postmenopausal women treated with risedronate for up to 5 years and premenopausal women ([Borah et al 2006](#)).

Additional data from the clinical studies have been published that support the continued use of risedronate. In Study RVN008993, trabecular architecture deteriorated in the placebo arm but was preserved with risedronate treatment ([Borah et al 2004](#)). The biopsy results from a study of early postmenopausal women also showed that those subjects who were on placebo experienced deterioration of trabecular architecture, while those on risedronate treatment did not ([Dufresne et al 2003](#)). Degradation of trabecular architecture leads to compromised bone properties, including a reduction in strength, which predisposes the patient to an increased risk for fractures ([Parfitt 1992](#); [Kleerekoper et al 1985](#)). In a recent study, risedronate was shown to reduce intra-cortical porosity in paired biopsies from patients treated with risedronate 5 mg daily for 5 years ([Borah et al 2010](#)).

6.5.3. Observations in Clinical Studies

As shown in [Table 1](#), 22 risedronate clinical studies (including extension studies) supporting daily, weekly, and monthly dosing regimens for the treatment and prevention of postmenopausal osteoporosis were evaluated for hip and femur fractures. These studies followed over 21,000 subjects who were treated with placebo or risedronate. The majority of subjects were treated for up to 3 years, with some subjects receiving up to 7 years of continuous risedronate treatment.

Hip Fractures

In 14 of the 15 placebo-controlled studies, the incidence of hip fracture reported as AEs was the same or higher in the placebo group compared to the risedronate 2.5 and 5 mg groups; in 1 study (Study RBL004494) 1 subject in the 5 mg risedronate group had a hip fracture, compared to 0 in the placebo group.

In placebo-controlled studies with risedronate 35 mg once a week, 1 hip fracture was reported in the placebo group and none were reported with risedronate. In active-controlled studies in which subjects received intermediate doses of risedronate compared to 5 mg daily (active control), the hip fracture AEs in the intermittent groups were similar to the active-control group.

Femur and Subtrochanteric Fractures

Among the 22 risedronate IR clinical studies, adverse events coded as femur fracture or subtrochanteric fracture were reported in 61 subjects. This number includes all such fractures, with no accounting for exogenous causality (eg, intraoperative, significant trauma, etc) or for the changing terms used to define and differentiate these fractures since the studies started in 1993.

[Table 5](#) summarizes the reports of fractures coded as the AE “femur fracture.” The incidence of femur fracture reported as an AE was low (38 total) and similar across the risedronate, placebo, and active-control groups (5 mg risedronate). It is important to note that the 5 mg group was included in more studies than the placebo and other risedronate dose groups, as 5 mg was used as an active control in the later studies. In the recent Phase 3 study with DR risedronate (Study 2007008), femur fractures were reported in 2 subjects receiving risedronate 5 mg daily.

The incidence of fractures coded as the AE “subtrochanteric fractures” was also low (23 total) and similar among the placebo and treatment groups (9 fractures in the placebo group, 7 in the 2.5 mg group, and 7 in the 5 mg group), with all but one of the fractures (placebo patient) occurring in the hip fracture studies RHN009193 and RHE009293.

Study Number	Number of Subjects (ITT)	Duration (months)	Placebo n/N (%)	2.5 mg Daily* n/N (%)	5 mg daily n/N (%)	35 mg weekly n/N (%)	50 mg weekly n/N (%)	75 mg 2CDM n/N (%)	150 mg monthly n/N (%)
RVN008993	2439	36	0/815	1/811 (0.1)	0/813				
RVE009093	1222	36	2/407 (0.5)	3/408 (0.7)	4/407 (1.0)				
RON009393	643	12-18	0/217	0/210	0/216				
ROE009493	541	24	0/180	1/184 (0.5)	0/177				
RHN009193	4899	36	2/1646 (0.1)	3/1615 (0.2)	2/1638 (0.1)				
RHE009293	4432	36	4/1488 (0.3)	2/1478 (0.1)	2/1466 (0.1)				
HMR4003E/3002	730	6			0/730				
RVE1996077	265	24	1/130 (0.8)		0/135				
RVE1998080	164	24			2/164 (1.2)				
RVE2001079	61	12	0/61						
RVE2002157	32	24			0/32				
RVN1996052	86	24	0/42		0/44				
HMR4003E/3001	1456	24			3/480 (0.6)	2/485 (0.4)	2/491 (0.4)		
2004012	1229	24			0/613			1/616 (0.2)	
2005032	1292	24			0/642				1/650 (0.2)
RBL004494	381	24	0/126	0/126	0/129				
RPE002494	520	12-18	0/259	0/261					
HMR4003B/3001	170	24	0/56		0/114				
HMR4003F/4001	278	12	0/142			0/136			
2001092	284	24	0/93			0/191			
RCP009993	224	12	0/76	0/73	0/75				
RCT009893	285	12	0/94	0/92	0/99				

n = number of fractures reported in the treatment group; N = number of ITT subjects in the treatment group.
 *2.5 mg was discontinued early due to protocol amendment in studies RVN008993, RVE009093, ROE009493, and RCP009993

6.5.4. Post-marketing Experience Related to Atypical Fractures

Of the non-vertebral fracture reports received during the latest post-marketing reporting period, the case reports that are relevant to this report are subtrochanteric or femoral shaft fractures that have similar attributes to those reported as subtrochanteric insufficiency fractures in publications by [Goh et al \(2007\)](#), [Kwek et al \(2008\)](#) and [Neviasser et al \(2008\)](#). These have included low energy femoral shaft fractures, femoral fracture prodromal pain, simple transverse or short oblique femoral fracture, and thickening of the lateral femoral cortex; all coincident with long-term oral BP use.

Against a global cumulative post-marketing exposure estimated at 27.7 million patient-years, a reporting rate of less than 1 report per 100,000 patient-years of exposure to risedronate is estimated, with a reporting rate increase from 0.13/100,000 patient-years in 2008 to 0.27/100,000 patient-years in 2010. History demonstrates that stimulated reporting of an event, such as an atypical subtrochanteric fracture, will occur with an increase in literature reports. Consistent with this, several of the femoral fracture case reports received in this period indicated that literature concerning postulated long-term effects was the reason to suspect causality between fractures and therapy. Objective evidence such as an x-ray was generally not available.

6.5.5. ASBMR Task Force Report on Atypical Fractures

Reports linking long-term use of BPs with atypical fractures of the femur led the leadership of the American Society for Bone and Mineral Research (ASBMR) to appoint a Task Force to address key questions related to this problem. This multi-disciplinary expert group of 28 physicians with expertise in bone science reviewed pertinent reports published from January 1990 to 30 April 2010, as well as pre-clinical studies to evaluate the pathogenesis of atypical femur fractures ([Shane et al 2010](#)).

The Task Force found that the number of patient-years of exposure to drugs that are currently on the market for osteoporosis varied between 2 million and 54 million. In general, reporting rates of subtrochanteric and diaphyseal fractures, with or without atypical features, were very low (1-3/1,000,000 patient-years of exposure). The precise incidence of atypical femoral fractures is unknown. In order to clarify the pathogenesis and causality, it is necessary to understand the true incidence of these fractures in both the general population of subjects without known osteoporosis who are unexposed to BPs, in subjects with osteoporosis both exposed and unexposed to BPs and other agents used to treat osteoporosis, and in specific populations distinguished by concomitant drug exposures and co-morbid diseases.

A cross-sectional study of 11,944 Danish people over age 60 compared age-specific fracture rates and BP exposure in various kinds of proximal femur fractures ([Abrahamsen et al 2009](#)). Subjects in this study with subtrochanteric and diaphyseal fractures were no more likely to be on alendronate; however, they were more likely to use oral glucocorticoids than those with typical hip fractures. Consistent with these results, data from another Danish cohort suggest that the risk of subtrochanteric/diaphyseal fractures, and all fractures, is present before BP initiation ([Vestergaard et al 2010](#)).

Preliminary data on the incidence of atypical femoral fractures from a large US health maintenance organization (HMO) that serves 2.6 million people over age 45, 15,000 total hip and femur fractures were identified by both ICD-9 and CPT coding in subjects older than 45 over

a 3-year period between 2007 and 2009. This suggests that atypical femoral fractures are rare in both the general population and in BP-treated patients, but their incidence may increase with increasing duration of BP exposure. In this investigation there was no age-matched control group of subjects who did not use BPs, and it is possible that the incidence of all fractures in women at this age would increase over 6 years ([Dell et al 2010](#)).

The ASBMR task force did not establish a causal association between BPs and atypical fractures. Further, based on the published and unpublished data reviewed, and the widespread use of BPs, the incidence of atypical femoral fractures subsequent to the use of BP therapy for osteoporosis appears to be very low, particularly compared to the number of vertebral, hip and other fractures that are prevented by BPs. Moreover, a causal association between BPs and atypical fractures has not been established. However, recent observations suggest that the risk of atypical fractures rises with increasing duration of exposure and there is concern that lack of awareness and under-reporting may mask the true incidence of the problem.

One of the recommendations by the task force was that the labels on BPs be changed to inform physicians and patients of the possibility of atypical femoral fractures and of the potential for bilaterality. In the US, class labeling changes for BPs addressing atypical femoral fractures were made in 2011.

6.5.6. FDA-approved Labeling Changes Related to Atypical Femur Fractures

In January 2011, FDA approved the following class labeling safety changes in the ‘Warnings and Precautions’ section of risedronate labels:

Atypical, low-energy, or low trauma fractures of the femoral shaft have been reported in bisphosphonate-treated patients. These fractures can occur anywhere in the femoral shaft from just below the lesser trochanter to above the supracondylar flare and are traverse or short oblique in orientation without evidence of comminution. Causality has not been established as these fractures also occur in osteoporotic patients who have not been treated with bisphosphonates.

Atypical femur fractures most commonly occur with minimal or no trauma to the affected area. They may be bilateral and many patients report prodromal pain in the affected area, usually presenting as dull, aching thigh pain, weeks to months before a complete fracture occurs. A number of reports note that patients were also receiving treatment with glucocorticoids (e.g. prednisone) at the time of fracture.

Any patient with a history of bisphosphonate exposure who presents with thigh or groin pain should be suspected of having an atypical fracture and should be evaluated to rule out an incomplete femur fracture. Patients presenting with an atypical fracture should also be assessed for symptoms and signs of fracture in the contralateral limb. Interruption of bisphosphonate therapy should be considered, pending a risk/benefit assessment, on an individual basis.

6.5.7. EMA-recommended Labeling Related to Atypical Femur Fractures

In Europe, the CHMP recently reviewed the available data from non-clinical and histological studies, relevant clinical trials, epidemiological studies, post-marketing reports and published literature related to atypical fractures and concluded that use of bisphosphonates can be associated with the risk of atypical femoral fractures and therefore recommended that additional information regarding atypical fracture be included in the Product Information of all bisphosphonates ([EMA 2011](#)).

6.6. Osteonecrosis of the Jaw

6.6.1. Observations in Clinical and Nonclinical Studies

No observations of jaw necrosis were identified in risedronate clinical or animal studies. This includes long-term toxicity and carcinogenicity studies in multiple species (mouse, rat and dog) and Phase 3 clinical studies including over 21,000 subjects.

6.6.2. Post-marketing Experience Related to Osteonecrosis of the Jaw

In post-marketing experience with risedronate, very rare cases of osteonecrosis of the jaw have been reported. Many of these reports lack sufficient clinical details (eg, histopathology, radiography, or full subject history) to make definitive assessments. Some case reports include confounding factors such as history of IV bisphosphonate use, corticosteroid use, cancer and chemotherapy. As of 31 March 2011, the reporting rate of osteonecrosis of the jaw subsequent to risedronate use continues to be very rare (CIOMS < 1/10,000) and estimated to be 2.3 per 100,000 subject-years exposure, without attribution of causation. It is important to note that cases of ONJ and analogous conditions were reported in the medical literature for many years before BPs were approved, and cases of ONJ have been reported in people who have never taken a BP.

6.6.3. ASBMR Task Force Report on Osteonecrosis of the Jaw

Reports linking long-term use of BPs with ONJ led the leadership of ASBMR to appoint a Task Force to address key questions related to this problem. This multi-disciplinary expert group of 24 physicians with expertise in clinical and basic bone biology, epidemiology, radiology, oncology, dentistry, periodontal disease, and oral surgery reviewed all pertinent published data, as well as FDA drug AE reports. The group addressed case definition, epidemiology, risk factors, diagnostic imaging, clinical management, and future areas for research related to the disorder ([Khosla et al 2007](#)).

The task force estimated the incidence of ONJ to be relatively low in patients receiving oral BPs for osteoporosis or Paget's disease (between 1 in 10,000 and <1 in 100,000 patient-treatment years) and considerably higher in patients with cancer treated with high doses of intravenous BPs (in the range of 1–10 per 100 patients, depending on duration of therapy).

6.6.4. FDA-approved Labeling Changes Related to Osteonecrosis of the Jaw

In July 2009, the FDA approved updated safety labeling in the 'Warnings and Precautions' section of the label:

Osteonecrosis of the jaw (ONJ), which can occur spontaneously, is generally associated with tooth extraction and/or local infection with delayed healing, and has been reported in patients taking bisphosphonates, including ACTONEL. Known risk factors for osteonecrosis of the jaw include invasive dental procedures (e.g., tooth extraction, dental implants, bony surgery), diagnosis of cancer, concomitant therapies (e.g., chemotherapy, corticosteroids), poor oral hygiene, and co-morbid disorders (e.g., periodontal and/or other pre-existing dental disease, anemia, coagulopathy, infection, ill-fitting dentures).

For patients requiring invasive dental procedures, discontinuation of bisphosphonate treatment may reduce the risk for ONJ. Clinical judgment of the treating physician and/or oral surgeon should guide the management plan of each patient based on individual benefit/risk assessment.

Patients who develop osteonecrosis of the jaw while on bisphosphonate therapy should receive care by an oral surgeon. In these patients, extensive dental surgery to treat ONJ may exacerbate the condition. Discontinuation of bisphosphonate therapy should be considered based on individual benefit/risk assessment. [see Adverse Reactions (6.2)].

6.7. Esophageal Cancer

6.7.1. Observations in Clinical Studies

The potential issue of esophageal cancer was first identified in a published letter in the New England Journal of Medicine (NEJM) concerning spontaneous reports of esophageal cancer among individuals who had been taking oral BPs, primarily alendronate (Wyslowski 2009).

There is no substantive evidence to support an association between esophageal cancer and use of risedronate. There were a small number of subjects with esophageal cancer in the large risedronate placebo-controlled clinical studies, with no difference between active and placebo group incidence. There were 5 cases of esophageal cancer reported in placebo-controlled risedronate clinical studies that enrolled over 16,000 subjects worldwide:

- 2 cases in subjects who received placebo
- 2 cases in subjects who received risedronate 2.5 mg daily
- 1 case in a subject who received risedronate 5 mg daily.

The incidence of esophageal cancer was 18.6 per 100,000 subject-years of observation in placebo subjects, 22.4 per 100,000 subject-years in 2.5 mg daily subjects and 9.1 per 100,000 subject-years in the 5 mg daily subjects. The subjects included 4 females and 1 male, ranging in age from 64 to 80 years. There were no prior or concomitant diagnoses of Barrett's esophagus noted for these subjects. The male subject who received risedronate 5 mg daily was reported to have died from an unknown cause 13 months after having withdrawn from the study. In the 5 cases, the time from start of study drug to onset of the adverse event of esophageal cancer ranged from 89 to 663 days.

In addition, there was 1 case reported in the active-controlled study (HMR4003E/3001) in a subject taking the 5 mg dose. There were no reports of esophageal cancer in subjects taking higher doses of risedronate.

It should be noted that Barrett's esophagus is diagnosed from endoscopy and subjects with a moderate-to-severe complaint of upper gastrointestinal disturbance in the PMO studies were encouraged but not required to undergo an endoscopy exam; the percentage of subjects with AEs of esophagitis were similar between placebo and 5 mg controls in the PMO studies.

There were 9 cases of Barrett's esophagus reported in placebo-controlled risedronate Phase 3 clinical studies as follows:

- 2 cases in subjects who received placebo
- 3 cases in subjects who received risedronate 2.5 mg daily
- 4 cases in subjects who received risedronate 5 mg daily.

The incidence rate for these reports was 18.6 per 100,000 subject-years of observation in placebo subjects, 33.6 per 100,000 in 2.5 mg daily subjects and 36.4 per 100,000 in the 5 mg daily subjects.

In addition, there was 1 case reported in the active-controlled study (2005032) in a subject taking the 150 mg dose and 1 case reported in the open label extension study (RVE1998080) in a subject taking the 5 mg dose.

6.7.2. Retrospective Cohort Mortality Study

The results of a retrospective cohort mortality study among the subjects enrolled in 3 of the North American risedronate osteoporosis studies (RVN008993, RON009393, RHN009193) were previously published (Steinbuch et al 2002). The study determined the vital status for 7845 (98.3%) of the 7981 subjects who were randomized and received study drug or placebo (ITT population). The total number of subject-years of observation of the North American cohort was 25,578 (placebo, 8558; 2.5 mg risedronate, 8462; 5 mg risedronate, 8558). The mortality rates by treatment group were calculated on the basis of these data. While only overall GI tract cancer deaths were reported in the published manuscript, there was an identified subset of esophageal cancer deaths in the mortality study. The observed deaths included those subjects with esophageal cancer listed on the death certificate through 31 Dec 1997, and the expected deaths were based on the US National Cancer Institute's Surveillance Epidemiology and End Results (SEER), age-adjusted esophageal cancer mortality rates (10.9 per 100,000), 1993-1997 for white women 65+ years. Based on the 95% confidence limits (Table 6), this systematic and unbiased mortality follow-up of subjects in the 3 North American studies indicated no difference in the observed number of deaths compared to the expected numbers.

Treatment Group	Observed Deaths	Expected Deaths	O/E Ratio	95% CI
Placebo	1	0.92	1.08	(0.03, 6.01)
2.5 mg risedronate	2	0.91	2.19	(0.26, 7.90)
5 mg risedronate	0	0.92	0	--
Combined risedronate	2	1.84	1.09	(0.13, 3.93)

CI = confidence interval

6.7.3. Post-marketing Experience Related to Esophageal Cancer

In post-marketing experience with risedronate, from the start of marketing shortly after the initial approval in March 1998 through 31 March 2011, 5 cases of esophageal cancer have been reported from Health Care Professionals (1 esophageal neoplasm and 4 esophageal carcinoma reports). The cumulative combined total exposure since start of marketing is estimated to be more than 27 million subject-years. Therefore, the reporting rate of esophageal cancer subsequent to risedronate use is estimated to be <1/1,000,000 subject-years exposure without attribution of causation. The reporting rate to date is less than the incidence of esophageal cancer in the general population as reported by SEER.

The clinical study and post-marketing data for esophageal cancer or Barrett's esophagus coincident with risedronate (< 1 per 1,000,000 subject years) use, compared to expected background rates, do not support an association between risedronate treatment and the occurrence of these events.

6.7.4. FDA-approved Labeling Changes Related to Esophageal Cancer

Following a safety review conducted by FDA to assess the potential association between esophageal cancer and oral BP use, the following labeling was approved on 31 December 2009:

CONTRAINDICATIONS

Abnormalities of the esophagus which delay emptying such as stricture or achalasia.

WARNINGS AND PRECAUTIONS

Upper Gastrointestinal Adverse Reactions

Actonel, like other bisphosphonates administered orally, may cause local irritation of the upper gastrointestinal mucosa. Because of these possible irritant effects and a potential for worsening of the underlying disease, caution should be used when Actonel is given to patients with active upper gastrointestinal problems (such as known Barrett's esophagus, dysphagia, other esophageal diseases, gastritis, duodenitis or ulcers).

Esophageal adverse experiences, such as esophagitis, esophageal ulcers and esophageal erosions, occasionally with bleeding and rarely followed by esophageal stricture or perforation, have been reported in patients receiving treatment with oral bisphosphonates. In some cases, these have been severe and required hospitalization. Physicians should therefore be alert to any signs or symptoms signaling a possible esophageal reaction and patients should be instructed to discontinue Actonel and seek medical attention if they develop dysphagia, odynophagia, retrosternal pain or new or worsening heartburn.

The risk of severe esophageal adverse experiences appears to be greater in patients who lie down after taking oral bisphosphonates and/or who fail to swallow it with the recommended full glass (6 to 8 oz) of water, and/or who continue to take oral bisphosphonates after developing symptoms suggestive of esophageal irritation. Therefore, it is very important that the full dosing instructions are provided to, and understood by, the patient. In patients who cannot comply with dosing instructions due to mental disability, therapy with Actonel should be used under appropriate supervision.

There have been post-marketing reports of gastric and duodenal ulcers with oral bisphosphonate use, some severe and with complications, although no increased risk was observed in controlled clinical trials.

6.8. Conclusions Regarding Long-term Treatment with Risedronate

Treatment with risedronate increased BMD, reduced BTMs, and decreased both vertebral and nonvertebral fractures. The data from clinical studies support continued long-term use of risedronate based on continued demonstration of efficacy at both vertebral and nonvertebral sites with risedronate over 5 years in a placebo-controlled study (Study 1996077) and bone safety demonstrated by bone biopsies obtained at 5 years in a placebo-controlled study (Study 1996052). Risedronate given to subjects for as long as 7 years demonstrated continued fracture protection (Study 1998080).

With regard to femur fractures, evidence from nonclinical studies, bone biopsy data, long-term clinical studies, and post-marketing information all indicate that bone quality is maintained and the incidence of femur fractures with risedronate treatment is low and a causal relationship to risedronate treatment has not been established. In addition, the ASBMR task force stated that, based on the published and unpublished data reviewed and the widespread use of BPs, the incidence of atypical femoral fractures subsequent to the use of BP therapy for osteoporosis appears to be very low, particularly compared to the number of vertebral, hip and other fractures that are prevented by BPs. Moreover, a causal association between BPs and atypical fractures has not been established.

No observations of jaw necrosis in clinical or nonclinical studies were noted with risedronate treatment. ONJ is a rare occurrence and may also occur in osteoporotic subjects who have not been treated with BPs. Some professional dental associations have recommended discontinuation of BP treatment for subjects requiring invasive dental procedures as something that may reduce the risk for ONJ, although there is no scientific evidence that supports this recommendation and no consensus within the dental community that this is necessary or advantageous. Dental associations have all recommended that the clinical judgment of the treating physician and/or oral surgeon should guide the management plan of each subject based on individual benefit/risk assessment ([Murad et al 2007](#)).

The clinical study and post-marketing data for esophageal cancer or Barrett's esophagus coincident with risedronate (<1 per 1,000,000 subject years) use, compared to expected background rates, do not support an association between risedronate treatment and the occurrence of these events.

The reporting rate of esophageal cancer in risedronate-treated subjects to date is less than the incidence of esophageal cancer in the general population as reported by the National Cancer Institute's Surveillance Epidemiology and End Results (SEER).

Warner Chilcott believes the current labeling statements, along with FDA-approved patient labeling (Medication Guide), provide appropriate information and recommendations for healthcare practitioners and patients regarding warnings and precautions for the use of risedronate-containing products.

7. DISCUSSION OF DURATION OF USE AND "DRUG HOLIDAYS" FOR PATIENTS REQUIRING LONG-TERM TREATMENT

7.1. Observations in Clinical Studies

7.1.1. One Year Off Drug Extension Study Following 3 Years of Treatment

The 3-year North American core study (RVN008993) was extended for one year, during which subjects were taken off risedronate and placebo and monitored (Study RVN008993 Addendum). Of the 818 subjects who completed the original 3-year core study, 759 subjects (93%) accepted the invitation to enter the drug-free, calcium supplemented, one-year extension, and of those, 599 subjects (79%) completed the extension study.

The results showed that during the 1 year after risedronate was discontinued, BTMs returned to similar levels as the control group and BMD decreased at the lumbar spine and femoral neck. In the original analysis dexopyridinoline-creatinine ratios were measured. A reanalysis of samples

from this study showed that after stopping risedronate treatment, type-I collagen N-telopeptide (NTx) increased significantly from a median of 30.3 nmol BCE/mmol creatinine at the end of 3 years to 50.9 nmol BCE/mmol creatinine during the 4th year (drug-free year), not significantly different than placebo (Watts et al 2008).

Vertebral (based on the protocol-specified semi-quantitative method of Genant) and nonvertebral fracture incidences were similar for the two treatment groups, implying a compromised clinical benefit on stopping treatment with risedronate. However, when both quantitative and semi-quantitative assessments were used with adjudication to determine prevalent (Year 3) and incident (Year 4) vertebral fractures, a statistically significant 46% vertebral fracture risk reduction was observed in the risedronate-treated group versus placebo (Watts et al 2008). Nonvertebral fractures occurred in 5% of the previous placebo group and 4.8% in the previously risedronate-treated group. Taken together, the vertebral and nonvertebral fracture incidences indicate that the clinical benefit may be compromised when treatment with risedronate is discontinued.

7.1.2. One Year Off Drug Following 2 or 7 Years of Treatment with Risedronate

Subjects from the 3-year study RVE009093 who were studied up to 7 years in Extension Study 1998080, were taken off open-label risedronate therapy during Year 8 (Study 2001079). Of the 136 subjects who completed Year 7, 61 subjects enrolled in the Year 8 extension, and of those, 60 subjects completed Month 12 of the extension. In both treatment groups, NTx increased from levels recorded at the end of Year 7 and were comparable to NTx levels in the 5-year placebo group (Hannon et al 2009).

7.2. FDA-approved Labeling on Limitation of Use

FDA-approved labeling for risedronate products (Actonel, Actonel with Calcium, and Atelvia) provide current and appropriate information and recommendations for healthcare practitioners and patients regarding the use of risedronate-containing products. In addition to providing specific safety information as detailed above, the 'Indication and Usage' section of labeling includes the following 'Important Limitation of Use' statement:

The safety and effectiveness of Actonel (Atelvia) for the treatment of osteoporosis are based on clinical data of three (one) years duration. The optimal duration of use has not been determined. All patients on bisphosphonate therapy should have the need for continued therapy re-evaluated on a periodic basis.

Additionally, FDA-approved patient information is now required for all oral BPs for the treatment of postmenopausal osteoporosis and it is a requirement that patients receive a Medication Guide whenever a product is dispensed to the patient or an agent of the patient.

7.3. EMA-recommended Labeling on Limitation of Use

Recently, the CHMP recommended that information be added to the product information for bisphosphonates authorized for osteoporosis, about the need to periodically evaluate the need for continuing bisphosphonate treatment, particularly after 5 years of treatment, on an individual patient basis (EMA 2011).

7.4. Conclusions Regarding Duration of Use and “Drug Holidays”

As with many chronically administered therapies, the optimal duration of BP therapy for the treatment of osteoporosis is unknown. Scientific evidence exists with regard to differences between and among BPs with regard to affinity for the bone and potency, which may affect clinical outcomes.

There are no data supporting the restriction of duration of use or implementing a drug holiday for risedronate treatment that would be beneficial to subjects. The 5-year safety data, together with the data from Studies RVN008993 Addendum and 2001079 where risedronate treatment was discontinued, do not provide evidence of increased benefit/risk by implementation of a drug holiday for subjects on risedronate therapy. Rather, the data showing BTMs return to pre-treatment levels following discontinuation of risedronate therapy suggest the potential for compromised changes in BMD and bone biomarkers that may result in an increased risk of vertebral and nonvertebral fractures if therapy is discontinued. The available evidence suggests that drug holidays should not be recommended for all patients treated with risedronate; the risks and benefits of a drug holiday must be assessed on an individual patient basis.

Year 4 data and Year 8 data from controlled clinical studies in which a subset of subjects demonstrated a return of BTMs to the level of placebo control subjects, indicated a continuation of vertebral fracture benefit for up to 1 year, and a less-than-optimal nonvertebral fracture benefit after 1 year. If the result desired from a holiday is to eradicate the pharmacological effects of risedronate, this can be achieved by inducing a drug holiday with this drug.

Warner Chilcott believes that the FDA-approved labeling for risedronate products provides current and appropriate information and recommendations for healthcare practitioners and patients regarding the use of risedronate-containing products. Important safety information is provided in the ‘Warnings and Precautions’ section of labeling and an ‘Important Limitation of Use’ statement is included in the ‘Indications and Usage’ section of labeling. This allows for the prescriber to decide what is appropriate for each patient depending on the bisphosphonate they are being treated with, their individual disease status, risk factors, and treatment goals.

8. OVERALL CONCLUSIONS

Bisphosphonates have been shown to be safe and effective for the treatment of postmenopausal osteoporosis, a debilitating disease that affects 1 out of 3 postmenopausal women. Data from a 5-year, randomized, controlled study, support continuous fracture protection with risedronate.

Bisphosphonates have been FDA-approved since 1992 and the known and potential risks associated with bisphosphonates are well characterized and labeled appropriately, with additional risk mitigation including FDA-approved patient labeling (Medication Guide) that must be provided to a patient or agent of a patient each time a risedronate-containing product is dispensed.

There is no consensus within the scientific community nor is there conclusive evidence to support a prescribed holiday for all patients at a specific time point or for a specific duration. In some patients, the clinical benefit of risedronate treatment may be compromised when risedronate is discontinued. Therefore, any change to a patient’s treatment regimen must be done as part of an assessment of long-term therapy for that individual patient, with decisions regarding

the need for and value of drug holidays following long-term bisphosphonate use left to the treating physician and patient.

Approved labeling includes an 'Important Limitation of Use' statement highlighting the fact that physicians and patients need to have an ongoing dialogue about the need for continued therapy. We believe that the FDA approval of the most recent class labeling and implementation of the Medication Guide requirements in January 2011 are adequate to guide and inform the physician and patient in making the risk/benefit assessment of continued long-term treatment based on an assessment of the patient's constellation of factors required to make a treatment decision regarding long-term BP use and the potential value of a drug holiday.

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