PRODUCT INFORMATION

ACTONATE™, ACTONATE™ COMBI & ACTONATE™ COMBI D

NAME OF THE MEDICINE

Australian Approved Name

Risedronate, Calcium carbonate, Cholecalciferol

Non-proprietary Name

Risedronate

Each ACTONATE™ tablet contains the equivalent of 5, 30, 35, 75 or 150 mg of risedronate sodium. The empirical formula for risedronate sodium is $C_7H_{10}NO_7P_2Na$. The chemical name of risedronate sodium is [1-hydroxy-2-(3- pyridinyl)ethylidene]bis(phosphonic acid) monosodium salt.

Calcium Carbonate Tablet

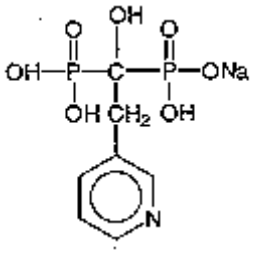
Also contains 1250 mg calcium carbonate tablets. Each calcium tablet contains 1250 mg calcium carbonate, which is equivalent to 500 mg elemental calcium.

Calcium Carbonate/Cholecalciferol Sachet

Each sachet contains 2500 mg calcium carbonate and 22 μg (880 IU) cholecalciferol, which is equivalent to 1000 mg elemental calcium and 22 μg (880 IU) vitamin D3. The terms cholecalciferol and vitamin D3 are equivalent. The chemical name of cholecalciferol is (5Z,7E)-9,10-secocholesta-5,7,10(19)-trien-3β-ol. Molecular formula: $C_{27}H_{44}O$.

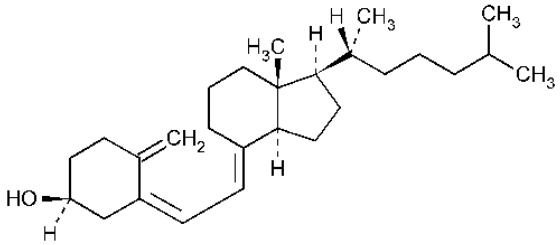
Chemical Structure

The chemical structure of risedronate sodium is the following:
Molecular Weight: 305.10



The CAS registry number is 115436-72-1

The chemical structure of cholecalciferol:



Molecular Weight: 384.6

The CAS registry number is 67-97-0

DESCRIPTION

Risedronate sodium is a fine, white to off-white, odourless, crystalline powder. It is soluble in water and in aqueous solutions and essentially insoluble in common organic solvents.

Calcium carbonate is a white powder, practically insoluble in water, with a relative molecular weight of 100.1.

Cholecalciferol is a secosterol that is a natural precursor of the calcium-regulating hormone calcitriol (1,25-dihydroxyvitamin).

Risedronate

Each ACTONATE™ tablet contains risedronate sodium (5, 30, 35, 75 or 150 mg), lactose (5, 30 or 35 mg tablets only), crospovidone, magnesium stearate, microcrystalline cellulose, hydroxypropyl cellulose, hypromellose, macrogol 400, macrogol 8000, colloidal anhydrous silica, iron oxide yellow (5 mg and 35 mg tablets only), iron oxide red (35 and 75 mg tablet only), indigo carmine (150 mg tablet only) and titanium dioxide.

Calcium Carbonate Tablet

Calcium carbonate is a white powder, practically insoluble in water, with a relative molecular weight of 100.1. Each calcium carbonate tablet contains pregelatinised maize starch, sodium starch glycollate, indigo carmine, magnesium stearate, macrogol 3350, hypromellose, polysorbate 80 and Opaspray Color coating dispersion K-1-4213 Blue (PI 1359).

Calcium Carbonate/Cholecalciferol Sachet

Each sachet of calcium carbonate/cholecalciferol contains alpha tocopherol, hydrogenated soya oil, gelatin, sucrose, maize starch, anhydrous citric acid, malic acid, gluconolactone, maltodextrin, sodium cyclamate, saccharin sodium, rice starch, potassium carbonate and Lemon Flavour BSL 119 (ARTGPI # 3787).

PHARMACOLOGY

Risedronate

Risedronate is a potent pyridinyl bisphosphonate that binds to bone hydroxyapatite and inhibits osteoclast-mediated bone resorption. Risedronate is a third generation bisphosphonate. In preclinical studies risedronate demonstrated potent anti-osteoclast and anti-resorptive activity, increasing bone mass and biomechanical strength dose-dependently. The activity of risedronate was confirmed by bone marker measurements during pharmacodynamic and clinical studies. With risedronate 5 mg daily, decreases in biochemical markers of bone turnover were observed within 1 month of treatment and reached a maximum decrease in 3-6 months, remaining stable during the course of therapy. This data demonstrates that risedronate causes a moderate reduction in bone resorption and bone turnover. The new steady state approximates the rate of bone turnover seen in pre-menopausal women. Decreases in biochemical markers of bone turnover were similar with risedronate 35 mg Once-a-Week and risedronate 5 mg daily. In a study in men with osteoporosis, decreases in biochemical markers of bone turnover were observed at the earliest time point of 3 months and continued to be observed at 24 months.

Comparison of 5 mg daily dose and 35 mg Once-a-Week dose

Based on a lumbar spine BMD (bone mineral density), risedronate 35 mg Once-a-Week (n = 485) was shown to be therapeutically equivalent to risedronate 5 mg daily (n = 480) in a one-year, double blind multicentre study of postmenopausal women with osteoporosis. The two treatment groups were also similar at one year with regard to BMD increases at the total proximal femur, femoral neck and trochanter.

Comparison of 5 mg daily dose and 75 mg on two consecutive days a month

Based on effects on mean percent change in lumbar spine BMD, risedronate sodium 75 mg (n=524) on two consecutive days a month was shown to be equivalent to risedronate sodium 5 mg (n=527) daily in a one-year, double-blind, multicentre study of postmenopausal women with osteoporosis. Both groups had statistically significant mean percent increases from baseline to Month 6, 12 and endpoint in lumbar spine BMD. The two treatment groups were also similar at one year with regard to BMD increases at the total proximal femur and trochanter. Swallowing the 75 mg tablet with hard water was shown to decrease bioavailability by about 60% compared with soft water.

Comparison of 5 mg daily dose and 150 mg Once-a-Month

Based on effects on mean percent change in lumbar spine BMD, risedronate sodium 150 mg (n = 561) once a month was shown to be equivalent to risedronate sodium 5 mg (n = 561) daily in a one-year, double-blind, multicentre study of postmenopausal women with osteoporosis. Both groups had statistically significant mean percent increases in lumbar spine BMD from baseline to Month 6, 12 and endpoint. The two treatment groups were also similar with regard to BMD increases at the total proximal femur and trochanter.

Calcium Carbonate/Cholecalciferol

In case of calcium deficiency, oral intake of calcium supplementation supports the remineralisation of the skeleton. Cholecalciferol increases the intestinal absorption of calcium. Administration of calcium and cholecalciferol counteracts the calcium-deficiency induced increase in parathyroid hormone (PTH) and bone resorption. A meta-analysis of randomised controlled trials has suggested that oral vitamin D supplementation between 700-800 IU per day reduces the risk of hip and nonvertebral fractures in elderly patients. These results were complemented by a subsequent meta-analysis suggesting that oral vitamin D reduces the risk of hip fractures only when calcium supplementation is added.

Pharmacokinetics

Risedronate

Absorption:

Risedronate is relatively rapidly absorbed (t_{max}≈1hour) throughout the upper gastrointestinal (GI) tract. Absorption is independent of dose over the range studied (single dose study, 2.5 to 30 mg; multiple dose studies, 2.5 to 5 mg daily and up to 150 mg monthly). In a 13-week pharmacokinetic study with 5 mg daily and 35 mg weekly and 50 mg weekly dosing (N~19/group), a comparison of the average serum concentration (C_{avg}) for 35 mg/week and 5 mg/day was not statistically significantly different. The 95% confidence interval for C_{avg} was 57.1-101.2, with a point estimate of 76.0% for the 35 mg dose compared to the 5 mg dose. Steady-state conditions in the serum are observed within 57 days of daily dosing. Mean oral bioavailability of the tablet is 0.63% and is decreased when risedronate is administered with food. Bioavailability was similar in men and women. Although administration of risedronate either 30 minutes prior to breakfast or 2 hours after dinner reduces absorption of risedronate by 55% compared to administration in the fasting state (i.e., no food or beverages for 10 hours prior to, or 4 hours after, dosing), and administration one hour prior to breakfast reduces absorption by 30%, ACTONATE™ has been shown to be effective in clinical trials when administered 30 minutes (or longer) before the first meal or beverage of the day (eg., breakfast) and also when administered 2 hours (or longer) prior to and following food or beverages at other times of the day.

Distribution:

The mean steady state volume of distribution is 6.3 L/kg in humans. Human plasma protein binding of risedronate is about 24%. Preclinical studies in rats and dogs dosed intravenously with single doses of [^{14}C] risedronate indicate that 40-45% of the dose was distributed in the bone after 72 hours. At the same time, risedronate levels in soft tissues of rats and dogs were at least 40 and 16 times lower than those in bone respectively. The remainder of the dose was mainly excreted in the

urine. This is likely to be considerably lower in humans who excrete 65% of an intravenously administered dose in the urine in 24 hours. After multiple oral dosing in rats, accumulation of risedronate was observed in bone but not in soft tissues.

Metabolism:

There is no evidence of systemic metabolism of risedronate.

Excretion:

Approximately half the absorbed dose is excreted in the urine within 24 hours. 85% of an intravenous dose is recovered in the urine over 28 days. Mean renal clearance is 105 mL/min and mean total clearance is 122 mL/min. The difference primarily reflects non-renal clearance or clearance due to adsorption to bone. The renal clearance is not concentration dependent and there is a linear relationship between renal clearance and creatinine clearance. In the same pharmacokinetic study mentioned in the "Absorption" section, the percent of dose excreted in urine was measured. The point estimate for the 35 mg versus 5 mg doses was 66.8% (95%CI, 48.0-95.8). Although this was statistically significantly different, the clinical relevance is unknown.
Unabsorbed risedronate is eliminated unchanged in the faeces. Following absorption, the serum concentration-time profile is multi-phasic with an initial half-life of about 1.5 hours and a terminal exponential half-life of 480 hours. Although the elimination rate from human bone is unknown, the 480 hour half-life is hypothesised to represent the dissociation of ACTONATE™ from the surface of the bone.

Calcium Carbonate Tablets

Calcium is eliminated through faeces, urine and sweat. Renal excretion depends on glomerular filtration and calcium tubular reabsorption.

Calcium Carbonate/Cholecalciferol Sachet

Absorption:

During dissolution the calcium salt contained in the effervescent granules is transformed into calcium citrate. Calcium citrate is well absorbed, approximately 30% to 40% of the ingested dose. Cholecalciferol is easily absorbed from the small intestine.

Distribution and Metabolism:

Approximately 99% of calcium in the body is concentrated in the hard structure of bones and teeth. The remaining 1% is present in the intra- and extra-cellular fluids. About 50% of the total blood calcium content is the physiologically active ionised form. Of this approximately 10% is complexed with citrate, phosphate or other anions, and the remaining 40% being bound to proteins, principally albumin. Cholecalciferol and its metabolites circulate in the blood bound to a specific globulin. Cholecalciferol is converted in the liver by hydroxylation to the active form 25-hydroxycholecalciferol. It is then further converted in the kidneys to 1, 25-dihydroxycholecalciferol, which is the metabolite responsible for increasing calcium absorption. Vitamin D which is not metabolised is stored in adipose and muscle tissue.

Excretion:

Calcium is eliminated through the faeces, urine and sweat. Renal excretion depends on glomerular filtration and calcium tubular reabsorption. Vitamin D is excreted in faeces and urine.

Special Groups:

Paediatric: Safety and efficacy of risedronate have not been established in patients under 18 years of age.

Gender: Bioavailability and pharmacokinetics following oral administration are similar in men and women.

Use in the elderly: Risedronate pharmacokinetics are similar in older subjects (age 45 to 76 years) with normal renal function (creatinine clearance 80 to 120 mL/min) to that observed in young subjects (age 18 to 45 years). No dosage adjustment is necessary (see DOSAGE AND

ADMINISTRATION).

Ethnicity: Pharmacokinetic differences due to ethnicity have not been studied.

Renal Insufficiency: Risedronate is excreted intact primarily via the kidney. There is limited clinical data in patients with severe renal impairment (creatinine clearance $<$ 30 mL/min) and therefore ACTONATE™ is not recommended for this patient group.

No dosage adjustment is necessary in patients with a creatinine clearance $\geq$ 30 mL/min.

Hepatic Insufficiency: No studies have been performed to assess the safety or efficacy of ACTONATE™ in patients with hepatic impairment. Risedronate is not metabolised in rat, dog, and human liver preparations. Insignificant amounts ($<$ 0.1% of intravenous dose) of risedronate are excreted in the bile in rats. Therefore, dosage adjustment is unlikely to be needed in patients with hepatic impairment.

CLINICAL TRIALS

Treatment Osteoporosis

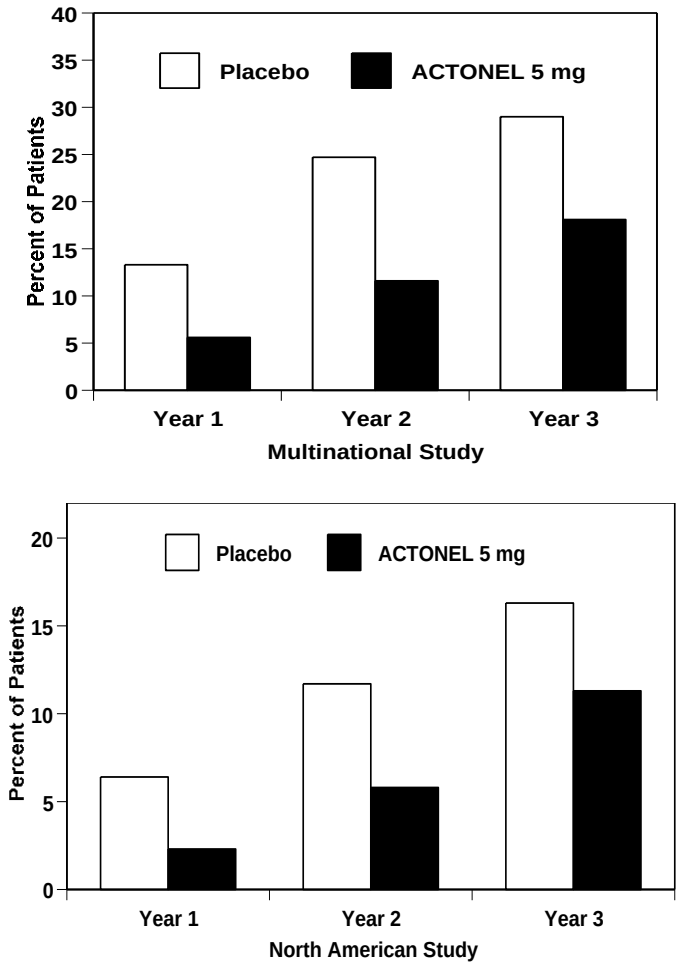
The clinical program involved a wide range of early and late postmenopausal women with and without fracture, including those with a history of GI disease and those using aspirin, NSAIDs, proton pump inhibitors and H_2–blockers.

The fracture efficacy of ACTONATE™ 5 mg daily in the treatment of postmenopausal osteoporosis was demonstrated in two large, randomised, placebo-controlled, double-blind studies which enrolled a total of almost 4000 women under similar protocols. The multinational study (RVE) was conducted primarily in Europe and Australia; a second study was conducted in North America (RVN). Patients were selected on the basis of radiographic evidence of previous vertebral fracture, and had established disease. The average number of prevalent vertebral fractures per patient at study entry was 4 in the multinational study, and 2.5 in the North American study, with a broad range of baseline BMD levels. All patients in these studies received supplemental calcium 1000 mg/day. Patients with low vitamin D levels also received supplemental vitamin D 500 IU/day. The number of evaluable patients treated were :
RVN – 5 mg risedronate n = 696; placebo n = 678
RVE – 5 mg risedronate n = 344; placebo n = 346
RVN and RVE: n = 1040; placebo n = 1024

Effect on Vertebral Fracture:

The pivotal studies of ACTONATE™ in the treatment of postmenopausal osteoporosis clearly demonstrate that ACTONATE™ 5 mg daily reduces vertebral fracture incidence in patients with low bone mass and vertebral fractures, regardless of age, years since menopause, or disease severity at baseline. ACTONATE™ 5 mg daily significantly reduced the risk of new vertebral fractures in each of the two large treatment studies. In the multinational study, treatment with ACTONATE™ 5 mg daily for 3 years significantly reduced the risk of new vertebral fractures by 49% compared to treatment with placebo ($p < 0.001$) (Figure 1). A similar, significant reduction of 41% was seen in the North American study ($p = 0.003$). The effect of ACTONATE™ 5 mg daily on vertebral fracture incidence was seen as early as the end of the first year of treatment in each study. In the multinational study, the incidence of new vertebral fractures after 1 year was reduced from 13.3 to 5.6%, an absolute risk reduction of 8% and a relative risk reduction of 61% ($p< 0.001$). In the North American study, the incidence of new vertebral fractures after 1 year was reduced from 6.4 to 2.4%, an absolute risk reduction of 4% and a relative risk reduction of 65% ($p< 0.001$). At both 1 and 3 years, the reduction in risk seen in the subgroup of patients who had 2 or more vertebral fractures at study entry was similar to that seen in the overall study population. Treatment with ACTONATE™ 5 mg daily also significantly reduced the proportion of patients experiencing new and worsening vertebral fractures in each of the studies.

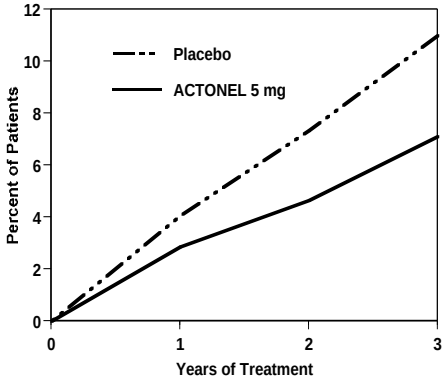
Figure 1:Cumulative Incidence of New Vertebral Fractures



Effect on Non-Vertebral Fractures:

In a prospectively-planned analysis of pooled data from the multinational and North American studies, ACTONATE™ 5 mg daily significantly reduced the cumulative incidence of patients experiencing osteoporosis-related non-vertebral fractures (wrist, humerus, clavicle, pelvis, hip, and leg) over 3 years by 36% (p = 0.005). See Figure 2.

Figure 2: Cumulative Incidence of Osteoporosis-Related Non-Vertebral Fractures - Treatment Studies



The incidence of non-vertebral fractures in the pooled analysis (RVN and RVE) was lower in the 5 mg risedronate group than in the placebo group for all fractures at these sites combined, as well as for the wrist, humerus, pelvis, and leg separately. This difference was significant for all non-vertebral osteoporosis-related fractures (p=0.005), as well as for the humerus (p=0.024) and pelvis (p=0.044), while a trend was seen at the wrist (p=0.075) (Table 1).

These findings demonstrate a beneficial effect of risedronate in preventing non-vertebral, osteoporosis-related fractures.

Table 1: Cumulative Non-Vertebral Osteoporosis-Related Fracture Incidence Year 0-3, RVN008993 and RVE009093 Combined Intent-to-Treat

Skeletal Site	Patients with Incident Fracture	%[a]	Relative Risk[b]	95% CI[b]	P Value[c]
All Placebo	103	11.00	--	--	--
5mg Risedronate	69	7.11	0.643	(0.474, 0.874)	0.005
Hip Placebo	19	2.12	--	--	--
5mg Risedronate	20	1.99	1.029	(0.549, 1.930)	0.928
Wrist Placebo	43	4.66	--	--	--
5mg Risedronate	29	3.05	0.653	(0.408, 1.047)	0.075
Humerus Placebo	24	2.55	--	--	--
5mg Risedronate	11	1.13	0.447	(0.219, 0.913)	0.024
Pelvis Placebo	15	1.64	--	--	--
5mg Risedronate	6	0.59	0.391	(0.152, 1.008)	0.044
Clavicle Placebo	1	0.08	--	--	--
5mg Risedronate	5	0.55	4.892	(0.571, 41.877)	0.108
Leg Placebo	13	1.34	--	--	--
5mg Risedronate	11	1.18	0.823	(0.369, 1.838)	0.635

Number of patients with baseline and at least one non-follow-up visit during the 3-year studies: Placebo=1221, 5mg Risedronate=1218.

[a] Cumulative proportion of patients with osteoporosis-related fractures based on the Kaplan-Meier estimate of the survival function.

[b] Relative risk and 95% confidence interval based upon Cox regression model comprising terms for treatment group and study.

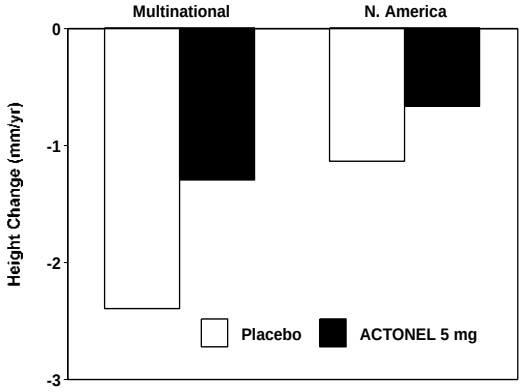
[c] P-value for testing the difference between the placebo and the 5mg risedronate groups using stratified (by study) log-rank test.

-- Not applicable.

Effect on Height:

In the two 3-year osteoporosis treatment studies, standing height was measured yearly by stadiometer. As shown in Figure 3, treatment with ACTONATE™ 5 mg daily was associated with a significant reduction of about 50% in the annual rate of height loss compared to treatment with placebo.

Figure 3: Median Annual Height Change Treatment Studies



Effect on Bone Mineral Density:

The results of four, large, randomised, placebo-controlled trials in women with postmenopausal osteoporosis demonstrate that ACTONATE™ 5 mg daily reverses the progression of disease, increasing BMD at the spine, hip, and wrist compared to the effects seen with placebo. In the large multinational vertebral fracture treatment study previously described, ACTONATE™ 5 mg daily produced increases in lumbar spine BMD which were progressive over at least 2 years of treatment, and were statistically significant relative to baseline and to placebo at 6 months and at all later time points. The mean increase in BMD at the lumbar spine was 5.9%, compared to placebo at the end of 3 years. In the North American fracture trial, similarly progressive and significant increases were seen; the mean increase was 4.3%, compared to placebo. ACTONATE™ 5 mg also produced significant mean increases in BMD at the hip (femoral neck and trochanter) in each trial, compared to losses in BMD in the placebo group. The increases compared to placebo were 3.1% at the femoral neck and 6.4% at the trochanter in the multinational study, and 2.8% and 3.9%, respectively, in the North American study. Significant mean increases in the BMD of the midshaft radius, a skeletal site high in cortical bone, were also observed in each study in patients receiving ACTONATE™ treatment. These findings indicate that ACTONATE™ treatment produces positive effects at all measured skeletal sites of clinical importance for osteoporotic fractures.

Positive effects of ACTONATE™ treatment on BMD were also demonstrated in each of two large, randomised, placebo-controlled trials in which almost 1200 postmenopausal women were recruited on the basis of low lumbar spine bone mass (more than 2 SD below the pre-menopausal mean) rather than a history of vertebral fracture. After 1.5 to 2 years, ACTONATE™ produced significant mean increases in BMD of the lumbar spine compared to placebo (5% and 4.1% in the two studies), femoral neck (2.8% and 2.3%), and trochanter (3.3% and 3.3%) in these women with low bone mass.

Histology/Histomorphometry:

Histological evaluation of 278 bone biopsy samples from 204 postmenopausal women who received ACTONATE™ or placebo once daily for 2 to 3 years (including 74 pairs of biopsies, 43 from ACTONATE™ -treated patients) showed a moderate decrease in bone turnover in ACTONATE™-treated women. Histological assessment showed no osteomalacia, impaired bone mineralisation, or other adverse effects on bone in ACTONATE™-treated women. These findings demonstrate that the bone formed during ACTONATE™ administration is of normal quality.

Bone Markers:

In clinical studies, dose-dependent decreases in biochemical markers of bone turnover were observed with ACTONATE™ 5 mg treatment. These effects were seen within 1 month of treatment and reached a plateau, with levels about 40% below baseline values, by the sixth month of treatment which remained stable during continuous treatment for up to 3 years. These data

demonstrate that 5 mg ACTONATE™ causes a moderate reduction in bone resorption without over-suppression of bone formation. This new steady-state approximates the rate of bone turnover seen in pre-menopausal women.

Combined Administration with Hormone Replacement Therapy:

The effects of combining ACTONATE™ 5 mg daily with conjugated oestrogen treatment (0.625 mg daily) were compared to the effects of conjugated oestrogen alone in a 1-year, randomised, double-blind study in more than 500 postmenopausal women (mean lumbar spine BMD 1.3 SD below the pre-menopausal mean). ACTONATE™ 5 mg daily in postmenopausal women taking oestrogen produced significant mean increases from baseline in BMD of the femoral neck (2.7%) and the midshaft radius (0.7%) at 12 months. These increases were greater than the increases observed in the oestrogen alone group, and reached statistical significance in favour of the combined treatment at the femoral neck and midshaft radius.

Consistent with the changes in BMD, the reduction in bone turnover was significantly greater in the combined ACTONATE™ plus oestrogen group compared to the oestrogen alone group (40% to 47% versus 35% to 40%) and remained within the pre-menopausal range. Histologic evaluation of 93 bone biopsy samples from 61 women on oestrogen therapy who received either placebo or ACTONATE™ once daily for 1 year (including 32 pairs of biopsies, 16 from ACTONATE™ treated patients) found decreases in bone turnover in the ACTONATE™ treated patients that were consistent with the changes in bone turnover markers. Bone histology demonstrated that the bone of patients treated with ACTONATE™ plus oestrogen was of normal lamellar structure and normal mineralisation.

Endoscopic findings:

ACTONATE™ Endoscopic findings from patients with moderate to severe GI complaints in both ACTONATE™ and control patients showed no evidence of treatment related gastric, duodenal or oesophageal ulcers. Duodenitis was rarely observed in the ACTONATE™ group. Four out of five patients with endoscopically-diagnosed oesophageal strictures had been taking risedronate 5 mg for more than 6 months.

35 mg Once-a-Week Dose

ACTONATE™ 35 mg Once-a-Week (n = 485) was shown to be therapeutically equivalent to ACTONATE™ 5 mg daily (n = 480) in a 1-year double-blind multicentre study of postmenopausal women with osteoporosis. In the primary efficacy analysis of completers, the mean increases from baseline in lumbar spine BMD at 1 year were 4.0% (3.7,4.3; 95% CI) in the 5 mg group (n = 391) and 3.9% (3.6,4.3; 95% CI) in the 35 mg group (n = 387) and the mean difference between 5 mg daily and 35 mg Once-a-Week was 0.1% (-0.42, 0.55; 95% CI) (see Table 2). While once a week doses of ACTONATE™ resulted in slightly smaller increases in lumbar spine BMD compared to daily doses of 5 mg after 6 months, the two regimens are equivalent after 12 months. The clinical relevance of these 6-month BMD differences is unknown. The results of the intent-to-treat analysis with the last observation carried forward were consistent with the primary efficacy analysis of completers. The 2 treatment groups were also similar with regard to BMD increases at other skeletal sites. This study is of 2 years' duration, the results of which will be included as soon as they are available.

Table 2: Study HMR 4003E/3001 Bone Mineral Density by Visit - Mean Percent Change from Baseline (Intent-to-treat Population)					
	5 mg Daily Risedronate		35 mg Once-a-Week Risedronate		Mean Difference (95% CI)
Analysis Visit	N	Mean	N	Mean	5 mg Daily vs.35 mg Once-a-Week
Lumbar spine					
Month 6	402	3.12[a]	389	2.68[a]	0.44[b] (0.01; 0.87) p=0.045
Month 12	391	4.00[a]	387	3.94[a]	0.06 (-0.42; 0.55) p=0.799
[a]Indicates statistically significant difference from baseline [b]Indicates statistically significant difference between treatment groups					

Very few patients in any treatment group had new fractured vertebrae at Month 12 (5 mg daily: 1.5%; 35 mg Once-a-Week: 1.3%). No patient had more than one new fractured vertebra. There were no statistically significant differences in the percentage of patients with new vertebral fractures among the 2 treatment groups.

75 mg on two consecutive calendar days a month

Clinical equivalence has been demonstrated against a 5 mg daily dose of risedronate sodium. In a double-blind, multicentre study of postmenopausal women with osteoporosis, 1 year of treatment with ACTONATE™ 75 mg two consecutive days/month (n = 616) was shown to be non-inferior to ACTONATE™ 5 mg daily (n = 613). In the primary efficacy analysis of completers, the mean increases from baseline in lumbar spine BMD at 1 year were 3.6% (3.3, 3.9; 95% CI) in the 5 mg daily group (n = 527) and 3.4% (3.1, 3.7; 95% CI) in the 75 mg two days/month group (n = 524) with a mean difference between groups being 0.2% (-0.2, 0.6; 95% CI). The results of the intent-to-treat analysis with the last observation carried forward were consistent with the primary efficacy analysis of completers. The 2 treatment groups were also similar with regard to BMD increases at other skeletal sites. The numbers of patients with new vertebral fractures at Month 12 and Endpoint were similar in the 75 mg two-days month group and the 5 mg daily group (at Endpoint, 75 mg two-day month 1.09%; 5 mg daily 1.46%).

150 mg Once-a-Month Dose

In a double-blind, active-controlled, multicenter study of postmenopausal women with osteoporosis, 1 year of treatment with ACTONATE™ 150 mg Once-a-Month (n = 650) was shown to be non-inferior to ACTONATE™ 5 mg daily (n =642). In the primary efficacy analysis of completers, the mean increases from baseline in lumbar spine BMD at 1 year were 3.4% (3.0, 3.8; 95% CI) in the 5 mg daily group (n = 561) and 3.5% (3.1, 3.9; 95% CI) in the 150 mg Once-a-Month group (n = 561) with a mean difference between groups being -0.1% (-0.5, 02; 95% CI). The 2 treatment groups were also similar with regard to BMD increases at other skeletal sites. The numbers of patients with new vertebral fractures at Month 12 and Endpoint were similar in the 150 mg Once-a-Month group and the 5 mg daily group (at Endpoint, 150 mg 1.4%; 5 mg daily 1.4%).

Treatment of Osteoporosis in Men

ACTONATE™ 35 mg Once-a-Week demonstrated efficacy in men with osteoporosis (age range 36 to 84 years) in a 2-year, double-blind, placebo-controlled study in 284 patients (risedronate sodium 35mg n = 191). All patients received supplemental calcium and vitamin D. The primary efficacy endpoint was assessed by the percentage change from baseline in lumbar spine BMD at endpoint (Month 24 or last post-baseline observation). Secondary efficacy measures included lumbar spine and proximal femur BMD at 6, 12 and 24 months; BMD responders (defined as patients who had a positive lumbar spine BMD change at Month 24); bone turnover markers at 6, 12 and 24 months; body height; incidence of new vertebral fractures and incidence of clinical fractures. Increases in BMD were observed as early as 6 months following initiation of risedronate sodium treatment. The primary analysis showed a statistically significant difference between risedronate and placebo in least squares mean percent change from baseline to endpoint ($p<0.0001$). The estimated difference at endpoint between risedronate and placebo in the ITT population was 4.53% (95% CI:

3.46%, 5.60%). ACTONATE™ 35 mg Once-a-Week produced mean increases in BMD at the lumbar spine, femoral neck, trochanter and total hip compared to placebo after 2 years of treatment. The bone effect (BMD increase and BTM decrease) of risedronate sodium is similar in males and females.

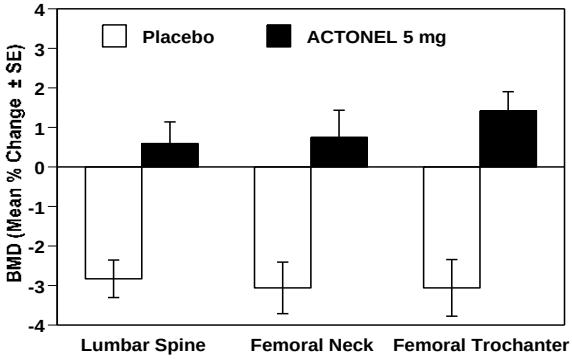
Corticosteroid-Induced Osteoporosis

Bone Mineral Density:

Two 1-year, double-blind, placebo-controlled trials demonstrated that ACTONATE™ 5 mg once daily was effective in maintaining or increasing BMD in men and women initiating or continuing corticosteroid therapy. The first study enrolled 228 patients, each of whom had initiated corticosteroid therapy (≥ 7.5 mg/day of prednisone or equivalent) within the previous 3 months for rheumatic, skin, and pulmonary diseases. The mean lumbar spine BMD was normal at baseline. All patients in this study received supplemental calcium 500 mg/day. After 1 year of treatment, the placebo group lost BMD at the lumbar spine, femoral neck, and trochanter, as shown in Figure 4. ACTONATE™ 5 mg once daily prevented this bone loss with a statistically significant difference from placebo of 3.8% at the lumbar spine, 4.1% at the femoral neck, and 4.6% at the trochanter. The results at these three sites were also statistically significant when the subgroups of men or postmenopausal women were analysed separately. ACTONATE™ prevented bone loss regardless of underlying disease, age, race, gender, corticosteroid dose, or baseline BMD.

The effect of risedronate discontinuation on bone mineral density was studied in a double blind, placebo controlled study in postmenopausal women with glucocorticoid-dependent rheumatoid arthritis. Women were treated for 2 years with risedronate 2.5 mg daily, cyclic risedronate (averaged 2.5 mg of risedronate per day over the 96 Week active period), or placebo and then followed without treatment for one more year. Patients continued glucocorticoid treatment during the third year of the study. Risedronate discontinuation resulted in bone loss at all skeletal sites (proximal femur and lumbar spine) during the third year. The rate of bone loss, however, was similar to the placebo group indicating that bone loss was not accelerated after risedronate was discontinued. The study supports the use of continuous treatment with risedronate to prevent bone loss.

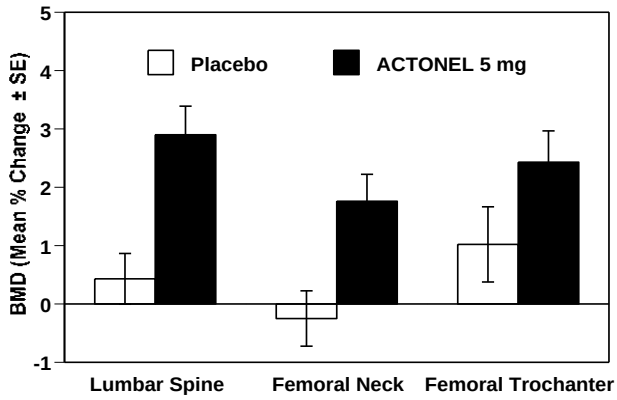
Figure 4: Change in BMD from Baseline Patients Recently Initiating Corticosteroid Therapy 1-Year Study



A second study of similar design enrolled 290 patients with continuing, long-term use (≥ 6 months) of corticosteroids for rheumatic, skin, and pulmonary diseases. The baseline mean lumbar spine BMD was low (1.64 SD below the young healthy population mean), with 28% of the patients more than 2.5 SD below the mean. All patients in this study received supplemental calcium 1000 mg/day. Patients also received supplemental vitamin D 400 IU/day. After 1 year of treatment, the BMD of the placebo group remained near baseline levels at the lumbar spine, femoral neck, and trochanter. ACTONATE™ 5 mg once daily improved bone mass with a statistically significant mean increase compared to placebo of 2.7% at the lumbar spine and 1.9% at the femoral neck as shown in Figure 5. At the trochanter, a statistically significant increase from baseline was demonstrated

(2.4%). ACTONATE™ was effective regardless of age, race, gender, underlying disease, corticosteroid dose, or baseline BMD.

Figure 5: Change in BMD from Baseline Patients on Long-Term Corticosteroid Therapy (1-Year Study)



Vertebral Fractures:

Vertebral fractures were monitored for safety in the two placebo-controlled studies. The incidence of vertebral fractures in each study was 15% to 17% in the placebo patients. The risk of vertebral fractures was reduced approximately 70% in the patients treated with ACTONATE™ 5 mg compared to patients treated with placebo. This decrease reached statistical significance when the studies were pooled, but not when analysed individually**.**

Bone Marker Data:

ACTONATE™ 5 mg daily produced significant reductions in biochemical markers of bone turnover relative to placebo. Deoxypyridinoline/creatinine and bone-specific alkaline phosphatase (SAP) were significantly reduced by approximately 20% relative to placebo after 1 and 3 months of treatment, respectively, and remained reduced (maximum 35% and 26%, respectively) for the duration of the treatment period.

Histology/Histomorphometry:

Histologic evaluation of 70 bone biopsy samples from 48 women on corticosteroid therapy who received either placebo or ACTONATE™ once daily for 1 year (including 22 pairs of biopsies, 16 from ACTONATE™ treated patients) showed that bone formed during treatment with ACTONATE™ was of normal lamellar structure and normal mineralisation, with no bone or marrow abnormalities observed. Histomorphometric evaluation indicated that ACTONATE™ reduces bone resorption and produces a mild-to-moderate decrease in the rate of bone turnover. The rate of bone formation was preserved or increased and there was no evidence of impaired mineralisation. The structure of the cortical bone (cortical thickness and porosity) was maintained in the ACTONATE™ treated patients; cortical porosity increased, however, in the placebo group. These findings indicate that bone formed during ACTONATE™ treatment is of normal quality.

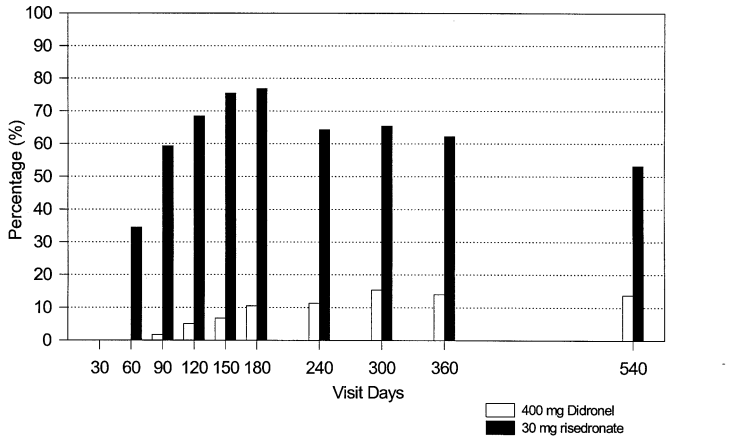
Paget's Disease

Paget's disease is a chronic, focal skeletal disorder characterised by increased and disordered bone remodelling. Excessive osteoclastic bone resorption is followed by osteoblastic new bone formation. This leads to the replacement of normal bone architecture by disorganised, enlarged and weakened bone structure. Clinical manifestations of Paget's disease range from no symptoms to severe bone pain, bone deformity, pathological fractures and neurological disorders. Serum alkaline phosphatase (SAP), the most frequently used biochemical marker of disease activity provides an objective measure of disease severity and response to therapy.

The efficacy of ACTONATE™ was demonstrated in two clinical studies involving 120 male and 65

female patients. In a double-blind, active-controlled study of patients with moderate-to-severe Paget's disease (SAP levels of at least two times the upper limit of normal), patients were treated with ACTONATE™ 30 mg daily for 2 months or etidronate 400 mg daily for 6 months. Figure 6 shows that at Day 180, 77% (43/56) of ACTONATE™ treated patients achieved normalisation of SAP levels compared to 10.5% of patients treated with etidronate ($p < 0.001$). At day 540, 16 months after discontinuation of therapy, 53% (17/32) of ACTONATE™ treated patients and 14% (4/29) of etidronate treated patients with available data remained in biochemical remission.

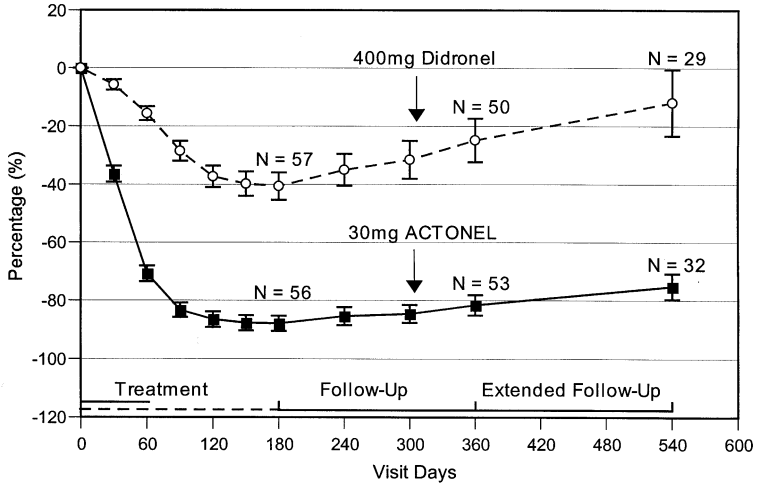
Figure 6: Patients with normal serum alkaline phosphatase values by visit



During the first 180 days of the active-controlled study, 85% (51/60) of ACTONATE™ treated patients demonstrated a ≥ 75% reduction from baseline in excessive SAP levels (difference between measured level and midpoint of the normal range). This was achieved with 2 months of treatment compared to 20% (12/60) in the etidronate treated group with 6 months of treatment ($p < 0.001$).

Changes in excessive SAP levels over time (shown in the figure below) are significant following only 30 days of treatment, with a 36% reduction in SAP levels at that time compared to only 6% seen with etidronate treatment at the same time point ($p < 0.01$).

Figure 7: Mean % change from baseline in serum alkaline phosphatase excess by visit



Response to ACTONATE™ therapy was similar in patients with Paget's disease, irrespective of disease severity. Table 3 shows the mean percent reduction from baseline at Day 180 in excess SAP levels in patients with mild, moderate, or severe disease.

Table 3 Mean Percent Reduction From Baseline At Day 180 In Excess Total Serum Alkaline Phosphatase Levels By Disease Severity						
	30mg ACTONATE™			400mg Etidronate		
Subgroup: Baseline Disease Severity (SAP)	N	Baseline Serum SAP (U/L)*	Mean % Reduction	N	Baseline Serum SAP (U/L)*	Mean % Reduction
>2 and <3 x ULN ≥3 and <7x ULN ≥7x ULN	32 14 8	271.6 ± 5.3 475.3 ± 28.8 1336.5 ±134.19	-88.1 -87.5 -81.8	22 25 6	277.9 ± 7.45 480.5 ± 26.44 1331.5 ± 167.58	-44.6 -35.0 -47.2
* Values shown are mean ± SEM; ULN = upper limit of normal; U/L = upper limit						

Response to ACTONATE™ was similar between patients who had previously received anti-pagetic therapy and those who had not. In the active-controlled study, four patients previously non-responsive to one or more courses of anti-pagetic therapy (calcitonin, etidronate) responded to treatment with ACTONATE™ 30 mg daily (defined by at least a 30% change from baseline). Each of these patients achieved at least 90% reduction from baseline in excess serum alkaline phosphatase levels with three patients achieving normalisation of serum alkaline phosphatase levels.

Histomorphometry of the bone was studied in 14 patients with paired bone biopsies. Nine patients had paired biopsies from pagetic bone lesions and five patients from non-pagetic bone. Bone biopsy results in non-pagetic bone did not reveal osteomalacia, impairment of bone remodelling or induction of a significant decline in bone turnover in patients treated with ACTONATE™.

INDICATIONS

ACTONATE™ 5 mg, 35 mg, 75 mg and 150 mg Tablets, ACTONATE™ Combi, ACTONATE™ Combi D

- Treatment of osteoporosis
- Treatment of glucocorticoid-induced osteoporosis
- Preservation of bone mineral density in patients on long term corticosteroid therapy

30 mg Tablet

- Treatment of Paget's disease of bone

CONTRAINDICATIONS

Risedronate

- Known hypersensitivity to the drug or any of the ingredients.
- Hypocalcaemia (see Precautions)
- Inability to stand or sit upright for at least 30 minutes.

Calcium Carbonate

- Known hypersensitivity to the drug or any of the ingredients
- Hypercalcaemia
- Hypercalciuria
- Nephrolithiasis

Cholecalciferol

- Hypercalcaemia
- Hypercalciuria
- Nephrolithiasis
- Hypervitaminosis D

- Diseases and/or conditions (such as prolonged immobilisation) associated with hypercalcaemia and/or hypercalciuria
- Pregnancy and lactation.
- Severe renal impairment (creatinine clearance <30 ml/min)

PRECAUTIONS

Risedronate

General

Food, certain medication and beverages (except plain water) can interfere with the absorption of ACTONATE™ and should not be taken at the same time as ACTONATE™.

Bisphosphonates have been associated with oesophagitis, gastritis, oesophageal ulcerations and gastroduodenal ulcerations. Thus caution should be used:

- In patients who have a history of oesophageal disorders which delay oesophageal transit or emptying e.g. stricture or achalasia
- In patients who are unable to stay in the upright position for at least 30 minutes after taking the tablet
- If ACTONATE™ is given to patients with active or recent oesophageal or upper gastrointestinal problems (including known Barrett's oesophagus**)**

For patients to gain maximum benefit from ACTONATE™, doctors must stress the importance of taking ACTONATE™ as per the dosage instructions (see DOSAGE AND ADMINISTRATION section). This is especially important in the case of patients with a history of oesophageal disorders.

Hypocalcaemia must be corrected before starting ACTONATE™ therapy.
Bone and mineral metabolism dysfunction (eg. Vitamin D deficiency and parathyroid abnormalities) should be effectively treated before starting ACTONATE™ therapy.
Patients should receive supplemental calcium and vitamin D if dietary intake is inadequate. This is especially important in patients with Paget's disease in whom bone turnover is significantly elevated.

Gastrointestinal

ACTONATE™ like other bisphosphonates may cause local irritation of the upper GI mucosa. Since some bisphosphonates have been associated with oesophagitis and oesophageal ulcerations and gastroduodenal ulceration, doctors should therefore be alert to any signs or symptoms signalling a possible oesophageal reaction, especially in patients with a history of upper GI disease or who are using NSAIDS or aspirin concomitantly. Doctors should be particularly careful to emphasise the importance of taking ACTONATE™ as per the dosage instructions to patients who have a history of oesophageal disorders.

There is very little experience with risedronate in patients with inflammatory bowel disease.

Osteonecrosis of the Jaw

Osteonecrosis of the jaw, generally associated with tooth extraction and/or local infection (including osteomyelitis) has been reported in patients with cancer receiving treatment regimens including primarily intravenously administered bisphosphonates. Many of these patients were also receiving chemotherapy and corticosteroids. Osteonecrosis of the jaw has also been reported in patients with osteoporosis receiving oral bisphosphonates.

A dental examination with appropriate preventive dentistry should be considered prior to treatment with bisphosphonates in patients with concomitant risk factors (e.g. cancer, chemotherapy,

radiotherapy, corticosteroids, poor oral hygiene).

While on treatment, these patients should avoid invasive dental procedures if possible. For patients who develop osteonecrosis of the jaw while on bisphosphonate therapy, dental surgery may exacerbate the condition. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of osteonecrosis of the jaw. Clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

Osteonecrosis of the external auditory canal has been reported with bisphosphonates, mainly in association with long-term therapy. Possible risk factors for osteonecrosis of the external auditory canal include steroid use and chemotherapy and/or local risk factors such as infection or trauma. The possibility of osteonecrosis of the external auditory canal should be considered in patients receiving bisphosphonates who present with ear symptoms including chronic ear infections.

ACTONATE COMBI / ACTONATE COMBI D presentations only:
In patients with mild to moderate renal impairment or a history of absorptive or renal hypercalciuria, nephrocalcinosis, kidney stone formation, or hypophosphataemia, renal function, serum and urinary calcium and phosphate should be monitored regularly.

Atypical Stress Fractures

A small number of patients on long-term bisphosphonate therapy (usually longer than three years), mostly in connection with the use of alendronate have developed stress fractures of the proximal femoral shaft (also known as insufficiency or atypical fractures), some of which occurred in the absence of apparent trauma. Some of these patients experienced prodromal pain in the affected area, often associated with imaging features of stress fracture, weeks to months before a complete fracture occurred. Approximately one third of these fractures were bilateral; therefore the contralateral femur should be examined in patients who have sustained a femoral shaft stress fracture. The number of reported cases of this condition is very low (some 40 reported cases world-wide in connection with alendronate as of 2009).

It is not known to what extent other agents of the aminobisphosphonate class, including ACTONATE™, may be associated with this adverse event. Prior treatment with alendronate should be a cause for added vigilance. Patients with suspected stress fractures should be evaluated, including evaluation for known causes and risk factors (e.g., vitamin D deficiency, malabsorption, glucocorticoid use, previous stress fracture, lower extremity arthritis or fracture, extreme or increased exercise, diabetes mellitus, chronic alcohol abuse), and receive appropriate orthopaedic care.

During bisphosphonate treatment patients should be advised to report any thigh, hip or groin pain and any patient presenting with such symptoms should be evaluated for an incomplete femur fracture.

Discontinuation of bisphosphonate therapy in patients with stress fractures is advisable pending evaluation of the patient, based on individual benefit/risk assessment. Causality has not been excluded in regard to bisphosphonate use and stress fractures.

Osteomalacia

The potential for risedronate to induce osteomalacia was investigated in the Schenk rat assay. This assay is based on histologic examination of the epiphyses of the growing rats after drug treatment. Risedronate did not interfere with bone mineralisation even at the highest dose tested (5 mg/kg/day, subcutaneously) which was $>$ 3000 times the lowest anti-resorptive dose (1.5 μg/kg/day). These data indicate that risedronate administered at therapeutic doses is unlikely to induce osteomalacia.

Calcium Carbonate/Cholecalciferol

The dose of cholecalciferol in the sachets should be considered when prescribing other drugs containing vitamin D. Additional doses of calcium or vitamin D should be taken under close medical supervision. In such cases it is necessary to monitor serum calcium levels and urinary calcium excretion frequently.

Vitamin D should be used with caution in patients with impairment of renal function and the effect on calcium and phosphate levels should be monitored. The risk of soft tissue calcification should be taken into account. In patients with severe renal insufficiency, vitamin D in the form of colecalciferol is not metabolised normally and another form of vitamin D should be used (see CONTRAINDICATIONS).

During long term treatment, serum and urinary calcium levels should be followed and renal function should be monitored through measurement of serum creatinine. Monitoring is especially important in elderly patients on concomitant treatment with cardiac glycosides or diuretics (see INTERACTIONS WITH OTHER MEDICINES) and in patients with a high tendency to calculus formation. Treatment must be reduced or suspended if urinary calcium exceeds 7.5 mmol/24 hours (300 mg/24 hours). In case of hypercalcaemia or signs of impaired renal function, treatment with calcium/vitamin D sachets should be discontinued.

The dose of vitamin D in the sachets should be considered when prescribing other medicinal products containing vitamin D. Additional doses of calcium or vitamin D should be taken under close medical supervision. In such cases it is necessary to monitor serum calcium levels and urinary calcium excretion frequently.

Calcium/cholecalciferol sachets should be used with caution in patients suffering from sarcoidosis because of the increased risk of metabolism of vitamin D to its active metabolite. In these patients, serum calcium levels and urinary calcium excretion must be monitored.
Calcium/cholecalciferol sachets should be used with caution in immobilised patients with osteoporosis due to the increased risk of hypercalcaemia. The calcium/vitamin D treatment might be discontinued in prolonged immobilisation and should only be resumed once the patient becomes mobile again.

Cholecalciferol may increase the magnitude of hypercalcemia and/or hypercalcinuria when administered to patients with diseases associated with unregulated overproduction of calcitriol (eg. leukaemia, lymphoma, sarcoidosis). Urine and serum calcium should be monitored in these patients.
Patients with malabsorption may not adequately absorb cholecalciferol.

Effects on Fertility

Risedronate
A fertility study in male and female rats showed no adverse effects at oral doses up to 16 mg/kg/day, corresponding to systemic exposure (serum AUC 0-24h) about 30 times higher than that in humans dosed at 30 mg/day. At higher dose levels, systemic toxicity, testicular atrophy and reduced fertility were seen in male rats, but these effects are unlikely to have clinical relevance

Use in Pregnancy: Category B3

Risedronate
Risedronate has not been studied in pregnant women. Risedronate should only be used during pregnancy if the potential benefit justifies the potential risk to mother and foetus. If administration during pregnancy is contemplated, serum calcium levels should be monitored and calcium supplementation provided in late gestation. Animal studies suggest that periparturient maternal hypocalcaemia and foetal ossification effects may occur.

Animal studies have shown that risedronate sodium crosses the placenta to a minimal extent in rats. The drug had no teratogenic activity in rats or rabbits at oral doses up to 80 and 10 mg/kg/day respectively. However, suppression of foetal growth and retardation of ossification were observed at the highest dose level in rats. When administered to rats during late gestation, maternal deaths and parturition failure were observed at oral dose levels greater than 2 mg/kg/day. These effects were probably secondary to maternal hypocalcaemia. Systemic exposure (AUC 0-24 h) at the no-effect level in rats was similar to that in patients with Paget's disease, and about 6 times higher than that in patients with corticosteroid-induced osteoporosis. Systemic exposure in rabbits was not measured.

Calcium Carbonate/Cholecalciferol Sachet
During pregnancy the daily intake should not exceed 1500 mg calcium and 600 IU cholecalciferol (15 µg vitamin D3). Studies in animals have shown reproductive toxicity with high doses of vitamin D. In pregnant women, overdoses of calcium and cholecalciferol should be avoided as permanent hypercalcemia has been related to adverse effect on the developing foetus. There are no indications that cholecalciferol at therapeutic doses is teratogenic in humans.

Use in Lactation

Risedronate
Risedronate was detected in feeding pups exposed to lactating rats for a 24-hour period post-dosing, indicating a small degree of lacteal transfer. It is not known whether risedronate is excreted in human milk. Due to the potential for serious adverse reactions in nursing infants from bisphosphonates, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

As with other bisphosphonates in preclinical models, foetuses from risedronate treated dams showed ossification changes in sternebrae and/or skull at doses as low as 3.2 mg/kg/day. This is equivalent to the human 30 mg dose and 6 times the human 5 mg dose based on surface area, mg/m2. Treatment with risedronate during mating and gestation with doses of 3.2 mg/kg/day has resulted in periparturient hypocalcaemia and mortality in rats allowed to deliver.

Calcium Carbonate/Cholecalciferol Sachet
Calcium and cholecalciferol pass into breast milk. Due to the high dosage of cholecalciferol, this medicinal product should not be used during lactation.

Genotoxicity

Risedronate
Risedronate did not cause gene mutations in bacterial or mammalian cells in vitro, nor did it cause DNA damage in rat hepatocytes in vitro. In clastogenicity assays, risedronate was positive in an in vitro assay using Chinese hamster ovary cells at cytotoxic concentrations (7-18% cell survival), but there was no evidence of chromosomal damage when the assay was repeated at concentrations leading to 48-74% cell survival. Risedronate was negative at oral doses up to 1336 mg/kg in an in vivo assay (chromosomal aberrations in rat bone marrow).

Carcinogenicity

Risedronate
No evidence of carcinogenicity was observed in either rats (treated for 104 weeks with up to 24 mg/kg/day) or mice (treated for 80 weeks with up to 32 mg/kg/day). Systemic exposure (serum AUC 0-24h) at the high dose in rats was 160 times greater than that in humans dosed at 30 mg/day. Systemic exposure was not assessed in mice, but the highest dose in the carcinogenicity study was at least 30 times higher than the dose required for pharmacological effects on bone. Thus, risedronate sodium appears to have no carcinogenic potential at therapeutic dose levels.

Effect on Laboratory Tests

Bisphosphonates are known to interfere with the use of bone-imaging agents. However specific studies with risedronate have not been performed.

Small asymptomatic decreases in serum calcium and phosphorus levels have been observed in some patients

Renal impairment

Risedronate

Enteric-coated ACTONATE™ is not recommended for use in patients with severe renal impairment (creatinine clearance $<$ 30 mL/min).

Calcium Carbonate/Cholecalciferol

Cholecalciferol should be used with caution in patients with impairment of renal function and the effect on calcium and phosphate levels should be monitored. The risk of soft tissue calcification should be taken into account. In patients with severe renal insufficiency, vitamin D in the form of cholecalciferol is not metabolised normally and another form of vitamin D should be used. During long-term treatment, serum calcium levels should be followed and renal function should be monitored through measurement of serum creatinine.

Monitoring is especially important in elderly patients on concomitant treatment with cardiac glycosides or diuretics and in patients with high tendency to calculus formation. In the case of hypercalcemia or signs of impaired renal function, treatment with calcium/cholecalciferol should be discontinued.

Paediatric Use

Safety and efficacy of risedronate have not been established in patients under 18 years of age.

Use in the elderly

No dose adjustment is necessary.

INTERACTIONS WITH OTHER MEDICINES

Risedronate

No specific drug interactions studies have been performed. However ACTONATE™ is not systemically metabolised, does not induce or inhibit hepatic microsomal drug metabolising enzymes (cytochrome P450) and has low protein binding.

Concomitant intake of medications containing polyvalent cations (e.g. calcium, magnesium, iron, aluminium, antacids) will interfere with the absorption of ACTONATE™ and should be taken at a different time of the day.

ACTONATE™ may be used concomitantly with hormone replacement therapy or the contraceptive pill.

During clinical trials, patients were exposed to a wide variety of commonly used concomitant medication while taking ACTONATE™. No clinically relevant interactions were noted. The medications included NSAIDs, aspirin, H2 blockers, proton pump inhibitors, antacids, calcium channel blockers, beta-blockers, thiazides, glucocorticoids, anticoagulants, anticonvulsants and cardiac glycosides. There are no clinical data concerning the concomitant medication with 2 or more bisphosphonates and such concomitant medication is not recommended.

In the Phase III postmenopausal trials with 5 mg daily dosing, 29% and 37% of patients used aspirin and NSAIDs respectively. The incidence of upper GI adverse events in ACTONATE™ patients (aspirin/NSAIDs taken $\geq$3 days /week) was similar to that in placebo treated patients. In the Phase III Once-a-Week study, 57% and 40% of patients used aspirin and NSAIDs respectively. In the Phase III study comparing 75 mg on 2 consecutive days a month and 5 mg daily in postmenopausal women, acetyl salicylic acid/NSAID use was reported by 54.8% of patients.

Similar percentages of patients experienced upper gastrointestinal adverse events regardless of NSAIDs and aspirin use.

Calcium Carbonate/Cholecalciferol

Thiazide diuretics reduce the urinary excretion of calcium. Due to increased risk of hypercalcemia serum calcium should be regularly monitored during concomitant use of thiazide diuretics.
Systemic corticosteroids reduce calcium absorption. During concomitant use, it may be necessary to increase the dose of Calcium Carbonate.

Calcium carbonate may interfere with the absorption of concomitant administered tetracycline preparations. For this reason, tetracycline preparations should be administered at least two hours before or four to six hours after oral intake of calcium/vitamin D.

Hypercalcaemia may increase the toxicity of cardiac glycosides during treatment with calcium combined with vitamin D. Such patients should be monitored with regard to electrocardiogram (ECG) and serum calcium levels.

If a bisphosphonate or sodium fluoride is used concomitantly, this preparation should be administered at least three hours before intake of calcium carbonate/vitamin D since gastrointestinal absorption may be reduced.

Oxalic acid (found in spinach and rhubarb) and phytic acid (found in whole cereals) may inhibit calcium absorption through formation of insoluble compounds with calcium ions. The patient should not take calcium products within two hours of eating foods high in oxalic acid and phytic acid.

Simultaneous treatment with ion exchange resins such as cholestyramine or laxatives such as paraffin oil may reduce the gastrointestinal absorption of vitamin D.

Concurrent administration of antacids containing aluminium hydroxide and cholecalciferol is not recommended in patients on haemodialysis as absorption of aluminium may be increased. Concurrent use should be avoided.

ADVERSE EFFECTS

Osteoporosis – ACTONATE™ 5 mg daily dosing

The Phase IIIA clinical trials were designed to include patients with a history of upper GI disorder. Patients were permitted concomitant use of NSAIDs and aspirin. In these patients the incidence of upper GI adverse reactions in the ACTONATE™ group was similar to that in the placebo control group.

Abdominal and musculoskeletal pain were commonly reported (1% to 10%). Glossitis, iritis, and duodenitis were reported uncommonly (0.1% to 1%). There were rare reports (< 0.1%) of abnormal liver function tests.

Laboratory Test Findings: Asymptomatic, small decreases in serum calcium and phosphorus levels have been observed in some patients.

ACTONATE™ has been studied for up to 3 years in over 5000 women enrolled in Phase 3 clinical trials for treatment or prevention of postmenopausal osteoporosis. Most adverse events reported in these trials were either mild or moderate in severity, and did not lead to discontinuation from the study. The incidence of serious adverse events in the placebo group was 24.9% and in the ACTONATE™ group was 26.3%. The percentage of patients who withdrew from the study due to adverse events was 14.4% and 13.5% for the placebo and ACTONATE™ groups respectively.

Table 4 lists adverse events reported in ≥ 5% of ACTONATE™ treated patients and at an incidence higher than in the placebo group in Phase 3 postmenopausal osteoporosis trials. Adverse events

are shown without attribution of causality.

Table 4: Adverse Events Reported in ≥ 5% of ACTONATE™ Treated Patients and Occurring at ≥ 1.1 Times the Placebo Rate in Phase 3 Postmenopausal Osteoporosis Trials

Body System	Placebo % (N = 1744)	ACTONATE™ 5 mg % (N = 1742)
Cardiovascular System		
Hypertension	9.4	10.6
Digestive System		
Abdominal Pain	9.5	11.8
Musculoskeletal System		
Joint Disorder	5.5	7.1
Neck Pain	4.6	5.4
Bone Pain	4.5	5.1
Nervous System		
Dizziness	5.5	6.7
Asthenia	4.5	5.1
Respiratory System		
Pharyngitis	5.2	6.0
Rhinitis	5.0	5.9
Special Senses		
Cataract	5.3	6.1

Endoscopic Findings: ACTONATE™ clinical studies enrolled over 5000 postmenopausal women and included patients with pre-existing gastrointestinal disease and concomitant use of NSAIDs or aspirin. Investigators were encouraged to perform endoscopies in any patients with moderate-to-severe gastrointestinal complaints while maintaining the blind. These endoscopies were ultimately performed on equal numbers of patients between the treated and placebo groups [75 (11.9%) ACTONATE™; 75 (14.5%) placebo]. Across treatment groups, the percentage of patients with normal oesophageal, gastric, and duodenal mucosa on endoscopy was similar [20% placebo and 21% ACTONATE™]. Positive findings on endoscopy were also generally comparable across treatment groups [58 (82.9%) placebo and 57 (81.4%) ACTONATE™].

Gastrointestinal Adverse Events: There was a higher number of reports of mild duodenitis [11(15.7%)] in the ACTONATE™ group [7(10%) placebo], however there were more duodenal ulcers [33(47.1%)] in the placebo group [26(37.1%) ACTONATE™]. The number of patients who had positive findings and withdrew from the studies was similar across treatment groups [26 (37.1%) placebo and 27 (38.6%) ACTONATE™] and there was no evidence of treatment-related oesophageal, gastric, or duodenal ulcers/erosions.

ACTONATE™ has been studied in Phase 3 corticosteroid-induced osteoporosis trials enrolling more than 500 patients. The adverse event profile in this population was similar to that seen in postmenopausal osteoporosis trials, except for musculoskeletal events, which were reported by > 10% of patients and occurred at a greater frequency in the ACTONATE™ 5 mg treatment group [75 (43.1%)] compared to the placebo group [57 (33.5%)]. The adverse experiences reported [165 placebo and 167 ACTONATE™] have usually been mild or moderate and generally have not required discontinuation of treatment. The occurrence of adverse events does not appear to be related to patient age, gender, or race.

Osteoporosis – ACTONATE™ 35 mg Once-a-Week dosing

In a one-year, double-blind, multicentre study comparing ACTONATE™ 5 mg daily and ACTONATE™ Once-a-Week 35 mg in postmenopausal women with osteoporosis, the overall safety and tolerability profiles were similar. Table 5 lists the adverse events in >5% of patients from this trial. Events are shown without attribution of causality.

Table 5: Adverse Events Occurring in ≥ 5% of Patients of Either Treatment Group in the Daily vs Once-a-Week Osteoporosis Treatment Study in Postmenopausal Women		
Body System	**5 mg Daily ACTONATE™ % (N = 480)**	**35 mg Once-a-Week ACTONATE™ % (N = 485)**
Body as a Whole		
Infection	19.0	20.6
Accidental Injury	10.6	10.7
Pain	7.7	9.9
Back Pain	9.2	8.7
Flu Syndrome	7.1	8.5
Abdominal Pain	7.3	7.6
Headache	7.3	7.2
Overdose	6.9	6.8
Asthenia	3.5	5.4
Cardiovascular System		
Hypertension	5.8	4.9
Digestive System		
Constipation	12.5	12.2
Dyspepsia	6.9	7.6
Nausea	8.5	6.2
Diarrhoea	6.3	4.9
Musculoskeletal System		
Arthralgia	11.5	14.2
Traumatic Bone Fracture	5.0	6.4
Myalgia	4.6	6.2
Nervous System		
Dizziness	5.8	4.9

In a 2-year study in men with osteoporosis, the overall safety and tolerability were similar between the treatment and the placebo groups. Adverse experiences were consistent with those previously observed in women.

Osteoporosis – ACTONATE™ 75 mg on two consecutive days a month:
One year of treatment with ACTONATE™ 5 mg daily was compared to ACTONATE™ 75 mg two consecutive days/month in a double-blind, multicentre study in postmenopausal women with osteoporosis. The overall safety and tolerability profiles of the 2 oral dosing regimens were similar. The incidence of serious adverse events was 4.7% in the ACTONATE™ 5 mg daily group and 7.5% in the ACTONATE™ 75 mg two consecutive days/month group. The percentage of patients who withdrew from treatment due to adverse events was 8.8% in the ACTONATE™ 5 mg daily group and 8.9% in the ACTONATE™ 75 mg two consecutive days/month group. Table 6 lists the adverse events in ≥2% of patients from this trial. Events are shown without attribution of causality.

Table 6: Adverse Events Occurring in ≥ 2% of Patients in Either Treatment Group in the Daily vs. the 2 Consecutive Days/Month Treatment Study in Postmenopausal Women (1-year data)		
System Organ Class/Preferred Term	**5 mg Daily ACTONATE™ % (N=613)**	**75 mg two Consecutive Days/Month ACTONATE™% (N=616)**
Gastrointestinal disorders		
Dyspepsia	7.3	9.1
Constipation	7.3	7.6
Nausea	5.9	7.3
Diarrhoea	5.9	6.2
Abdominal pain upper	6.4	4.9
Abdominal pain	3.6	3.2
Vomiting	2.9	3.2
Flatulence	1.5	2.6
Gastritis	2.1	1.6

Musculoskeletal and connective tissue disorders		
Arthralgia	9.5	10.4
Back pain	10.8	8.8
Pain in extremity	6.5	3.9
Shoulder pain	2.4	3.2
Osteoarthritis	3.1	2.9
Muscle spasms	2.3	2.8
Neck pain	2.8	1.9
Infections and infestations		
Influenza	5.4	6.0
Urinary tract infection	4.6	5.7
Nasopharyngitis	5.4	5.2
Bronchitis	3.9	3.6
Upper respiratory tract infection	3.3	3.6
Nervous system disorders		
Headache	4.6	6.3
Dizziness	1.6	2.4
Sciatica	1.0	2.1
General disorders and administration site conditions		
Fatigue	1.5	6.3
Injury, poisoning and procedural complications		
Fall	3.9	4.9
Vascular disorders		
Hypertension	4.2	4.9
Respiratory, thoracic and mediastinal disorders		
Cough	2.6	1.9
Psychiatric disorders		
Anxiety	2.3	1.3
Insomnia	2.3	1.0
Metabolism and nutrition disorders		
Hypercholesterolaemia	2.1	2.1
Ear and labyrinth disorders		
Vertigo	0.8	2.4

ACTONATE™ 150 mg Once-a-Month:

One year of treatment with ACTONATE™ 5 mg daily was compared to ACTONATE™ 150 mg Once-a-Month in a double-blind, multicentre study in postmenopausal women with osteoporosis. The overall safety and tolerability profiles of the 2 oral dosing regimens were similar. The incidence of serious adverse events was 4.2% in the ACTONATE™ 5 mg daily group and 6.2% in the ACTONATE™ 150 mg Once-a-Month group. The percentage of patients who withdrew from treatment due to adverse events was 9.5% in the ACTONATE™ 5 mg daily group and 8.6% in the ACTONATE™ 150 mg Once-a-Month group. Table 7 lists the adverse events in ≥ 2% of patients from this trial. Events are shown without attribution of causality.

Table 7: Adverse Events occurring in ≥ 2% of Patients in either treatment group in the 5 mg Daily vs. 150 mg Once a Month (1-year data)

System Organ Class/Preferred Term	5 mg Daily ACTONATE™ % (N=642)	150 mg Once a Month % (N=650)
Gastrointestinal disorders		
Abdominal pain upper	6.1	8.2
Diarrhoea	4.7	8.2
Nausea	6.9	6.2
Constipation	7.3	5.8

Dyspepsia	4.4	5.1
Vomiting	3.6	4.5
Abdominal pain	3.3	3.5
Flatulence	2.6	2.3
Gastritis	1.9	2.3
Abdominal distension	2.0	2.2
Hiatus hernia	2.3	0.8
Dry mouth	2.0	0.3
Infections and infestations		
Influenza	4.2	8.9
Nasopharyngitis	6.2	5.8
Urinary tract infection	3.6	5.7
Bronchitis	4.4	3.1
Gastroenteritis	2.2	2.8
Upper respiratory tract infection	1.2	2.0
Cystitis	2.0	0.9
Musculoskeletal and connective tissue disorders		
Back pain	6.4	5.7
Arthralgia	7.3	5.5
Osteoarthritis	3.0	3.7
Pain in extremity	2.6	2.8
Muscle spasms	1.2	2.6
Musculoskeletal pain	1.1	2.0
Neck pain	2.0	1.7
General disorders and administration site conditions		
Asthenia	2.2	3.1
Chest pain	1.2	2.0
Pyrexia	0.8	2.0
Nervous system disorders		
Headache	4.8	4.5
Dizziness	1.9	2.0
Injury, poisoning and procedural complications		
Fall	3.3	4.6
Vascular disorders		
Hypertension	4.8	4.6
Respiratory, thoracic and mediastinal disorders		
Cough	1.2	2.3
Psychiatric disorders		
Depression	1.2	2.0
Metabolism and nutrition disorders		
Hypercholesterolaemia	0.8	2.2

Acute Phase Reactions: Acute phase reaction-like events, defined as adverse events of fever or influenza-like illness with onset within the first 3 days of treatment and duration of 7 days or less, were reported by 9 (1.4%) patients on ACTONATE™ 150 mg Once-a-Month, and 1 (0.2%) patient on ACTONATE™ 5 mg daily.

Gastrointestinal Adverse Events: The ACTONATE™ 150 mg Once-a-Month regimen resulted in a slightly higher incidence of discontinuation due to diarrhoea (0.8% vs. 0.0%) compared to the ACTONATE™ 5 mg once daily regimen. All of these events occurred within a few days of the first dose. The incidence of vomiting that led to discontinuation was the same in both groups (0.3% vs. 0.3%).

Ocular Adverse Events: None of the patients treated with ACTONATE™ 150 mg Once-a-Month experience ocular inflammation such as uveitis, scleritis or iritis; of patients treated with 5 mg daily, 2 patients reported iritis.

Laboratory Test Findings: When ACTONATE™ 5 mg daily and ACTONATE™ 150 mg Once-a-Month were compared in postmenopausal women with osteoporosis, the mean percent changes from baseline at 12 months were 0.1% and 0.3% for serum calcium, -2.3% and -2.3% for phosphate, and 8.3% and 4.8% for PTH, respectively. Compared to the ACTONATE™ 5 mg daily regimen, ACTONATE™ 150 mg Once-a-Month resulted in a slightly higher incidence of hypocalcemia at the end of the first month of treatment (0.2%, 5 mg daily vs. 2.2%, 150 mg). Thereafter, the incidence of hypocalcemia with these regimens was similar at approximately 2%.

Paget's Disease

ACTONATE™ was studied in 392 patients with Paget's disease. The adverse events reported were usually mild or moderate and did not generally require discontinuation of treatment. There was no correlation between adverse events and the age or gender of the patient. In a double-blind, active-controlled study, the adverse event profile was similar for ACTONATE™ and etidronate. 6.6% (4/61) of patients treated with ACTONATE™ 30 mg/day for 2 months discontinued treatment due to adverse events, compared with 8.2% (5/61) of patients treated with etidronate 400 mg/day for 6 months.

Adverse events reported in ≥ 5% of ACTONATE™ treated patients in the Phase 3 study are shown in Table 8 below:

Table 8 Adverse Events Reported In ≥ 5% Of ACTONATE™ Treated Patients[T]

BODY SYSTEM	30 mg/day x 2 months ACTONATE™ % (N=61)	400 mg/day x 6 months Etidronate % (N=61)
Body as a Whole		
Flu Syndrome	9.8	1.6
Chest Pain	6.6	3.3
Gastrointestinal		
Diarrhoea	19.7	14.8
Abdominal Pain	11.5	8.2
Nausea	9.8	9.8
Constipation	6.6	8.2
Metabolic & Nutritional		
Peripheral Oedema	8.2	6.6
Musculoskeletal		
Arthralgia	32.8	29.5
Nervous		
Headache	18.0	16.4
Dizziness	6.6	4.9
Skin		
Rash	11.5	8.2

[T]Considered to be possibly or probably causally related in at least one patient

Three patients that received ACTONATE™ 30 mg/day experienced acute iritis in one supportive study. All three patients recovered from their events; however, in one of these patients, the event recurred during ACTONATE™ treatment and again during treatment with pamidronate. All patients were effectively treated with topical steroids.

In the Phase 3 comparative study vs etidronate, patients with a history of upper GI disease or abnormalities and patients on NSAIDs or aspirin were also included. The proportion of ACTONATE™ treated patients [12 (19.7%)] with mild or moderate upper GI adverse events was similar to that in the etidronate treated group [12 (19.7%)]. No severe upper GI adverse events were observed in either group.

As expected the incidence of GI adverse events in patients who took concomitant NSAIDs or aspirin was higher than in non-users. However in these patients the incidence of GI adverse events was similar in the etidronate [10 (16.4%)] and ACTONATE™ [11 (18%)] treated patients.

ACTONATE™ Post-Marketing Data
The following additional adverse reactions have been very rarely reported during post-marketing use:

Eye disorders: Iritis, uveitis
Musculoskeletal and connective tissues disorders: Osteonecrosis of the jaw
Skin and subcutaneous tissue disorders: Hypersensitivity and skin reactions, including angioedema, generalised rash, and bulbous skin reactions, some severe

Calcium Carbonate/Cholecalciferol Data
The following additional adverse reactions have been described:
Uncommon: Hypercalcaemia and hypercalciuria
Rare: Constipation, flatulence, nausea, abdominal pain, diarrhoea, pruritus, rash and urticaria.

DOSAGE AND ADMINISTRATION

ACTONATE™ must only be taken with **plain water**.
Plain water is the only drink that should be taken with ACTONATE™ tablets. Please note that some mineral waters or water from regional areas may have a higher concentration of calcium and therefore should not be used.

ACTONATE™ must be taken 30 minutes before the first food or drink other than water. To facilitate delivery to the stomach, ACTONATE™ should be taken in an upright position and the patient should avoid lying down for 30 minutes. Patients should not chew or suck on the tablet because of the potential for oropharyngeal irritation.

Osteoporosis:

ACTONATE™

ACTONATE™ 5 mg and 35 mg

The recommended dose is 5 mg daily, or 35 mg once a week taken on the same day each week.

ACTONATE™ 75 mg

The 75 mg tablets should be taken orally on two consecutive calendar days a month. The first tablet should be taken on the same day each month, followed by the second tablet the next day. Patients who miss a dose of ACTONATE™ 75 mg should be instructed to take one ACTONATE™ 75 mg tablet the morning after the day it is remembered, unless the time to the next month's scheduled doses are within 7 days. Patients should then return to taking ACTONATE™ 75 mg tablet on two consecutive days a month on the day the tablet is normally taken. If the next month's scheduled doses of ACTONATE™ 75 mg are within 7 days, patients should wait until their next month's scheduled doses and then continue taking ACTONATE™ 75 mg on two consecutive days each month as originally scheduled. Three tablets should not be taken in the same week.

ACTONATE™ 150 mg

ACTONATE™ 150 mg tablets should be taken orally once a month. The tablet should be taken on the same date each month.

Patients who miss a dose of ACTONATE™ 150 mg Once-a-Month should be instructed to take one ACTONATE™ 150 mg tablet the morning after the day it is remembered, unless the time to the next month's scheduled doses are within 7 days.

If the next month's scheduled doses of ACTONATE™ 150 mg are within 7 days, patients should wait until their next month's scheduled doses and then continue taking ACTONATE™ 150 mg as originally scheduled.

Paget's disease:
The recommended treatment regimen is 30 mg once daily for 2 months.
ACTONATE™ is indicated in patients whose symptoms are attributed to Paget's disease and in patients who are at risk for future complications from their disease, to induce remission (normalisation of serum alkaline phosphatase).

Retreatment may be considered (following post-treatment observation of at least 2 months) if relapse occurs, or if treatment fails to normalise serum alkaline phosphatase. For retreatment the dose and duration of therapy are the same as for initial treatment. No data are available on more than one course of retreatment.

N.B. Suppression of Paget's disease may last up to 12 months or longer and re-treatment should be withheld until there are further manifestations of the disease.

ACTONATE™ Combi:
ACTONATE™ Combi is a two component therapy consisting of 7 tablets in a blister, 1 ACTONATE™ 35 mg film-coated tablet (light-orange tablet) and 6 Calcium Carbonate 1250 mg (equivalent to elemental calcium 500 mg) film-coated tablets (blue tablets). ACTONATE™ Combi is intended for patients for whom the amount of calcium included is considered to provide adequate supplementation, based on individual assessment. Supplemental vitamin D should be considered if the dietary intake is inadequate.

The recommended dose in adults is 1 ACTONATE™ 35 mg tablet on the first day, followed, beginning on the next day, by 1 Calcium Carbonate 1250 mg (equivalent to elemental calcium 500 mg) tablet daily for 6 days. This 7 day sequence is then repeated each week.
The ACTONATE™ 35 mg tablet should always be taken on the same day each week, in accordance with the directions described above.

The calcium component should commence on the day after the ACTONATE™ 35 mg tablet is taken, one calcium tablet should be taken each day for the next 6 days. The tablet should be swallowed whole. Calcium absorption is improved if taken with food. Therefore, patients should take the calcium tablet with a meal.

Patients should be instructed that if the ACTONATE™ dose is missed, the ACTONATE™ tablet should be taken on the next day in the morning according to the dosing instructions. On the following day they should take their next calcium tablet (blue tablet). Patients should not take more than 1 tablet from the blister strip per day.

If the calcium dose (blue tablet) is missed, the patient should be instructed to continue taking one tablet of calcium each day beginning on the day the missed dose is remembered. Any remaining calcium tablets in the blister at the end of the weekly cycle should be discarded.
Patients should be instructed to start a new blister strip every 7 days. They should begin the new strip by taking the ACTONATE™ 35 mg tablet (light-orange tablet) on their originally chosen day of the week.

ACTONATE™ Combi D:
A weekly unit of ACTONATE™ Combi D consists of 1 ACTONATE™ 35 mg film-coated tablet and 6 calcium carbonate/cholecalciferol sachets in a box. ACTONATE™ Combi D is intended for patients for whom the amount of calcium and cholecalciferol included is considered to provide adequate supplementation, based on individual assessment.

The recommended dose in adults is 1 ACTONATE™ 35 mg tablet on the first day, followed by, beginning on the next day 1 calcium carbonate/cholecalciferol sachet daily for 6 days. This 7-day sequence is then repeated each week starting with the ACTONATE™ 35 mg Tablet.

The ACTONATE™ 35 mg tablet should always be taken on the same day each week, in accordance with the directions described above.
The calcium carbonate/cholecalciferol sachet should be taken each day for 6 days per week starting on the day after the ACTONATE™ 35 mg Tablet is taken. The contents of the sachet should be poured into a glass of plain water, stirred and drunk immediately once the fizzing has subsided.

Patients should be instructed that if the ACTONATE™ dose is missed, the ACTONATE™ tablet should be taken on the next day in the morning according to the dosing instructions. On the following day they should take their calcium carbonate/cholecalciferol sachet. Patients should never take the tablet and sachet on the same day.

If the calcium carbonate/cholecalciferol sachet is missed, patients should be instructed to continue taking one sachet each day each day beginning on the day the missed dose is remembered. Patients should not take two sachets on the same day. Any remaining sachets at the end of the weekly cycle should be discarded.

Use in the Elderly:

No dose adjustment is necessary.

Renal insufficiency:

No dose adjustment is necessary in patients with mild to moderate renal insufficiency (creatinine clearance 30 to 60 mL/minute). ACTONATE™ is not recommended in patients with severe renal impairment (creatinine clearance $<$ 30 mL/minute) due to limited clinical data.

Hepatic insufficiency

Dose adjustments are unlikely to be needed in patients with hepatic impairment.

Paediatrics:

Safety and efficacy of ACTONATE™ has not been established in patients under 18 years of age.

Compatibility with other Drugs:

Calcium, antacids, aluminium and some oral medications will interfere with the absorption of risedronate and therefore should be taken at a different time of the day.

OVERDOSAGE

Risedronate

No specific information is available on the treatment of overdose with ACTONATE™. Decreases in serum calcium following substantial overdose may be expected in some patients. Signs and symptoms of hypocalcaemia may also occur in some of these patients. Administration of milk or antacids (containing magnesium, calcium or aluminium) to chelate ACTONATE™ may be helpful. Standard procedures that are effective for treating hypocalcaemia, including the administration of calcium intravenously, would be expected to restore physiologic amounts of ionised calcium and to relieve signs and symptoms of hypocalcaemia.

Calcium Carbonate

Because of its limited intestinal absorption, overdosage with calcium carbonate is not likely. However, overdose can lead to hypercalcaemia.

Calcium Carbonate/Cholecalciferol

Overdose can lead to hypervitaminosis and hypercalcaemia.

Contact the Poisons Information Centre (telephone 131126) for advice on management of overdosage.

PRESENTATION AND STORAGE CONDITIONS

ACTONATE™
ACTONATE™ 5 mg and 30 mg tablets are packaged in an opaque PVC/aluminium foil blister strip contained in a carton. The 5 mg tablets are supplied in pack sizes of 28 tablets and the 30 mg tablets are supplied in pack sizes of 28 tablets. ACTONATE™ 5 mg tablets: oval, yellow film-coated tablets with RSN embossed on one side and 5 mg on the other. Store below 25°C.ACTONATE™ 30 mg tablets: oval, white film-coated tablets with RSN embossed on one side and 30 mg on the other. Store below 25°C.

ACTONATE™ 75 mg tablets are packaged in a clear PVC/aluminium foil blister strip contained in a carton. Pack sizes are 2, 4, 6 and 8 tablets. ACTONATE™ 75 mg tablets: oval, pink film-coated tablets with RSN on one side and 75 mg on the other. Store below 25°C.

ACTONATE™ 35 mg Once-a-Week tablets are packaged in a clear PVC/aluminium foil blister strip contained in a carton. Pack sizes are 1 and 4 tablets. ACTONATE™ 35 mg Once-a-Week tablets: oval, light orange film-coated tablets with RSN on one side and 35 mg on the other. Store below 25°C.

ACTONATE™ 150 mg Once-a-Month tablets are packaged in a clear PVC/aluminium foil blister strip contained in a carton. The pack size is 1 tablet. ACTONATE™ 150 mg Once-a-Month tablets are oval, light-blue film-coated tablets with RSN on one side and 150 mg on the other. Store below 25°C.

ACTONATE™ Combi
ACTONATE™ Combi is packaged in a clear PVC/aluminium foil blister contained in a carton. Pack sizes are 7 and 28 tablets. ACTONATE™ 35 mg tablets are oval, light orange film-coated tablets with RSN on one side and 35 mg on the other. The calcium carbonate tablets in ACTONATE™ Combi are capsule-shaped, blue, film-coated tablet with NE 2 on both sides. Store below 25°C.

ACTONATE™ Combi D
The ACTONATE™ 35 mg Once-a-Week tablets contained within ACTONATE™ Combi D are packaged in a clear PVC/aluminium foil blister. The 2500 mg calcium carbonate/22 μg (880 IU) cholecalciferol effervescent granules for oral solution are enclosed in individual sachets for daily use. ACTONATE™ 35 mg tablets are oval, light orange film-coated tablets with RSN on one side and 35 mg on the other. The calcium carbonate/cholecalciferol sachet contains white free-flowing granules. These components are contained in a carton which is available in 1 and 4 weeks of therapy. Store below 25°C.

NAME AND ADDRESS OF THE SPONSOR

Sanofi-Aventis Australia Pty Ltd

12-24 Talavera Road

POISON SCHEDULE OF THE MEDICINE

Schedule 4

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS

13 July 2010

DATE OF MOST RECENT AMENDMENT

11 May 2016