PRODUCT INFORMATION

ACTONATE™ EC, ACTONATE™ EC COMBI & ACTONATE™ EC COMBI D

NAME OF THE MEDICINE

Australian Approved Name
Risedronate, Calcium carbonate, Cholecalciferol

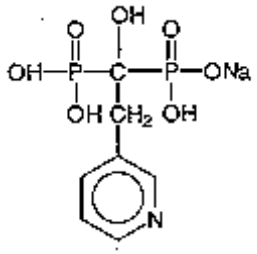
Non-proprietary Name

Risedronate
Each ACTONATE™ EC enteric-coated tablet contains the equivalent of 35 mg of anhydrous risedronate sodium in the form of the hemi-pentahydrate with small amounts of monohydrate. 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.

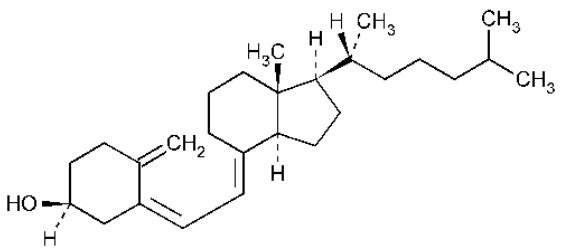
Calcium Carbonate Tablet
ACTONATE™ EC Combi also contains 1250 mg calcium carbonate tablets. Each calcium tablet contains 1250 mg calcium carbonate, which is equivalent to 500 mg elemental calcium.

Calcium Carbonate/Cholecalciferol Sachet
ACTONATE™ EC Combi D also contains calcium carbonate/cholecalciferol sachets. 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
Anhydrous: 305.10
Hemi-pentahydrate: 350.13



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

ACTONATE™ EC tablets have a pH-sensitive enteric-coating and contain a chelating agent edetate disodium (EDTA). The formulation is designed to allow dosing with food, reducing the impact of food on risedronate absorption. Each ACTONATE™ EC tablet also contains, microcrystalline cellulose, colloidal anhydrous silica, sodium starch glycollate, type A, stearic acid, magnesium stearate, methacrylic acid-ethyl acrylate copolymer (1:1), triethyl citrate, purified talc, iron oxide yellow, simethicone and polysorbate 80.

Calcium Carbonate Tablet

Each calcium carbonate tablet contains pregelatinised maize starch, sodium starch glycollate, type A, 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, gluconolactone, maltodextrin, sodium cyclamate, saccharin sodium, rice starch, potassium carbonate and Lemon Flavour BSL 119 (ARTG PI # 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. In a 2 year study comparing ACTONATE™ 5 mg daily immediate-release versus enteric-coated ACTONATE™ 35 mg once-a-week oral dosing regimens (i.e. taken either before or after breakfast) in postmenopausal women, there was no significant differences in mean percent change from baseline in urinary collagen cross-linked N-telopeptide (NTX/Cr) between the enteric-coated and the immediate-release groups. At 2 years, the mean reductions from baseline in urine NTX/Cr were 46% in the ACTONATE™ 5 mg daily group, 51% in the enteric-coated ACTONATE™ 35 mg once-a-week before breakfast group and 49% in the enteric-coated ACTONATE™ 35 mg once-a-week following breakfast group. In addition, serum bone-specific alkaline phosphatase at 2 years was reduced by 33% in the ACTONATE™ 5 mg daily group, 35% in the enteric-coated ACTONATE™ 35 mg once-a-week before breakfast group and 35% in the enteric-coated ACTONATE™ 35 mg once-a-week following breakfast group.

In a study with immediate-release ACTONATE™ 35 mg once-a-week 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.

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:
The mean absolute oral bioavailability of the 30 mg risedronate immediate-release tablet is 0.63% (90% confidence interval [CI]: 0.54% to 0.75%) and is similar to an oral solution. The peak concentration (T_{max}) for the immediate-release tablet is achieved at ~1 hour. The enteric-coated ACTONATE™ 35 mg tablet achieves T_{max} at ~3 hours when administered 4 hours prior to a meal. Using urinary excretion data, the fraction of the dose absorbed from enteric-coated ACTONATE™ 35 mg once-a-week is independent of risedronate dose over the range studied (single dose, from 20 mg to 100 mg).

Food Effect
A crossover pharmacokinetic study that evaluated the food effect in relation to the bioavailability of ACTONATE™ 35mg enteric-coated (EC) and ACTONATE™ 35mg immediate-release (IR) tablet was performed. An assessment of mean risedronate urinary excretion is summarised by treatment regimen in Table 1.

Table 1 Mean Risedronate Urinary Excretion over 72 Hours by Treatment

Parameter	35mg IR 30-min before food	35mg IR Fasted (4 hours before food)	35mg EC Fed (5 minutes after food)	35mg EC Fasted (4 hours before food)
A_e (µg)	57.7366	124.6796	126.3972	179.9608
A'_e (%)	0.1649	0.3562	0.3611	0.5142
A_e cumulative amount of drug excreted in urine A'_e cumulative amount of drug excreted in urine over the stated time interval, normalised for dose and expressed as a percentage.				

The bioavailability of the ACTONATE™ EC tablets decreased by ~30% when administered immediately after a high-fat breakfast compared to administration 4 hours before a meal. The bioavailability of the ACTONATE™ EC tablets administered after a high-fat breakfast was similar to ACTONATE™ IR tablets dosed 4 hours before a meal and was approximately 2-fold greater than the ACTONATE™ IR tablet administered 30 minutes prior to a high-fat breakfast. The bioavailability of the ACTONATE™ EC tablets administered 4 hours before a meal was approximately 3-fold greater than ACTONATE™ IR tablets administered 30 minutes prior to a high-fat breakfast.

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 for the immediate-release tablets. 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. 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: Of the patients receiving ACTONATE™ EC in postmenopausal osteoporosis studies, 59% were 65 and over, while 13% were 75 and over. No overall differences in safety or efficacy were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

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 of Osteoporosis

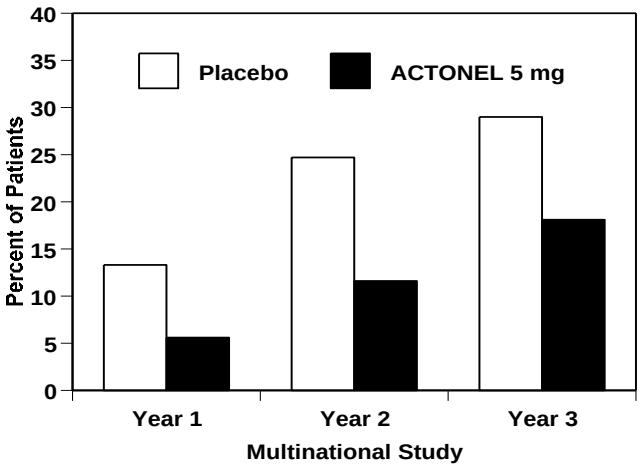
The clinical program involved a wide range of early and late postmenopausal women with and without fracture, including those with a history of GI disease and those using aspirin, NSAIDs, proton pump inhibitors and H_2 –blockers. The fracture efficacy of ACTONATE™ 5 mg daily (risedronate immediate-release formulation) 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 :

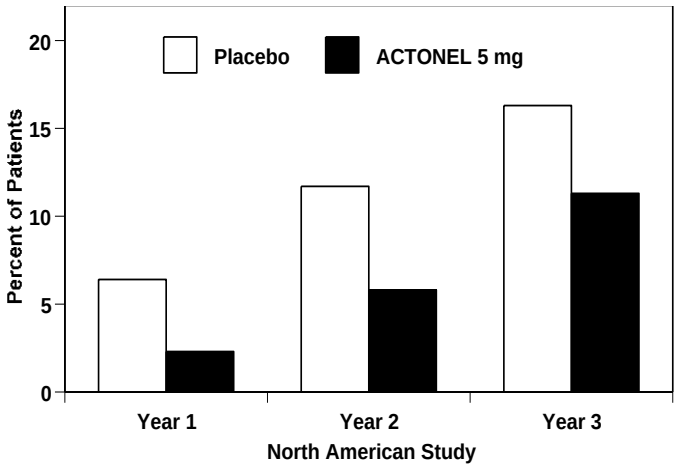
RVN – 5 mg risedronate n = 696; placebo n = 678
RVE – 5 mg risedronate n = 344; placebo n = 346
RVN and RVE: n = 1040; placebo n = 1024

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

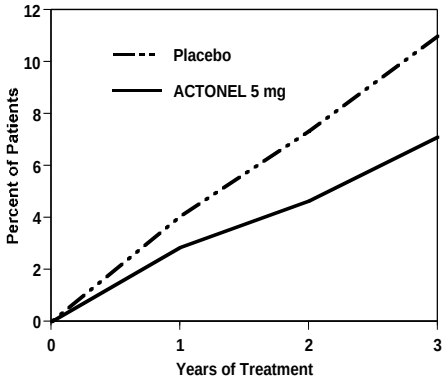




Effect on Non-Vertebral Fractures:

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 2).

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

Table 2: 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.

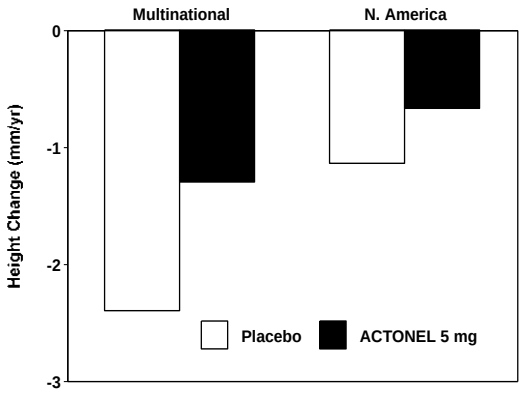
[c] P-value for testing the difference between the placebo and the 5mg risedronate groups using stratified (by study) log-rank test.

-- 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.

Treatment of Osteoporosis in Men
ACTONATE™ 35 mg Once-a-Week (immediate-release) 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 35 mg 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 (immediate-release) 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.

ACTONATE™ EC
Enteric-coated ACTONATE™ 35 mg once-a-week administered either before or after breakfast was shown to be therapeutically equivalent to ACTONATE™ 5 mg daily (immediate-release formulation) in a 2-year, double-blind, multicentre study of postmenopausal women with osteoporosis. The primary efficacy endpoint of percent change from baseline in lumbar spine BMD at week 52 was met. Secondary efficacy endpoints included percent change from baseline in lumbar spine BMD at week 104; non-vertebral fractures at week 104 which were consistent with the primary outcome measure; and change in bone turnover markers. Table 3 presents the primary efficacy analysis of intent-to-treat patients with last observation carried forward (LOCF) at 1 year, as well as the 2 year results.

Table 3
Lumbar Spine BMD - Percent Change from Baseline at 1 yr and 2 yr Endpoints [a]

	ACTONATE™ 5 mg Daily immediate-release N=307	ACTONATE™ 35 mg Once a Week enteric-coated Following Breakfast N=307	ACTONATE™ 35 mg Once a Week enteric-coated Before Breakfast N=308
Primary Efficacy (LOCF), at 1 year			
n	270	261	271
LS Mean (95% CI)	3.1* (2.7, 3.5)	3.4* (2.9, 3.8)	3.4* (3.0, 3.8)
LS Mean Difference [b] (95% CI)		-0.2 (-0.8, 0.3)	-0.3 (-0.9, 0.3)
2 year-endpoint			
n	274	265	273
LS Mean (95% CI)	4.1 (3.7, 4.6)	5.2 (4.7, 5.7)	5.1 (4.6,5.6)
LS Mean Difference[b] (95% CI)		-1.0 (-1.8, -0.2)	-0.8 (1.6, 0.0)

N = number of intent-to-treat patients within specified treatment; n = number of patients with values at the visit.
* Indicates a statistically significant difference from baseline determined from 95% CI unadjusted for multiple comparisons.
[a] at 1 year and 2 year LOCF
[b] LS Mean Difference is 5 mg daily minus 35 mg weekly treatment.

The mean percent change from baseline in lumbar spine BMD at week 104-endpoint was 4.1% for the 5 mg immediate-release before breakfast group, 5.2% for the 35 mg enteric-coated following breakfast group and 5.1% for the 35 mg enteric-coated before breakfast group. The 35 mg enteric-coated weekly regimen either before or following breakfast was determined to be non-inferior to the 5 mg immediate-release before breakfast regimen with respect to percent change in lumbar spine BMD at week 52 and week 104 endpoints. No clinically relevant differences in mean percent increases from baseline to week 104 for total proximal femur, femoral neck and trochanter BMD were seen in each of the 35 mg enteric-coated weekly groups compared to the 5 mg immediate-release daily group.
There were no clinically relevant differences in any of the bone turnover markers at any time point compared to 5mg IR daily dose.

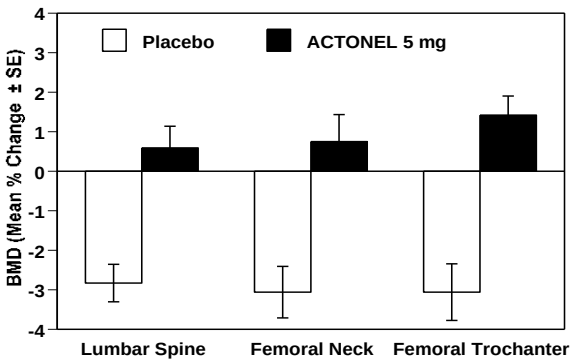
There were no statistically significant differences in either of the 35 mg enteric-coated groups compared to the 5 mg immediate-release group in incidence of new morphometric vertebral fractures at week 52, or at week 104 endpoint.

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.

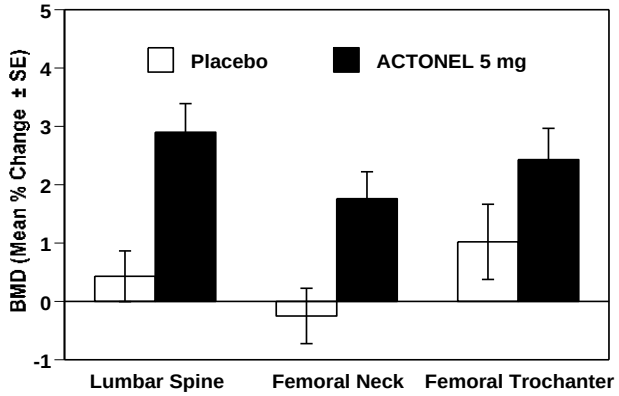
Figure 4: Change in BMD from Baseline Patients Recently Initiating Corticosteroid Therapy 1-Year Study



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.

INDICATIONS

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

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

Calcium supplements and antacids can interfere with the absorption of ACTONATE™ EC and should not be taken at the same time as ACTONATE™ EC.

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™ EC 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™ EC, doctors must stress the importance of taking ACTONATE™ EC 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™ EC therapy. Bone and mineral metabolism dysfunction (e.g. Vitamin D deficiency and parathyroid abnormalities) should be effectively treated before starting enteric-coated ACTONATE™ therapy. Patients should receive supplemental calcium and vitamin D if dietary intake is inadequate.

Gastrointestinal

ACTONATE™ EC 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™ EC 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™ EC Combi / ACTONATE™ EC 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
Of the patients receiving ACTONATE™ EC in postmenopausal osteoporosis studies, 59% were 65 and over, while 13% were 75 and over. No overall differences in safety or efficacy were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

INTERACTIONS WITH OTHER MEDICINES

Risedronate

Risedronate is not systemically metabolised, does not induce or inhibit hepatic microsomal drug metabolising enzymes (cytochrome P450) and has low protein binding.

The results of in-vitro studies indicated that the chelating agent (EDTA) in enteric-coated ACTONATE™ 35 mg once-weekly is not likely to result in changes in absorption of concomitant medications, including those with a narrow therapeutic index or antivirals.

A Phase 1 single-dose, cross-over study in 101 postmenopausal women evaluated the relative bioavailability of enteric-coated ACTONATE™ 35 mg once-a-week tablets taken after breakfast and following a 600 mg elemental calcium/400 IU vitamin D supplement, compared to enteric-coated ACTONATE™ 35 mg taken after breakfast alone. The addition of the calcium/vitamin D supplement following the meal resulted in an approximate 38% reduction in the amount of risedronate absorbed.

Although not specifically studied, if considered appropriate, enteric-coated ACTONATE™ 35 mg may be considered for concomitant use with hormone replacement therapy.

A Phase 1, single-dose, cross over study in 87 postmenopausal women evaluated the absorption of enteric-coated ACTONATE™ 35 mg following 5 days of esomeprazole 40 mg therapy compared to enteric-coated ACTONATE™ 35 mg alone. During concomitant use of esomeprazole, bioavailability of enteric-coated ACTONATE™ 35 mg is reduced by 32% to 48% depending on the time of esomeprazole administration (prior to the evening meal or prior to breakfast, respectively).
In the Phase 3 study evaluating enteric-coated ACTONATE™ 35 mg, efficacy as measured by mean percent change in BMD from baseline was not diminished in patients reporting concomitant use of H2 blockers or Proton Pump Inhibitors (PPIs).

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 (immediate-release tablets)
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™ EC Once-a-Week dosing

The safety of ACTONATE™ EC for the treatment of postmenopausal osteoporosis was assessed in a double-blind, multicentre study comparing ACTONATE™ 5 mg immediate-release daily (N = 307) and enteric-coated ACTONATE™ 35 mg once weekly administered either at least 30 minutes before (N = 308) or immediately following (N = 307) breakfast in postmenopausal women 50 years of age or older. The duration of the trial was 2 years, with 307 patients exposed to ACTONATE™ 5 mg immediate-release daily and 615 exposed to enteric-coated ACTONATE™ 35 mg once-a-week. Patients with pre-existing gastrointestinal disease (with the exception of those with a positive occult faecal blood test or history of inflammatory bowel disease, malabsorption or sprue) and concomitant use of non-steroidal anti-inflammatory drugs, proton pump inhibitors, and H2 antagonists were included in this clinical trial. All women received daily supplementation with 1000 mg of elemental calcium plus 800-1000 IU vitamin D.

The overall safety and tolerability profiles were similar across the immediate-release and enteric-coated treatment groups. The incidence of all-cause mortality was 0.3% in the ACTONATE™ 5 mg immediate-release daily group and 0.2% in the combined enteric-coated ACTONATE™ 35 mg once-a-week group. The incidence of serious adverse events was 10.1% in the ACTONATE™ 5 mg daily group and 10.4% in the combined enteric-coated ACTONATE™ 35 mg once-a-week group. The percentage of patients who withdrew from the study due to adverse events was 9.1% in the ACTONATE™ 5 mg immediate-release daily group and 10.1% in the combined enteric-coated ACTONATE™ 35 mg once-a-week group. Table 5 lists adverse events reported in ≥2% of patients, combining before and after breakfast dosing of enteric-coated ACTONATE™ 35 mg once-a-week. Adverse events are shown without attribution of causality.

Table 5
Most Common (>=2% in Any Treatment Group) Treatment-emergent Adverse Events by MedDRA SOC and PT
(Intent-to-treat)

	5 mg IRBB Daily (N=307)			35 mg ECFB Weekly (N=307)			35 mg ECBB Weekly (N=308)		
System Organ Class / Preferred Term	n	(%)	nAE	n	(%)	nAE	n	(%)	nAE
OVERALL	243	(79.2%)	1025	250	(81.4%)	1138	264	(85.7%)	1219
Infections and infestations	119	(38.8%)	193	135	(44.0%)	247	133	(43.2%)	241
Nasopharyngitis	24	(7.8%)	29	32	(10.4%)	38	38	(12.3%)	48
Influenza	23	(7.5%)	28	27	(8.8%)	33	25	(8.1%)	29
Urinary tract infection	20	(6.5%)	21	21	(6.8%)	27	22	(7.1%)	29
Bronchitis	20	(6.5%)	26	17	(5.5%)	25	21	(6.8%)	24
Upper respiratory tract infection	9	(2.9%)	9	13	(4.2%)	13	12	(3.9%)	17
Pharyngitis	7	(2.3%)	7	11	(3.6%)	12	12	(3.9%)	16
Cystitis	12	(3.9%)	13	9	(2.9%)	12	6	(1.9%)	6
Gastroenteritis	7	(2.3%)	7	9	(2.9%)	9	10	(3.2%)	10
Herpes zoster	3	(1.0%)	3	8	(2.6%)	8	3	(1.0%)	3
Sinusitis	8	(2.6%)	8	4	(1.3%)	6	3	(1.0%)	3
Gastrointestinal disorders	107	(34.9%)	193	119	(38.8%)	235	125	(40.6%)	270
Diarrhoea	19	(6.2%)	25	30	(9.8%)	32	21	(6.8%)	24
Abdominal pain	10	(3.3%)	11	19	(6.2%)	21	20	(6.5%)	23
Dyspepsia	16	(5.2%)	19	18	(5.9%)	24	12	(3.9%)	15
Constipation	11	(3.6%)	13	17	(5.5%)	17	17	(5.5%)	17
Vomiting	10	(3.3%)	10	15	(4.9%)	18	8	(2.6%)	12
Nausea	15	(4.9%)	17	12	(3.9%)	15	14	(4.5%)	16
Abdominal pain upper	8	(2.6%)	9	11	(3.6%)	15	26	(8.4%)	37
Haemorrhoids	4	(1.3%)	4	7	(2.3%)	7	4	(1.3%)	4
Gastrooesophageal reflux disease	9	(2.9%)	9	3	(1.0%)	3	11	(3.6%)	12
Hiatus hernia	4	(1.3%)	5	3	(1.0%)	3	10	(3.2%)	10
Musculoskeletal and connective tissue disorders	95	(30.9%)	157	103	(33.6%)	179	114	(37.0%)	174
Arthralgia	33	(10.7%)	38	29	(9.4%)	39	27	(8.8%)	33
Back pain	27	(8.8%)	31	29	(9.4%)	36	29	(9.4%)	31
Pain in extremity	13	(4.2%)	14	17	(5.5%)	18	14	(4.5%)	16
Musculoskeletal pain	13	(4.2%)	13	13	(4.2%)	14	11	(3.6%)	12
Osteoarthritis	10	(3.3%)	10	8	(2.6%)	8	5	(1.6%)	5
Tendonitis	6	(2.0%)	6	8	(2.6%)	8	3	(1.0%)	6
Muscle spasms	9	(2.9%)	9	5	(1.6%)	5	12	(3.9%)	16
Neck pain	6	(2.0%)	6	5	(1.6%)	5	8	(2.6%)	8
Injury, poisoning and procedural complications	50	(16.3%)	81	46	(15.0%)	68	46	(14.9%)	72
Fall	16	(5.2%)	18	18	(5.9%)	20	11	(3.6%)	11
Contusion	14	(4.6%)	15	11	(3.6%)	12	8	(2.6%)	12
Nervous system disorders	51	(16.6%)	76	42	(13.7%)	54	45	(14.6%)	49
Dizziness	10	(3.3%)	10	10	(3.3%)	10	11	(3.6%)	12
Headache	18	(5.9%)	18	9	(2.9%)	9	14	(4.5%)	14
Sciatica	7	(2.3%)	7	5	(1.6%)	6	2	(0.6%)	2
Vascular disorders	24	(7.8%)	30	32	(10.4%)	32	33	(10.7%)	39
Hypertension	20	(6.5%)	23	20	(6.5%)	20	21	(6.8%)	22
Skin and subcutaneous tissue disorders	19	(6.2%)	24	29	(9.4%)	36	33	(10.7%)	38
Dermatitis allergic	4	(1.3%)	4	5	(1.6%)	6	7	(2.3%)	7
General disorders and administration site conditions	27	(8.8%)	30	28	(9.1%)	41	41	(13.3%)	54
Fatigue	4	(1.3%)	4	7	(2.3%)	8	1	(0.3%)	1
Investigations	19	(6.2%)	28	26	(8.5%)	30	28	(9.1%)	33
Blood parathyroid hormone increased	3	(1.0%)	3	2	(0.7%)	3	7	(2.3%)	8
Cardiac disorders	20	(6.5%)	23	24	(7.8%)	35	31	(10.1%)	43
Respiratory, thoracic and mediastinal disorders	26	(8.5%)	35	23	(7.5%)	31	24	(7.8%)	28
Cough	10	(3.3%)	11	9	(2.9%)	9	6	(1.9%)	6

Metabolism and nutrition disorders	17 (5.5%) 18	21 (6.8%) 34	21 (6.8%) 22
Hypercholesterolaemia	6 (2.0%) 6	13 (4.2%) 13	9 (2.9%) 9
Blood and lymphatic system disorders	7 (2.3%) 7	15 (4.9%) 15	9 (2.9%) 9
Anaemia	3 (1.0%) 3	8 (2.6%) 8	3 (1.0%) 3
Psychiatric disorders	12 (3.9%) 14	15 (4.9%) 16	20 (6.5%) 25
Depression	5 (1.6%) 5	6 (2.0%) 6	7 (2.3%) 7
Eye disorders	22 (7.2%) 27	14 (4.6%) 17	16 (5.2%) 20
Cataract	7 (2.3%) 7	4 (1.3%) 6	6 (1.9%) 7
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	11 (3.6%) 11	13 (4.2%) 13	12 (3.9%) 13
Renal and urinary disorders	15 (4.9%) 17	13 (4.2%) 15	19 (6.2%) 25
Ear and labyrinth disorders	18 (5.9%) 21	11 (3.6%) 11	7 (2.3%) 8
Vertigo	7 (2.3%) 10	7 (2.3%) 7	3 (1.0%) 3
Endocrine disorders	12 (3.9%) 14	7 (2.3%) 7	13 (4.2%) 16
Reproductive system and breast disorders	13 (4.2%) 14	6 (2.0%) 8	9 (2.9%) 13
Hepatobiliary disorders	4 (1.3%) 4	5 (1.6%) 10	11 (3.6%) 12
Immune system disorders	6 (2.0%) 7	3 (1.0%) 3	10 (3.2%) 11

Treatment: IRBB = 5 mg/day risedronate immediate-release before breakfast, ECFB = 35 mg/week risedronate delayed-release following breakfast, ECBB = 35 mg/week risedronate delayed-release before breakfast.
N = number of patients within specified treatment.
n(%) = number (percent) of patients within specified category and treatment.
nAE = number of adverse events within the specified category and treatment.

Acute Phase Reactions: Symptoms consistent with acute phase reaction have been reported with bisphosphonate use. The overall incidence of symptoms consistent with acute phase reaction was 1.3% in the ACTONATE™ 5 mg immediate-release daily group, and 1.8% in the combined enteric-coated ACTONATE™ 35 mg once-a-week group. These incidence rates are based on reporting of one or more pre-specified acute phase reaction-like symptoms within 3 days of the first dose and for a duration of 7 days or less. Fever or influenza-like illness with onset within the same period were reported by 0.0% of patients on ACTONATE™ 5 mg immediate-release daily and 0.0% of patients on enteric-coated ACTONATE™ 35 mg once-a-week.

Gastrointestinal Adverse Events: The incidence of gastrointestinal adverse events in the ACTONATE™ 5 mg immediate-release daily group compared with the combined enteric-coated ACTONATE™ 35 mg once weekly group were: dyspepsia (5.2% vs. 4.9%), diarrhoea (6.2% vs. 8.3%), constipation (3.6% vs. 5.5%), abdominal pain (3.3% vs. 6.3%), abdominal pain upper (2.6% vs. 6.0%), gastro-oesophageal reflux disease (2.9% vs. 2.3%).

Musculoskeletal Adverse Events: The incidence of musculoskeletal adverse events in the ACTONATE™ 5 mg immediate-release daily group compared with the combined enteric-coated ACTONATE™ 35 mg once weekly group were: arthralgia (10.7% vs. 9.1%), back pain (8.8% vs. 9.4%), musculoskeletal pain (4.2% vs 3.9%).

Treatment discontinuations: The overall incidence of patients discontinuing treatment due to a treatment emergent adverse event was similar across all groups (9.1% vs 10.1% for the immediate release and combined enteric coated groups, respectively). Study discontinuations in the ACTONATE™ 5 mg immediate-release daily group compared with the combined enteric-coated ACTONATE™ 35 mg once-a-week group included: diarrhoea (0.7% vs. 0.7%),abdominal pain (0.7% vs. 1.3%), abdominal pain upper (0.0% vs. 1.1%), abdominal pain lower (1% vs 0.0%), gastro-oesophageal reflux disease (0.7% vs. 0.2%), myalgia (0.3% vs 0.3%), arthralgia (0.0% vs 0.5%).

Laboratory Test Findings: The mean values for serum calcium, phosphorus, and magnesium were within the normal range at all-time points and similar across treatment groups. The mean changes from baseline at each post-baseline time point were small for each parameter, with no clinically important differences across treatment groups.

The mean values for serum iPTH 1-84 were within the normal range at all-time points and similar across treatment groups. Mean changes from baseline at each post-baseline time point were small and most prominent at Day 14.

In all treatment groups, small mean decreases in serum calcium and the expected reciprocal small mean increases in iPTH 1-84 were seen at Day 14; these changes were as would be expected upon initiation of antiresorptive therapy, and were not symptomatic or clinically meaningful. At week 104, the number of patients shifting from normal to high iPTH 1-84 was similar across the 3 groups.

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™ EC
ACTONATE™ EC should be taken in the morning, either with or without food. To facilitate delivery to the stomach, and thus reduce the potential for oesophageal irritation, enteric-coated ACTONATE™ 35 mg once-a-week should be swallowed whole while the patient is in an upright position with plain water. Patients should not chew, cut or crush the tablet because of a potential for oropharyngeal irritation, and because the tablet coating is an important part of the formulation. Patients should avoid lying down for 30 minutes after taking the medication.

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

ACTONATE™ EC Combi (with enteric-coated ACTONATE™ 35 mg):
ACTONATE™ EC Combi is a two component therapy consisting of 7 tablets in a blister, 1 ACTONATE™ 35 mg enteric-coated tablet (yellow tablet) and 6 Calcium Carbonate 1250 mg (equivalent to elemental calcium 500 mg) film-coated tablets (blue tablets). ACTONATE™ EC 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 enteric-coated 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 enteric-coated ACTONATE™ 35 mg tablet EC 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 enteric-coated 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™ EC dose is missed, the enteric-coated ACTONATE™ 35 mg 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 enteric-coated ACTONATE™ 35 mg tablet (yellow tablet) on their originally chosen day of the week.

ACTONATE™ EC Combi D (with enteric-coated ACTONATE™ 35 mg):
A weekly unit of ACTONATE™ EC Combi D consists of 1 ACTONATE™ 35 mg enteric-coated tablet and 6 calcium carbonate/cholecalciferol sachets in a box. ACTONATE™ EC 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 enteric-coated 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 enteric-coated 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 enteric-coated 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 enteric-coated ACTONATE™ 35 mg 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). Enteric-coated ACTONATE™ 35 mg once-a-week 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 enteric-coated ACTONATE™ 35 mg once-a-week has not been established in patients under 18 years of age.

Compatibility with other Drugs:

Calcium supplements and antacids 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 risedronate. 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 risedronate may be helpful for ACTONATE™ immediate-release tablets and reduce absorption of the drug. The impact of this intervention for ACTONATE™ EC tablets has not been evaluated. The enteric-coated ACTONATE™ formulation is less sensitive to the binding effects of divalent cations. 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™ EC
ACTONATE™ EC Once-a-Week tablets are packaged in a clear PVC/aluminium foil blister strip contained in a carton. Pack sizes are 1, 2, 4, 10, 12 or 16 tablets. ACTONATE™ EC tablets are oval, yellow enteric-coated tablets engraved with EC 35 on one side. Store below 30°C.

ACTONATE™ EC Combi (with enteric-coated ACTONATE™ 35 mg)
ACTONATE™ EC Combi is packaged in ACLAR/PVC aluminium foil blister contained in a carton. Pack sizes are 7, 14, 28, 84 and 112 tablets. ACTONATE™ EC are oval, yellow enteric-coated tablets with EC 35 engraved on one side. The calcium carbonate tablets in ACTONATE™ EC Combi are capsule-shaped, blue, film-coated tablet with NE 2 on both sides. Store below 25°C.

ACTONATE™ EC Combi D (with enteric-coated ACTONATE™ 35 mg)
ACTONATE™ EC tablets contained within ACTONATE™ EC 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™ EC tablets are oval, yellow tablets with EC 35 engraved on one side. The calcium carbonate/cholecalciferol sachet contains white free-flowing granules. These components are contained in a carton which is available in 1, 2, 3 and 4 weeks of therapy. Store below 25°C.

NAME AND ADDRESS OF THE SPONSOR

Actavis Pty Ltd
Level 5, 117 Harrington Street
The Rocks, NSW, 2000

POISON SCHEDULE OF THE MEDICINE

Schedule 4

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS

10 March 2011

DATE OF MOST RECENT AMENDMENT

11 May 2016

AUST R 166991 ACTONATE™ EC Combi D
AUST R 166939 ACTONATE™ EC Combi
AUST R 166840 ACTONATE™ EC