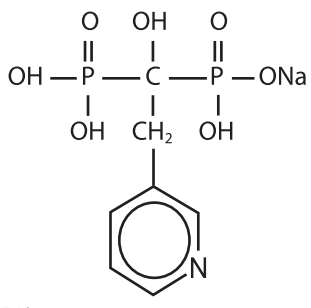
Actonel Once-a-Week 35mg

(Risedronate sodium)
film-coated tablets

NAME OF THE DRUG

Actonel is risedronate sodium.
Each Actonel tablet contains the equivalent of 35mg 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.
The chemical structure of risedronate sodium is the following:



Molecular Weight: 305.10

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.
Each Actonel (Once-a-Week 35mg) tablet contains risedronate sodium, lactose, crospovidone, magnesium stearate, microcrystalline cellulose, hydroxypropyl cellulose, hypromellose, macrogol 400, macrogol 8000, colloidal anhydrous silica, iron oxide yellow E172, iron oxide red E172 and titanium oxide E171.

PHARMACOLOGY

Actonel is a potent pyridinyl bisphosphonate that binds to bone hydroxyapatite and inhibits osteoclast-mediated bone resorption. Actonel is a third generation bisphosphonate.

In preclinical studies Actonel demonstrated potent anti-osteoclast and anti-resorptive activity, increasing bone mass and biomechanical strength dose-dependently. The activity of Actonel was confirmed by bone marker measurements during pharmacodynamic and clinical studies.

With Actonel 5mg 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 Actonel 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 Actonel Once-a-Week 35mg and Actonel 5mg daily.

Comparison of 5mg daily dose and 35mg once-a-week dose
Based on a lumbar spine BMD (bone mineral density), Actonel Once-a-Week 35mg (n=485) was shown to be therapeutically equivalent to Actonel 5mg 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.

35mg Once-a-Week Dose
Actonel Once-a-Week 35mg (n=485) was shown to be therapeutically non-inferior to Actonel 5mg daily (n=480) in a 2-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 5mg group (n=391) and 3.9% (3.6,4.3; 95% CI) in the 35mg group (n= 387) and the mean difference between 5mg daily and 35mg Once-a-Week 0.1% (-0.42, 0.55; 95% CI) (see Table 1). The weekly regimen was non inferior to the daily regimen at Month 12, the primary analysis. The month 6 and 24 analyses were consistent with the primary analysis. 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.

Table 1: Study HMR 4003E/3001 Bone Mineral Density by Visit-Mean Percent Change from Baseline (intent-to-treat Population)

Analysis Visit	5mg Daily Risedronate		35mg Weekly Risedronate		Mean Difference (95% CI)
	N	Mean	N	Mean	5mg Daily vs. 35mg Weekly
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
Month 24	364	5.17[a]	357	4.74[a]	0.43[b] (-∞; 0.92) p= 0.044

[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 24 (5mg daily:
3.3%; 35mg Once-a-Week: 1.4%). 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.

Treatment of Osteoporosis in Men
Risedronate sodium 35mg 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.

Increases in BMD were observed as early as 6 months following initiation of risedronate sodium treatment. Risedronate sodium 35mg 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. Antifracture efficacy was not demonstrated in this study.

The bone effect (BMD increase and BTM (bone turnover markers) decrease) of risedronate sodium is similar in males and females.

PHARMACOKINETICS

Absorption: Actonel is relatively rapidly absorbed (tmax=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 5mg daily and up to 50 mg dosed weekly). In a 13-week pharmacokinetic study with 5mg daily and 35mg weekly and 50mg weekly dosing (N~19/group), a comparison of the average serum concentration (Cavg) for 35mg/week and 5mg/day was not statistically significantly different. The 95% confidence interval for Cavg was 57.1-101.2, with a point estimate of 76.0% for the 35mg dose compared to the 5mg 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 Actonel is administered with food. Bioavailability was similar in men and women. Although administration of Actonel either 30 minutes prior to breakfast or 2 hours after dinner reduces absorption of risedronate by 55% compared to administration in the fasting state (ie., 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%, Actonel 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 [14C] 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. This is likely to be considerably lower in humans who excrete 65% of an intravenously administered dose in the urine in 24 hours. The remainder of the dose was mainly excreted in the urine. 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 Actonel.

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 35mg versus 5mg doses was 66.8% (95%CI, 48.0-95.8). Although this was statistically 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 halflife 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 Actonel from the surface of the bone.

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

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

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

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

Hepatic Insufficiency: No studies have been performed to assess the safety or efficacy of Actonel 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.

INDICATIONS

- Treatment of postmenopausal osteoporosis, to reduce the risk of vertebral fractures. Treatment of established postmenopausal osteoporosis, to reduce the risk of hip fractures.
- Prevention of osteoporosis in postmenopausal women with increased risk of osteoporosis.
- To maintain or increase bone mass in postmenopausal women undergoing long-term (more than 3 months), systemic corticosteroid treatment at doses > 7.5mg/day prednisone or equivalent.
- Treatment to increase bone mass in men with osteoporosis.

The optimal duration of use of bisphosphates for the treatment of osteoporosis has not been determined. All patients on bisphosphonate therapy should have the need for continued therapy re-evaluated on a periodic basis.

CONTRAINDICATIONS

- Known hypersensitivity to the drug or any of the ingredients.
- Hypocalcaemia (see Precautions)
- Inability to stand or sit upright for at least 30 minutes.
- Pregnancy & lactation
- Severe renal impairment (creatinine clearance <30ml/min)

PRECAUTIONS

Food, certain medication and beverages (except plain water) can interfere with the absorption of Actonel. Therefore, for patients to gain maximum benefit from Actonel, doctors must stress the importance of taking Actonel 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 Actonel therapy.

Bone and mineral metabolism dysfunction (eg. vitamin D deficiency and parathyroid abnormalities) should be effectively treated before starting Actonel therapy.

Patients should receive supplemental calcium and vitamin D if dietary intake is inadequate.

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

Actonel like other bisphosphonates may cause local irritation of the upper GI mucosa. 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 non-steroidal anti- inflammatory drugs (NSAIDs) or aspirin concomitantly.

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

Interactions with other Drugs
No specific drug interactions studies have been performed. However Actonel 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 (eg. calcium, magnesium, iron, aluminium, antacids) will interfere with the absorption of Actonel and should be taken at a different time of the day.

Actonel 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 Actonel. No clinically relevant interactions were noted. The medications included NSAIDs, aspirin, H2 blocker, proton pump inhibitors, antacids, calcium channel blockers, beta-blocker, 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 5mg daily dosing, 29% and 37% of patients used aspirin and NSAIDs respectively. The incidence of upper GI adverse events in Actonel patients (aspirin/NSAIDs taken ≥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.

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

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

Use in Pregnancy
Actonel has not been studied in pregnant women. Actonel 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 periparturientmaternal 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 2mg/kg/day. These effects were probably secondary to maternal hypocalcaemia. Systemic exposure (AUC 0-24h) 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.

Use in Lactation
Risedronate was detected in feeding pups exposed to lactating rats for a 24-hour period postdosing, 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 3.2mg/kg/day. This is equivalent to the human 30mg 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 3.2mg/kg/day has resulted in periparturient hypocalcaemia and mortality in rats allowed to deliver.

Carcinogenicity, Mutagenicity and Impairment of Fertility
No evidence of carcinogenicity was observed in either rats (treated for 104 weeks with up to 24mg/kg/day) or mice (treated for 80 weeks with up to 32mg/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.

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 1336mg/kg in an *in vitro* assay (chromosomal aberrations in rat bone marrow).

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.

Osteomalacia
The potential for Actonel 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. Actonel 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 Actonel administered at therapeutic doses is unlikely to induce osteomalacia.

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 bisphophonates. 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.

Atypical Subtrochanteric and Diaphyseal Femoral Fractures
Atypical, low-energy, or low trauma fractures of the femoral shaft have been reported in bisphosphonate-treated patients. These fractures can occur anywhere in the femoral shaft from just below the lesser trochanter to above the supracondylar flare and are transverse or short oblique in orientation without evidence of comminution. Causality has not been established as these fractures also occur in osteoporotic patients who have not been treated with bisphosphonates.
Atypical femur fractures most commonly occur with minimal or no impact to the affected area. They may be bilateral and many patients report prodromal pain in the affected area, usually presenting as dull, aching thigh pain, weeks to months before a complete fracture occurs. A number of reports note that patients were also receiving treatment with glucocorticoids (e.g. prednisone) at the time of fracture.

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

ADVERSE REACTIONS

The majority of the undesirable effects in clinical studies were mild to moderate and usually did not require cessation of therapy. The most common adverse reactions are pain in the bones, muscles and joints, dyspepsia, nausea, headache and abdominal pain. In a small number of patients, the following uncommon adverse reactions have been reported: gastritis, duodenitis, glossitis, dysphagia. Iritis was uncommonly

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4129243

Actavis
Actavis Dupnitsa

supplier:
Actavis Bulgaria Dupnitsa

dimensions: 190x600
pharmacode: 126778

colours/plates:
1. Black
2.
3.
4.

Non Printing Colours
1. Magenta
2.

approved for print
name/date

SUPPLIER INFORMATION TABLE

№	Parameter	PIL
1	Paper weight g/m^2	45
2	Pack line type	C80
3	Old AW ID	AAAK0351
4	New AW ID	AAAA09813
5	Old item code	4128775
6	New item code	4129243
7	Pharmcode	126778
8	Note	

reported in clinical trials. Early, transient, asymptomatic and mild decreases in serum calcium and phosphate levels have been observed in some patients. Rarely abnormal liver function tests have been reported. Very rare hypersensitivity and skin reactions, including angioedema, generalized rash, and bullous skin reactions, some severe, osteonecrosis of the jaw, uveitis and iritis have been reported.

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 – 35mg once-a-week dosing
In a one-year, double-blind, multicentre study comparing Actonel 5mg daily and Actonel Once a Week 35mg in postmenopausal women with osteoporosis, the overall safety and tolerability profiles were similar. Table 2 lists the adverse events in ≥5% of patients from this trial. Events are shown without attribution of causality.

Table 2: Adverse Events Occurring in ≥5% of Patients of Either Treatment Group In the Daily vs Weekly Osteoporosis Treatment Study in Postmenopausal Women

Body System	5mg Daily Actonel % (N = 480)	35mg Weekly Actonel % (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
Diarrhea	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
Urogenital System		
Urinary Tract Infection	2.9	5.2

DOSAGE AND ADMINISTRATION
Actonel must only be taken with plain water.

Actonel must be taken 30 minutes before the first food or drink other than water.

To facilitate delivery to the stomach, Actonel 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: The recommended dose is 35mg once a week, taken on the same day each week. Patients should be instructed that if they miss a dose of ACTONEL 35mg Once-A-Week, they should take 1 tablet on the morning after they remember and return to taking 1 tablet once a week, as originally scheduled on their chosen day. Patient should not take 2 tablets on the same day.

Use in the elderly: No dose adjustment is necessary.

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

Children: Safety and efficacy of Actonel has not been established in patients under 18 years of age.

Men: No dose adjustment is necessary.

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

OVERDOSAGE
No specific information is available on the treatment of overdose with Actonel.

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 Actonel 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.

PRESENTATION
The 35mg Once-a-Week tablets are packaged in a clear PVC/aluminium foil blister strip contained in a carton.

35mg Once-a-Week tablets: oval, light orange film-coated tablets with RSN on one side and 35mg on the other.

Manufacturer:
Balkanpharma-Dupnitsa AD,
3 Samokovsko Shosse Str.
2600 Dupnitsa, Bulgaria

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References: HPRG(PVB) 36:57/02-135

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