

# PRODUCT MONOGRAPH

## Pr **ACTONEL PLUS CALCIUM**

Risedronate Sodium (as the hemi-pentahydrate) 35 mg Tablets

USP

Bone Metabolism Regulator

and

Calcium Carbonate 1250 mg Tablets

USP

Mineral Supplement



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## ACTONEL PLUS CALCIUM

Risedronate Sodium (as the hemi-pentahydrate) 35 mg tablets and  
Calcium Carbonate 1250 mg tablets

### PART I: HEALTH PROFESSIONAL INFORMATION

#### SUMMARY PRODUCT INFORMATION

Route of Administration	Component of Combination Pack	Dosage Form/ Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	ACTONEL Once-a-Week (risedronate sodium)	Tablet, 35 mg	Lactose monohydrate <i>For a complete listing see Dosage Forms, Composition and Packaging Section.</i>
Oral	Calcium carbonate	Tablet, 1250 mg; elemental calcium 500 mg	<i>For a complete listing see Dosage Forms, Composition and Packaging Section.</i>

#### INDICATIONS AND CLINICAL USE

The ACTONEL (risedronate sodium) component of ACTONEL PLUS CALCIUM is indicated for the treatment and prevention of osteoporosis in postmenopausal women

**Treatment of Postmenopausal Osteoporosis:** In postmenopausal women with osteoporosis, ACTONEL prevents vertebral and nonvertebral osteoporosis-related fractures and increases bone mineral density (BMD) at all measured skeletal sites of clinical importance for osteoporotic fractures, including spine, hip, and wrist.

Osteoporosis may be confirmed by the presence or history of osteoporotic fracture, or by the finding of low bone mass (for example, at least 2 SD below the premenopausal mean).

**Prevention of Postmenopausal Osteoporosis:** In postmenopausal patients at risk of developing osteoporosis, ACTONEL preserves or increases BMD at sites of clinical importance for osteoporosis.

ACTONEL may be considered in postmenopausal women who are at risk of developing osteoporosis and for whom the desired clinical outcome is to maintain bone mass and to reduce the risk of fracture.

Factors such as family history of osteoporosis (particularly maternal history), previous fracture, smoking, moderately low BMD, high bone turnover, thin body frame, Caucasian or Asian race,

and early menopause are associated with an increased risk of developing osteoporosis and fractures.

The calcium component of ACTONEL PLUS CALCIUM contains calcium carbonate which is a calcium supplement to dietary intake of calcium.

The optimal duration of use has not been determined. Patients should have the need for continued therapy re-evaluated on a periodic basis.

**Geriatrics:** Of the patients receiving ACTONEL (risedronate) 5 mg daily in postmenopausal osteoporosis studies (see CLINICAL TRIALS), 43% were between 65 and 75 years of age, and 20% were over 75. In the 1-year study comparing daily versus weekly oral dosing regimens of ACTONEL in postmenopausal women, 41% of patients receiving ACTONEL 35 mg Once-a-Week were between 65 and 75 years of age and 23% were over 75.

Based upon the above study populations, no overall differences in efficacy or safety were observed between these patients and younger patients (< 65 years).

**Pediatrics:** Safety and efficacy of risedronate in children and growing adolescents have not been established.

**Important Limitations of Use:** The optimal duration of use has not been determined. Patients should have the need for continued therapy re-evaluated on a periodic basis (see DOSAGE AND ADMINISTRATION).

## CONTRAINDICATIONS

- Patients who are hypersensitive to ACTONEL PLUS CALCIUM or to any ingredients in the formulation. For a complete listing, see DOSAGE FORMS, COMPOSITION AND PACKAGING.

### ACTONEL

- Hypocalcemia (see WARNINGS AND PRECAUTIONS, General)

### Calcium

- Hypercalcemia from any cause including, but not limited to, hyperparathyroidism, hypercalcemia of malignancy, or sarcoidosis.

## WARNINGS AND PRECAUTIONS

### General

Before commencing ACTONEL PLUS CALCIUM, patients' calcium requirements should be assessed. It is recommended that patients receive at least 1200-1500 mg per day of calcium from all sources, as well as a daily vitamin D intake of at least 400-800 IU. The calcium carbonate

tablet in ACTONEL PLUS CALCIUM provides 500 mg elemental calcium per day and does not contain vitamin D.

Hypocalcemia and other disturbances of bone and mineral metabolism should be effectively treated before starting ACTONEL PLUS CALCIUM combination pack therapy.

### **Osteonecrosis of the Jaw**

In post-marketing reporting, osteonecrosis of the jaw has been reported in patients treated with bisphosphonates. The majority of reports occurred following dental procedures such as tooth extractions; and have involved cancer patients treated with intravenous bisphosphonates, but some occurred in patients receiving oral treatment for postmenopausal osteoporosis and other diagnoses. Many had signs of local infection, including osteomyelitis. Osteonecrosis has other well documented multiple risk factors. It is not possible to determine if these events are related to bisphosphonates, to concomitant drugs or other therapies, to the patient's underlying disease or to other co-morbid risk factors (e.g. anemia, infection, pre-existing oral disease). A dental examination with appropriate preventative dentistry should be considered prior to treatment with bisphosphonates in patients with concomitant risk factors (e.g. cancer, immune suppression, head and neck radiotherapy or poor oral hygiene). While on treatment, these patients should avoid invasive dental procedures if possible. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment prior to the procedure reduces the risk of osteonecrosis of the jaw. Clinical judgment, based on individual risk assessment, should guide the management of patients undergoing dental procedures.

### **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.

Atypical femur fractures most commonly occur with minimal or no impact trauma to the affected area. They may be bilateral and many patients report prodromal pain in the affected area, usually presenting as dull, aching thigh pain, weeks to months before a complete fracture occurs. Poor healing of these fractures was also reported.

Any patient with a history of bisphosphonate exposure who presents with thigh or groin pain should be suspected of having an atypical fracture and should be evaluated to rule out an incomplete femur fracture. Patients presenting with an atypical fracture should also be assessed for symptoms and signs of fracture in the contra-lateral limb. Interruption of bisphosphonate therapy should be considered, pending a risk/benefit assessment. Although causality has not been established, the role of bisphosphonates cannot be ruled out

Concomitant use of calcium-containing antacids should be monitored to avoid excessive intake of calcium. Total daily intake of calcium above 1500 mg has not demonstrated additional bone benefits, however daily intake above 2000 mg has been associated with increased risk of adverse effects, including hypercalcemia and kidney stones.

### **Gastrointestinal**

Bisphosphonates may cause upper gastrointestinal disorders such as dysphagia, esophagitis, esophageal ulcer, and gastric ulcer (see ADVERSE REACTIONS). Since some bisphosphonates have been associated with esophagitis and esophageal ulcerations, to facilitate delivery to the stomach and minimize the risk of these events, patients should take the ACTONEL tablet while in an upright position (i.e., sitting or standing) and with sufficient plain water ( $\geq 120$  mL). Patients should not lie down for at least 30 minutes after taking the drug. Health professionals should be particularly careful to emphasize the importance of the dosing instructions to patients with a history of esophageal disorders (e.g., inflammation, stricture, ulcer, or disorders of motility).

Patients with achlorhydria may have decreased absorption of calcium that may be attenuated by taking calcium with food. Taking calcium with food enhances absorption. See DOSAGE AND ADMINISTRATION.

**Musculoskeletal:** In postmarketing experience, severe and occasionally incapacitating bone, joint, and/or muscle pain has been reported in patients taking bisphosphonates (see ADVERSE REACTIONS). The time to onset of symptoms varied from one day to several months after starting the drug. Most patients had relief of symptoms after stopping the medication. A subset of patients had recurrence of symptoms when rechallenged with the same drug or another bisphosphonate. Consider discontinuing use if severe symptoms develop.

### **Ophthalmologic:**

Ocular disturbances including conjunctivitis, uveitis, episcleritis, iritis, and scleritis have been reported with Actonel therapy. Patients with ocular events other than uncomplicated conjunctivitis should be referred to an ophthalmologist for evaluation. If ocular inflammatory symptoms are observed, treatment may have to be discontinued.

### **Renal**

The ACTONEL component of ACTONEL PLUS CALCIUM is not recommended for use in patients with severe renal impairment (creatinine clearance  $< 30$  mL/min).

Administration of calcium has been associated with a slight increase in the risk of kidney stones. In patients with a history of kidney stones or hypercalciuria, metabolic assessment to seek treatable causes of these conditions is warranted. If administration of calcium tablets should be needed in these patients, urinary calcium excretion and other appropriate testing should be monitored periodically.

### **Special Populations**

**Pediatrics:** The safety and efficacy of ACTONEL in children and growing adolescents have not been established.

**Pregnant Women:** ACTONEL PLUS CALCIUM is not intended for use during pregnancy. There are no studies of ACTONEL PLUS CALCIUM in pregnant women.

Calcium crosses the placenta, reaching higher levels in fetal blood than in maternal blood.

**Nursing Women:** ACTONEL PLUS CALCIUM is not intended for use with nursing mothers. It is not known whether risedronate is excreted in human milk. Risedronate was detected in feeding pups exposed to lactating rats for a 24-hour period post-dosing, indicating a small degree of lacteal transfer. Since many drugs are excreted in human milk and because of 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.

Calcium is excreted in breast milk.

## **ADVERSE REACTIONS**

### **Adverse Drug Reaction Overview**

Bisphosphonates may cause upper gastrointestinal disorders such as dysphagia, esophagitis, esophageal ulcer, and gastric ulcer. It is therefore important to follow the recommended dosing instructions (see DOSAGE AND ADMINISTRATION).

Musculoskeletal pain, rarely severe, has been reported as a common side effect in patients who received the ACTONEL component of ACTONEL PLUS CALCIUM.

In osteoporosis studies with ACTONEL, the most commonly reported adverse reactions were abdominal pain, dyspepsia and nausea.

Most adverse events (AEs) reported in the Phase III trials with ACTONEL were mild or moderate in severity and did not generally lead to discontinuation of ACTONEL.

Calcium carbonate may cause gastrointestinal adverse effects such as constipation, flatulence, nausea, abdominal pain, and bloating.

### **Clinical Trial Adverse Drug Reactions**

*Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and approximate rates of occurrence.*

**Treatment of Postmenopausal Osteoporosis:** ACTONEL 5 mg daily has been studied for up to 3 years in over 5000 women enrolled in Phase III 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 distribution of severe adverse events was similar across treatment groups. In addition, the overall incidence of AEs was found to be comparable amongst ACTONEL and placebo-treated patients.

Table 1 lists adverse events considered possibly or probably drug related, reported in  $\geq 1\%$  of ACTONEL 5 mg daily-treated patients, in Phase III postmenopausal osteoporosis trials.

Discontinuation of therapy due to serious clinical adverse events occurred in 5.5 % of ACTONEL 5 mg daily-treated patients and 6.0% of patients treated with placebo.

<b>Table 1</b>		
<b>Drug-Related* Adverse Events Reported in <math>\geq</math> 1% of ACTONEL 5 mg Daily-Treated Patients in Combined Phase III Postmenopausal Osteoporosis Trials</b>		
Adverse Event	ACTONEL 5 mg N = 1742 (%)	Placebo Control N = 1744 (%)
<b>Body as a Whole</b>		
Abdominal Pain	4.1	3.3
Headache	2.5	2.3
Asthenia	1.0	0.7
<b>Digestive System</b>		
Dyspepsia	5.2	4.8
Nausea	4.8	5.0
Constipation	3.7	3.6
Diarrhea	2.9	2.5
Flatulence	2.1	1.8
Gastritis	1.1	0.9
<b>Skin and Appendages</b>		
Rash	1.4	0.9
Pruritus	1.0	0.5
* Considered to be possibly or probably causally related by clinical study Investigators.		

**Once a Week Dosing:** In the 1-year, double-blind, multicentre study comparing ACTONEL 35 mg Once-a-Week (the same formulation as the risedronate in ACTONEL PLUS CALCIUM) to ACTONEL 5 mg daily for the treatment of osteoporosis in postmenopausal women, the overall safety and tolerability profiles of the 2 oral dosing regimens were similar.

Patients with active or a history of upper gastrointestinal disorders at baseline and those taking ASA, non-steroidal anti-inflammatory drugs (NSAIDs) or drugs traditionally used for the treatment of peptic ulcers were not specifically excluded from participating in the ACTONEL once-a-week dosing study. The proportion of patients who experienced an upper gastrointestinal adverse event and the pattern of those events were found to be similar between the ACTONEL 35 mg Once-a-Week and ACTONEL 5 mg daily-treated groups.

In the 1-year, double-blind, multicentre study comparing ACTONEL 35 mg Once-a-Week to placebo for the prevention of osteoporosis in postmenopausal women, the overall safety and tolerability profiles of the two groups were comparable with the exception of “arthralgia”. Specifically, 13.9% of patients taking ACTONEL 35 mg Once-a-Week experienced arthralgia compared to 7.8% of placebo patients. The overall safety profile observed in this study showed no substantive difference from that observed in the ACTONEL 5 mg daily versus ACTONEL 35 mg Once-a-Week treatment study.

**Endoscopic Findings:** ACTONEL 5 mg daily clinical studies enrolled over 5700 patients for the treatment and prevention of postmenopausal and glucocorticoid-induced osteoporosis, many with pre-existing gastrointestinal disease and concomitant use of NSAIDs or ASA. 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 ACTONEL; 75 placebo).

Across treatment groups, the percentage of patients with normal esophageal, gastric, and duodenal mucosa on endoscopy was similar (21% ACTONEL; 20% placebo). Positive findings on endoscopy were also generally comparable across treatment groups. There were a higher number of reports of mild duodenitis in the ACTONEL group; however, there were more duodenal ulcers in the placebo group. Clinically important findings (perforations, ulcers, or bleeding) among this symptomatic population were similar between groups (39% ACTONEL; 51% placebo).

In the 1-year study comparing ACTONEL 35 mg Once-a-Week to ACTONEL 5 mg daily in the treatment of postmenopausal osteoporosis, endoscopies performed during the study revealed no dose dependent pattern in the number of patients with positive endoscopic findings or in the anatomical location of abnormalities detected.

#### **Less Common Clinical Trial Adverse Drug Reactions**

The following adverse drug reactions were reported in  $\leq 1\%$  of patients who received ACTONEL for all indications.

Uncommon (0.1-1.0%): duodenitis, iritis

Rare ( $<0.1\%$ ): abnormal liver function tests, glossitis

#### **Abnormal Hematologic and Clinical Chemistry Findings**

Asymptomatic mild decreases in serum calcium and phosphorus levels have been observed in some patients (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics).

Rare cases of leukemia have been reported following therapy with bisphosphonates. Any causal relationship to either the treatment or to the patients' underlying disease has not been established.

#### **Post-Market Adverse Drug Reactions**

**ACTONEL:**

**Hypersensitivity and Skin Reactions:** Reported rarely, angioedema, generalized rash and bullous skin reactions, some severe.

**Musculoskeletal and Connective tissue:** Reported very rarely, low-energy femoral shaft fractures (see WARNINGS AND PRECAUTIONS)

**Osteonecrosis of the Jaw:** Osteonecrosis of the jaw has been reported rarely (see WARNINGS AND PRECAUTIONS).

**Ophthalmologic:** Reported rarely, conjunctivitis, episcleritis, iritis, scleritis and uveitis (see WARNINGS AND PRECAUTIONS).

## **DRUG INTERACTIONS**

### **Overview**

No specific drug-drug interaction studies were performed with ACTONEL. Animal studies have demonstrated that risedronate is highly concentrated in bone and is retained only minimally in soft tissue. No metabolites have been detected systemically or in bone. The binding of risedronate to plasma proteins in humans is low (24%), resulting in minimal potential for interference with the binding of other drugs. In an additional animal study, there was also no evidence of hepatic microsomal enzyme induction. In summary, ACTONEL is not systemically metabolized, does not induce cytochrome P<sub>450</sub> enzymes and has low protein binding.

ACTONEL PLUS CALCIUM is therefore not expected to interact with other drugs based on the effects of protein binding displacement, enzyme induction or metabolism of other drugs.

### **Drug-Drug Interactions**

Patients in the risedronate clinical trials were exposed to a wide variety of commonly used concomitant medications (including NSAIDs, H<sub>2</sub>-blockers, proton pump inhibitors, antacids, calcium channel blockers, beta-blockers, thiazides, glucocorticoids, anticoagulants, anticonvulsants, cardiac glycosides) without evidence of clinically relevant interactions.

The drugs listed in this table are based on either drug interaction case reports or studies, or predicted interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

**Table 2**  
**Established or Predicted Drug-Drug Interactions with ACTONEL**

<b>Drug</b>	<b>Reference</b>	<b>Effect</b>	<b>Clinical Comment</b>
Acetylsalicylic acid (ASA)	CT	Among ASA users, the incidence of upper gastrointestinal adverse events were similar between the ACTONEL-treated patients and placebo-treated patients.	Of over 5700 patients enrolled in the ACTONEL 5 mg daily Phase III osteoporosis studies, ASA use was reported by 31% of patients.
		Among ASA users, the incidence of upper gastrointestinal adverse experiences was found to be similar between the weekly- and daily-treated groups.	In the 1-year study comparing ACTONEL 35 mg Once-a-Week to ACTONEL 5 mg daily in postmenopausal women, ASA use was reported by 56% of patients in the ACTONEL 35 mg Once-a-Week and 5 mg daily groups.
Antacids/supplements which contain polyvalent cations (e.g., calcium, magnesium, aluminum and iron)	T	Interference with the absorption of ACTONEL.	Such medications should be administered at a different time of the day (see DOSAGE AND ADMINISTRATION).
Hormone replacement therapy	CT	No clinically significant effect.	If considered appropriate, ACTONEL may be used concomitantly with hormone replacement therapy.
H <sub>2</sub> -blockers and proton pump inhibitors (PPIs)	CT	Among H <sub>2</sub> -blockers and PPIs users, the incidence of upper gastrointestinal adverse events was similar between the ACTONEL-treated patients and placebo-treated patients.	Of over 5700 patients enrolled in the ACTONEL 5 mg daily Phase III osteoporosis studies, 21% used H <sub>2</sub> -blockers and/or PPIs.
		Among H <sub>2</sub> -blockers and PPIs users, the incidence of upper gastrointestinal adverse experiences was found to be similar between the weekly- and daily-treated groups.	In the 1-year study comparing ACTONEL Once-a-Week and daily dosing regimens in postmenopausal women, at least 9% of patients in the ACTONEL 35 mg Once-a-Week and 5 mg daily groups used H <sub>2</sub> -blockers and/or PPIs.
Non-steroidal anti-inflammatory drugs (NSAIDs)	CT	Among NSAIDs users, the incidence of upper gastrointestinal adverse events was similar between the ACTONEL-treated patients and placebo-treated patients.	Of over 5700 patients enrolled in the ACTONEL 5 mg daily Phase III osteoporosis studies, 48% used NSAIDs.
		Among NSAIDs users, the incidence of upper gastrointestinal adverse experiences was found to be similar between the weekly- and daily-treated groups.	In the 1-year study comparing ACTONEL 35 mg Once-a-Week to ACTONEL 5 mg daily in postmenopausal women, 41% of patients in the ACTONEL 35 mg Once-a-Week and 5 mg daily groups used NSAIDs.

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

**Table 3**  
**Established or Predicted Drug-Drug Interactions with Calcium**

<b>Drug</b>	<b>Reference</b>	<b>Effect</b>	<b>Clinical Comment</b>
Iron	T	Calcium may interfere with the absorption of iron.	Iron and calcium should be taken at different times of the day.
Bisphosphonates	T	Decreased absorption of the bisphosphonate may occur.	Such medications should be administered at a different time of the day (see DOSAGE AND ADMINISTRATION).
Tetracyclines	CT	Calcium carbonate may interfere with the absorption of concomitantly administered tetracycline preparations.	Tetracycline preparations should be administered at least two hours before or four to six hours after oral intake of calcium carbonate.
Digoxin	T	Hypercalcemia may increase the toxicity of cardiac glycosides.	Patients should be monitored with regard to electrocardiogram (ECG) and serum calcium levels.
Phenytoin	T	May form a nonabsorbable complex with calcium.	Administration times of these medications should be separated by at least 3 hours.
Thyroid hormones: Levothyroxine	CT	Concomitant intake of levothyroxine and calcium carbonate was found to reduce levothyroxine absorption and increase serum thyrotropin levels. Levothyroxine may adsorb to calcium carbonate in an acidic environment, which may block its absorption.	Levothyroxine should be administered on an empty stomach and calcium should be taken with food. Monitor serum TSH in patients taking calcium and adjust dose accordingly.
Fluoroquinolones (e.g. ciprofloxacin, moxifloxacin, ofloxacin)	CT	Concomitant administration of a fluoroquinolone and calcium may decrease the absorption of the fluoroquinolone.	Administration times of these medications should be separated by several hours.
H <sub>2</sub> -blockers (e.g. cimetidine, famotidine, ranitidine)	T	Concomitant intake can cause decreased absorption of calcium.	Calcium should be taken with food to maximize absorption.
Proton Pump Inhibitors (e.g. lansoprazole, omeprazole, rabeprazole sodium)	T	Concomitant intake can cause decreased absorption of calcium.	Calcium should be taken with food to maximize absorption.
Systemic Glucocorticoids	T	Calcium absorption may be reduced and excretion increased when calcium is taken concomitantly with systemic glucocorticoids.	Additional calcium supplementation may be considered in patients taking long-term systemic glucocorticoids.
Vitamin D (e.g. calcitriol, ergocalciferol, doxercalciferol)	CT	Absorption of calcium may be increased when given concomitantly with vitamin D analogues.	Ensure adequate Vitamin D intake through diet or supplements for optimal calcium absorption.
Thiazide Diuretics	C	Reduced urinary excretion of calcium has been reported during concomitant use of calcium carbonate and thiazide diuretics.	Serum calcium should be monitored during concomitant use with thiazide diuretics, particularly in hyperparathyroid patients.

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

### **Drug-Food Interactions**

Clinical benefits may be compromised by failure to take ACTONEL on an empty stomach. For dosing information see DOSAGE AND ADMINISTRATION.

### **Drug-Herb Interactions**

Interactions with herbs have not been studied.

### **Drug-Laboratory Interactions**

Bisphosphonates are known to interfere with the use of bone-imaging agents. Specific studies with ACTONEL have not been performed.

## **DOSAGE AND ADMINISTRATION**

### **Dosing Considerations**

- Food and medications containing polyvalent cations (e.g., calcium, magnesium, aluminum, and iron) can interfere with the absorption of ACTONEL. Therefore, food and other medications should be administered at a different time of the day (see Recommended Dose and Dosage Adjustment and DRUG INTERACTIONS, Drug-Drug Interactions).
- The ACTONEL tablet should be swallowed whole while the patient is in an upright position and with sufficient plain water ( $\geq 120$  mL) to facilitate delivery to the stomach. Patients should not lie down for at least 30 minutes after taking the medication (see WARNINGS AND PRECAUTIONS, General).
- Other calcium-containing medications (e.g., multivitamins, antacids) should be administered at a different time of the day to prevent an interaction with ACTONEL and to maximize ACTONEL absorption.
- It is recommended that patients receive at least 1200 -1500 mg calcium per day from all sources, as well as, a vitamin D intake of at least 400-800 IU. ACTONEL PLUS CALCIUM provides 500 mg calcium and does not contain any vitamin D.
- ACTONEL PLUS CALCIUM is appropriate for additional supplementation of 500 mg of calcium for 6 out of 7 days, in conjunction with dietary and multivitamin intake, in patients whose calcium intake is 700 - 1000 mg/day. In patients who have a low daily calcium intake (i.e. less than 700 -1000 mg/day) or who require vitamin D supplementation, it may be advisable to prescribe Actonel 35 mg and a higher dose of calcium and/or vitamin D.
- The optimal duration of bisphosphonate treatment for osteoporosis has not been established. The need for continued treatment should be re-evaluated periodically based on the benefits and potential risks of ACTONEL PLUS CALCIUM on an individual patient basis.

### **Recommended Dose and Dosage Adjustment**

The patient should be informed to pay particular attention to the dosing instructions as clinical benefits may be compromised by failure to take the drug according to instructions. Specifically, ACTONEL should be taken on an empty stomach at least 30 minutes before the first food or drink (other than plain water) and/or any other medication of the day. The ACTONEL tablet should be swallowed whole – do not chew.

The calcium tablet should be taken with food.

The recommended regimen is one 35 mg risedronate tablet, taken orally once a week (Day 1 of the 7-day treatment cycle) followed by one 1250 mg calcium carbonate (500 mg elemental calcium) tablet, taken orally daily on each of the remaining six days (Days 2 through 7) of the 7-day treatment cycle.

**Renal Impairment:** No dosage adjustment is necessary in patients with a creatinine clearance  $\geq$  30 mL/min or in the elderly. Not recommended for use in patients with severe renal impairment (creatinine clearance  $<$  30 mL/min).

**Geriatrics:** No dosage adjustment is necessary in elderly patients (see INDICATIONS AND CLINICAL USE, Geriatrics).

**Achlorhydria:** Absorption of calcium from calcium carbonate is poor in patients with achlorhydria unless taken with food.

### **Missed Dose**

In case the ACTONEL tablet dose is missed, patients should be instructed that the ACTONEL tablet should be taken on the next day in the morning according to the dosing instructions. In this particular instance, patients should then take their calcium tablet on the following day. Patients should be instructed that the ACTONEL tablet and the calcium tablet should be taken on different days.

If the calcium tablet is missed, the patient should be instructed to take it as soon as she remembers. She should not take more than 1 tablet from the package on the same day. Any remaining calcium tablets at the end of the weekly cycle should be discarded.

### **OVERDOSAGE**

**ACTONEL:** Decreases in serum calcium following substantial overdose may be expected in some patients. Signs and symptoms of hypocalcemia may also occur in some of these patients.

Administration of milk or antacids containing calcium may be helpful to chelate ACTONEL and reduce absorption of the drug. In cases of substantial overdose, gastric lavage may be considered to remove unabsorbed drug if performed within 30 minutes of ingestion. Standard procedures that are effective for treating hypocalcemia, including the administration of calcium intravenously, would be expected to restore physiologic amounts of ionized calcium and to relieve signs and symptoms of hypocalcemia.

**Calcium:** Because of its limited intestinal absorption, overdosage with calcium carbonate is unlikely. However, prolonged use of very high doses can lead to hypercalcemia associated with milk alkali syndrome. Clinical manifestations of hypercalcemia may include anorexia, thirst, nausea, vomiting, constipation, abdominal pain, muscle weakness, fatigue, mental disturbances, polydipsia, polyuria, bone pain, nephrocalcinosis, renal calculi and in severe cases, cardiac arrhythmias.

**Treatment:** Calcium should be discontinued. Other therapies that may be contributing to the condition, such as thiazide diuretics, lithium, vitamin A, vitamin D and cardiac glycosides should also be discontinued. Gastric emptying of any residual calcium should be considered. Rehydration, and, according to severity, isolated or combined treatment with loop diuretics, bisphosphonates, calcitonin and corticosteroids should also be considered. Serum electrolytes, renal function and vital signs must be monitored. In severe cases, ECG and central venous pressure should be followed.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

## **ACTION AND CLINICAL PHARMACOLOGY**

### **Mechanism of Action**

**ACTONEL:** Risedronate sodium, a pyridinyl-bisphosphonate in the form of hemi-pentahydrate with small amounts of monohydrate, inhibits osteoclast bone resorption and modulates bone metabolism. Risedronate has a high affinity for hydroxyapatite crystals in bone and is a potent antiresorptive agent. At the cellular level, risedronate inhibits osteoclasts. The osteoclasts adhere normally to the bone surface, but show evidence of reduced active resorption (e.g., lack of ruffled border). Histomorphometry in rats, dogs, minipigs and humans showed that risedronate treatment reduces bone turnover (i.e., activation frequency, the rate at which bone remodelling sites are activated) and bone resorption at remodelling sites.

**Calcium:** Calcium is an important nutrient that must be ingested in sufficient quantities to promote bone health. A total intake of 1200 to 1500 mg per day of elemental calcium from both dietary and supplemental sources is recommended. Inadequate intake of calcium may result in reduced bone mass and increased risk of fractures. Calcium is a major substrate for mineralization and has an antiresorptive effect on bone. Calcium suppresses parathyroid hormone (PTH) secretion and decreases bone turnover. Increased levels of PTH are known to contribute to age-related bone loss, especially at cortical sites, while increased bone turnover is an independent risk factor of fractures.

### **Pharmacodynamics**

**ACTONEL:** Osteoporosis is a degenerative and debilitating bone disease characterized by decreased bone mass and increased fracture risk at the spine, hip, and wrist. The diagnosis can be confirmed by the finding of low bone mass, evidence of fracture on x-ray, a history of osteoporotic fracture, or height loss or kyphosis indicative of vertebral fracture. Osteoporosis occurs in both men and women but is more common among women following menopause.

In healthy humans, bone formation and resorption are closely linked; old bone is resorbed and replaced by newly-formed bone. In postmenopausal osteoporosis, bone resorption exceeds bone

formation, leading to bone loss and increased risk of bone fracture. After menopause, the risk of fractures of the spine and hip increases dramatically; approximately 40% of 50-year-old women will experience an osteoporosis-related fracture of the spine, hip, or wrist during their remaining lifetimes. After experiencing one osteoporosis-related fracture, the risk of future fracture increases 5-fold compared to the risk among a non-fractured population.

ACTONEL treatment decreases the elevated rate of bone turnover and corrects the imbalance of bone resorption relative to bone formation that is typically seen in postmenopausal osteoporosis. In clinical trials, administration of ACTONEL to postmenopausal women resulted in dose-dependent decreases in biochemical markers of bone turnover, including urinary markers of bone resorption and serum markers of bone formation, at doses as low as 2.5 mg daily. At the 5 mg daily dose, decreases in resorption markers were evident within 14 days of treatment. Changes in bone formation markers were observed later than changes in resorption markers, as expected, due to the coupled nature of bone formation and bone resorption; decreases in bone formation of about 20% were evident within 3 months of treatment. Bone turnover markers reached a nadir of about 40% below baseline values by the sixth month of treatment and remained stable with continued treatment for up to 3 years.

These data demonstrate that ACTONEL 5 mg administered daily to postmenopausal women produces a rapid reduction in bone resorption without over-suppression of bone formation. Bone turnover is decreased as early as 2 weeks and maximally within about 6 months of treatment, with achievement of a new steady-state which more nearly approximates the rate of bone turnover seen in premenopausal women.

In a 1-year study comparing ACTONEL 35 mg Once-a-Week to ACTONEL 5 mg daily for the treatment of osteoporosis in postmenopausal women, similar decreases in bone resorption (about 60%) and formation markers (about 40%) were observed for both dosage regimens.

As a result of the inhibition of bone resorption, asymptomatic and usually transient decreases from baseline in serum calcium (about 2%) and serum phosphate levels (about 5%) and compensatory increases in serum PTH levels were observed within 6 months in ACTONEL 5 mg daily-treated patients in postmenopausal osteoporosis trials. No further decreases in serum calcium or phosphate, or increases in PTH were observed in postmenopausal women treated for up to 3 years. In the 1-year study comparing ACTONEL 35 mg Once-a-Week to ACTONEL 5 mg daily for the treatment of osteoporosis in postmenopausal women, similar mean changes from baseline in serum calcium, phosphate and PTH were found for both dosage regimes.

Consistent with the effects of ACTONEL on biochemical markers of bone turnover, daily oral doses as low as 2.5 mg produced dose dependent, significant increases in lumbar spine bone mineral density (BMD) (2.5 mg, 3% to 3.7%; 5 mg, 4% to 4.5%) after 12 months of treatment in large-scale postmenopausal osteoporosis trials. A dose-dependent response to treatment was also observed in the BMD of the femoral neck over the same time (2.5 mg, 0.7% to 0.9%; 5 mg, 1.5% to 2%). In the 1-year study comparing ACTONEL 35 mg Once-a-Week to ACTONEL 5 mg daily for the treatment of osteoporosis in postmenopausal women, similar mean changes from baseline in BMD of the lumbar spine, total proximal femur, femoral neck and femoral trochanter were found for both dosage regimens (see CLINICAL TRIALS, Treatment of Osteoporosis in Postmenopausal Women).

**Calcium:** Calcium administration decreases the elevated rate of bone turnover typically seen in postmenopausal women with osteoporosis. In randomized, placebo controlled studies in postmenopausal women, calcium administration (500 mg to 1600 mg) decreased biochemical markers of bone turnover, including urine N-telopeptide, urine free pyridinoline (markers of bone resorption), alkaline phosphatase and osteocalcin (markers of bone formation) relative to placebo treated women.

Calcium administration may transiently increase levels of serum calcium with compensatory reductions in serum PTH and an increase in urinary calcium. However, urinary and serum calcium levels usually remain within the normal reference range.

## **Pharmacokinetics**

### **ACTONEL:**

<b>Table 4 Summary of Pharmacokinetic Parameters of Risedronate</b>						
	<b>C<sub>max</sub> (ng/mL)</b>	<b>t<sub>max</sub> (h)</b>	<b>t<sub>1/2,z</sub> (h)</b>	<b>AUC<sub>0-∞</sub> (ng·h/mL)</b>	<b>Clearance (L/h/kg)</b>	<b>V<sub>z</sub> (L/kg)</b>
5 mg tablet; single dose	0.85	0.93 <sup>a</sup>	206.1	3.45	19.94	5542
35 mg tablet; multiple dose, steady state	10.6	0.49	nd	53.3	12.9	nd
<sup>a</sup> Arithmetic mean t <sub>1/2, z</sub> is the half-life of the terminal exponential phase. V <sub>z</sub> is the terminal volume of distribution for IV doses and is uncorrected for bioavailability for oral doses. nd not determined						

**Absorption:** Absorption after an oral dose is relatively rapid (t<sub>max</sub> ~ 1 hour) and occurs throughout the upper gastrointestinal tract. Absorption is independent of dose over the range studied (single dose, 2.5 to 30 mg; multiple dose, 2.5 to 5 mg daily; and multiple dose, 35 and 50 mg weekly). 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 bioequivalent to a solution. Extent of absorption when administered 30 minutes before breakfast is reduced by 55% compared to dosing in the fasting state (i.e., no food or drink for 10 hours prior to or 4 hours after dosing). Dosing 1 hour prior to breakfast reduces extent of absorption by 30% compared to dosing in the fasting state. Dosing either 30 minutes prior to breakfast or 2 hours after a meal results in a similar extent of absorption.

**Distribution:** The mean steady-state volume of distribution is 6.3 L/kg in humans. Human plasma protein binding of drug is about 24%. Preclinical studies in rats and dogs dosed intravenously with single doses of [<sup>14</sup>C] risedronate indicate that approximately 60% of the dose is distributed to bone. The remainder of the dose is excreted in the urine. After multiple oral dosing in rats, the uptake of risedronate in soft tissues was found to be minimal (in the range of 0.001% to 0.01%), with drug levels quickly decreasing after the final dose.

**Metabolism:** There is no evidence that risedronate is systemically metabolized.

**Excretion:** Approximately half of the absorbed dose is excreted in urine within 24 hours, and 85% of an intravenous dose is recovered in the urine over 28 days. Mean renal clearance is 105 mL/min (CV = 34%) and mean total clearance is 122 mL/min (CV = 19%), with the difference primarily reflecting 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. Unabsorbed drug is eliminated unchanged in feces. Once risedronate is absorbed, 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 of bisphosphonates from human bone is unknown, the 480 hour half-life is hypothesized to represent the dissociation of risedronate from the surface of bone.

### **Calcium:**

**Absorption:** Calcium is released from calcium complexes during digestion in a soluble, ionized form, for absorption from the small intestine. Absorption can be by both passive and active mechanisms. As calcium intake increases, the active transfer mechanism becomes saturated and an increasing proportion of calcium is absorbed via passive diffusion. Absorption of calcium carbonate is dose-dependent, with fractional absorption being highest when taken at doses up to 500 mg and when taken with food.

**Distribution:** Approximately 50% of calcium in the plasma is in the physiologically active ionized form; about 10% is complexed to phosphate, citrate or other anions, while the remaining 40% is bound to proteins, primarily albumin.

**Elimination:** Unabsorbed calcium from the small intestine is excreted in the feces. Renal excretion depends largely on glomerular filtration and calcium tubular reabsorption with more than 98% of calcium reabsorbed from the glomerular filtrate.

### **Special Populations and Conditions**

**Pediatrics:** Risedronate pharmacokinetics have not been studied in patients < 18 years of age.

**Geriatrics:** Bioavailability and disposition of risedronate are similar in elderly (> 65 years of age) and younger subjects. No dosage adjustment is necessary.

**Gender:** Bioavailability and disposition following oral administration of risedronate are similar in men and women.

**Race:** Pharmacokinetic differences of risedronate due to race have not been studied.

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

**Renal Insufficiency:** Risedronate is excreted intact primarily via the kidney. Patients with mild-to-moderate renal impairment (creatinine clearance > 30 mL/min) do not require a dosage adjustment. Exposure to risedronate was estimated to increase by 44% in patients with

creatinine clearance of 20 mL/min. ACTONEL is not recommended for use in patients with severe renal impairment (creatinine clearance < 30 mL/min) because of a lack of clinical experience.

**Genetic Polymorphism:** No data are available.

## **STORAGE AND STABILITY**

Store at controlled room temperature (20°C–25°C).

## **DOSAGE FORMS, COMPOSITION AND PACKAGING**

ACTONEL PLUS CALCIUM is supplied as a monthly (28 days) course of therapy. Each carton contains four strips of blister packaged weekly therapy. Each strip contains:

- One risedronate tablet: film-coated, oval, light orange tablets with “RSN” on one face and “35 mg” on the other
- Six calcium tablets: film-coated, oval, blue tablets with “NE 2” engraved on both faces.

**Medicinal Ingredients:** Each ACTONEL tablet for oral administration contains the equivalent of 35 mg of anhydrous risedronate sodium in the form of the hemi-pentahydrate with small amounts of monohydrate. Each calcium tablet contains 500 mg elemental calcium as 1250 mg calcium carbonate.

### **Nonmedicinal Ingredients:**

**ACTONEL:** Crospovidone, ferric oxide, hypromellose, hydroxypropyl cellulose, lactose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, silicon dioxide, and titanium dioxide.

**Calcium:** FD&C Blue No. 2 aluminum lake, hypromellose, hydroxypropyl cellulose, indigo carmine, magnesium stearate, polyethylene glycol, polysorbate, pregelatinized starch, sodium starch glycolate, and titanium dioxide.

## PART II: SCIENTIFIC INFORMATION

### PHARMACEUTICAL INFORMATION

#### Drug Substance

**Proper Name:** risedronate sodium hemi-pentahydrate

calcium carbonate

**Chemical Name:** ACTONEL tablets contain risedronate sodium in the form of hemi-pentahydrate with small amounts of monohydrate. The chemical name of risedronate sodium is [1-hydroxy-2-(3-pyridinyl)ethylidene]bis[phosphonic acid] monosodium salt.

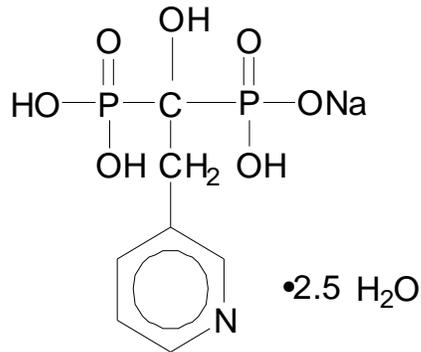
Calcium tablets contain calcium carbonate.

**Molecular Formula:** Risedronate sodium -  $C_7H_{10}NO_7P_2Na \cdot 2.5H_2O$

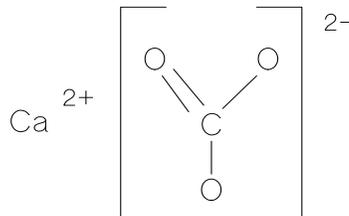
Calcium carbonate -  $CaCO_3$

#### Structural Formula:

##### Risedronate sodium



##### Calcium carbonate



**Molecular Weight:** Risedronate sodium - Anhydrous: 305.10  
Hemi-pentahydrate: 350.13

Calcium carbonate - 100.09

**Solubility:** Risedronate sodium is soluble in pH 7.0 potassium phosphate dibasic solution, 0.1 N sodium hydroxide, and water; very slightly soluble in 0.1N hydrochloric acid, practically insoluble in ethanol, and insoluble in isopropanol.

Calcium carbonate is practically insoluble in water; soluble in dilute acids.

**Solution pH:** The pH of a 1.0% aqueous solution of risedronate sodium is 4.15.

**Dissociation Constants:** The five  $pK_a$  values for risedronate sodium are as follows:  
 $pK_1 = 1.6 \pm 0.2$ ,  $pK_2 = 2.2 \pm 0.2$ ,  $pK_3 = 5.9 \pm 0.1$ ,  
 $pK_4 = 7.1 \pm 0.1$  and  $pK_5 = 11.7 \pm 0.3$ .

**Description:** Risedronate sodium is a fine, white to off-white, crystalline powder.

Precipitated calcium carbonate is a fine, white, odourless powder. It is stable and non-hygroscopic.

## CLINICAL TRIALS

### Treatment of Osteoporosis in Postmenopausal Women

#### Study Demographics and Trial Design

<b>Table 5</b> <b>Summary of Patient Demographics for Clinical Trials of ACTONEL</b> <b>in the Treatment of Osteoporosis in Postmenopausal Women</b>						
Study Number	Trial Design <sup>a</sup>	Dosage	Duration	Patients N = number	Age Range (Age Mean)	Gender
1 VERT-MN	R, PC, DB, MC, PG	2.5 mg/day 5 mg/day Placebo	2 years 3 years 3 years	1226	48-85 (71.0)	Postmenopausal female
2 VERT-NA	R, PC, DB, MC, PG	2.5 mg/day 5 mg/day Placebo	1 year 3 years 3 years	2458	28-85 (68.6)	Postmenopausal female
3	R, PC, DB, MC, PG	2.5 mg/day 5 mg/day Placebo	2 years	543	45-80 (64.7)	Postmenopausal female
4	R, PC, DB, MC, PG	2.5 mg/day 5 mg/day Placebo	12 – 18 months	648	39-80 (62.5)	Postmenopausal female
5	R, AC, DB, MC, PG	5 mg/day 35 mg/week* 50 mg/week* *Placebo other 6 days	12 months	1456	48-95 (67.9)	Postmenopausal female

<sup>a</sup> R: randomized; AC: active-controlled; PC: placebo-controlled; DB: double-blind; MC: multicentre; PG: parallel-group

In Studies 1 and 2, 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 Study 1, and 2.5 in Study 2, with a broad range of baseline bone mineral density (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. All fractures (symptomatic/painful/clinical vertebral fractures and asymptomatic/nonpainful/silent vertebral fractures) were systematically captured and measured by annual radiographs.

In Studies 3 and 4, postmenopausal women were recruited on the basis of low lumbar spine bone mass (i.e., more than 2 SD below the premenopausal mean) rather than a history of vertebral fracture.

#### Study Results

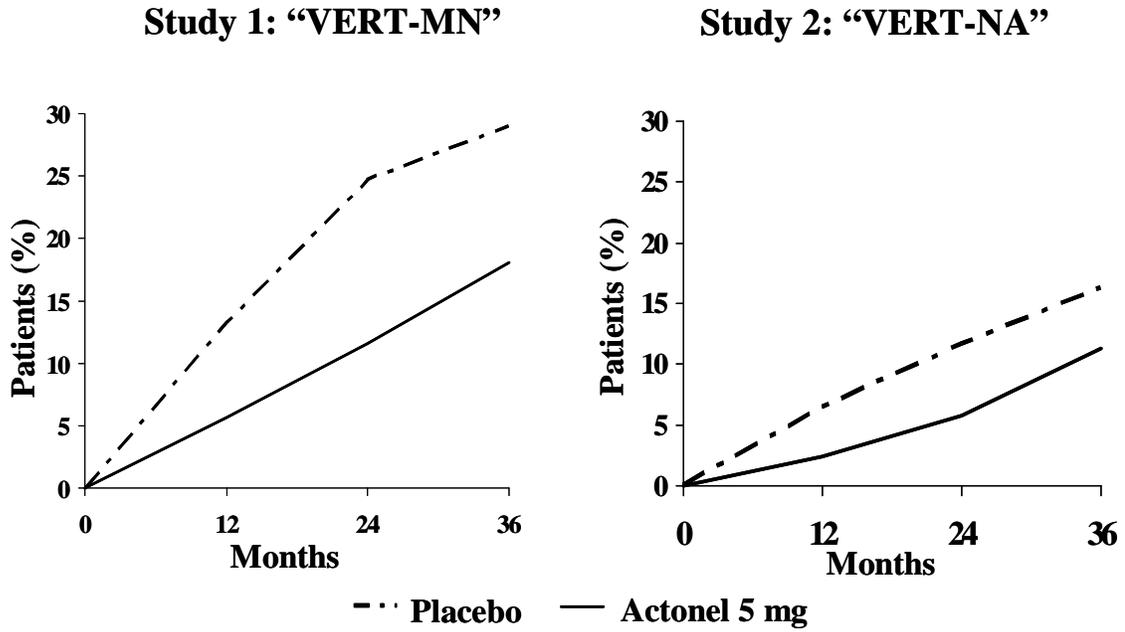
##### **Results of Studies Number 1 and 2:**

The pivotal studies of ACTONEL in the treatment of postmenopausal osteoporosis clearly demonstrate that ACTONEL 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. ACTONEL 5 mg daily significantly reduced the risk of new vertebral fractures in

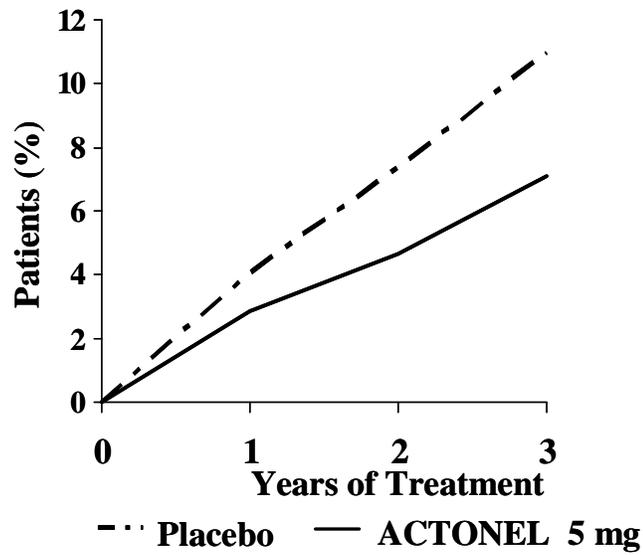
each of the two large treatment studies. When measured by annual radiographs, the effect of ACTONEL 5 mg daily on vertebral fracture incidence was seen at the first year of treatment in each study. In the North American study, treatment with ACTONEL 5 mg daily for 1 year significantly reduced the risk of new vertebral fractures by 65% compared to treatment with placebo ( $p < 0.001$ ). In the Multinational study, a similar significant reduction of 61% was seen ( $p = 0.001$ ). Treatment with ACTONEL 5 mg daily also significantly reduced the proportion of patients experiencing new and worsening vertebral fractures in each of the studies. Figures 1 and 2 below display the cumulative incidence of vertebral and nonvertebral fractures (i.e., hip, wrist, humerus, clavicle, pelvis, and leg). In both figures, the cumulative incidence of these types of fracture is lower with ACTONEL compared with placebo at all time points, consistent with ACTONEL's positive effect on bone strength.

<b>Table 6</b>					
<b>Effect of ACTONEL on Fracture, Height and Bone Mineral Density in the Treatment of Osteoporosis in Postmenopausal Women</b>					
Endpoints	ACTONEL 5 mg	Placebo	Mean Difference from Placebo	Relative Risk Reduction %	p-value
<b>Study 1: VERT-MN</b>					
Cumulative incidence of new vertebral fracture over 3 years (% of patients)	18.1	29.0		49	<0.001
Median annual height change <sup>b</sup> (mm/yr)	-1.33	-2.4			0.003
Mean increase in BMD (%)					
6 months Lumbar spine	3.3	-0.1	3.4		<0.001
36 months Lumbar spine	7.1	1.3	5.9		<0.001
Femoral neck	2.0	-1.0	3.1		<0.001
Trochanter	5.1	-1.3	6.4		<0.001
36 months Midshaft radius	0.5	-1.9	2.4		<0.001
<b>Study 2: VERT-NA</b>					
Cumulative incidence of new vertebral fracture over 3 years (% of patients)	11.3	16.3		41	0.003
Median annual height change <sup>b</sup> (mm/yr)	-0.67	-1.14			0.001
Mean increase in BMD (%)					
6 months Lumbar spine	2.7	0.4	2.2		<0.001
36 months Lumbar spine	5.4	1.1	4.3		<0.001
Femoral neck	1.6	-1.2	2.8		<0.001
Trochanter	3.3	-0.7	3.9		<0.001
36 months Midshaft radius	0.2	-1.4	1.6		<0.001
<b>Prospectively Combined Studies 1 and 2: VERT-MN and VERT-NA</b>					
Cumulative incidence of non-vertebral fracture <sup>a</sup> over 3 years (% of patients)	7.1	11.0		36	0.005
<sup>a</sup> Osteoporosis-related non-vertebral fractures (hip, wrist, humerus, clavicle, pelvis, and leg)					
<sup>b</sup> Measured by stadiometer					

**Figure 1**  
**Cumulative New Vertebral Fracture Incidence in Postmenopausal Women with Osteoporosis**



**Figure 2**  
**Cumulative Incidence of Osteoporosis-Related Non-vertebral Fractures Studies 1 and 2 Combined**



ACTONEL 5 mg daily was associated with a significant reduction of about 50% in the annual rate of height loss compared to treatment with placebo.

ACTONEL 5 mg daily produced increases in lumbar spine BMD which were progressive over the 3 years of treatment, and were statistically significant relative to baseline and to placebo at 6 months and at all later time points (12, 18, 24 and 36 months).

#### Results of Studies Number 3 and 4

<b>Table 7</b> <b>Effect of ACTONEL on Bone Mineral Density in the Treatment of Osteoporosis</b> <b>in Postmenopausal Women</b>				
Endpoints		ACTONEL 5 mg Mean Increase in BMD %	Placebo Mean Increase in BMD %	Mean Difference from Placebo %
<b>Study 3</b>				
6 months	Lumbar Spine	3.3	0.4	2.8**
24 months	Lumber Spine	4.1	0.0	4.1**
	Femoral Neck	1.3	-1.0	2.3*
	Trochanter	2.7	-0.6	3.3**
<b>Study 4</b>				
6 months	Lumbar Spine	3.3	0.7	2.6**
18 months	Lumber Spine	5.2	0.3	5.0**
	Femoral Neck	3.1	0.2	2.8**
	Trochanter	4.8	1.4	3.3**
vs placebo: *p<0.01; **p<0.001				

In Studies 3 and 4, in these women with low bone mass, ACTONEL 5 mg daily produced significant mean increases in BMD of the lumbar spine compared to placebo at 6 months. Compared to placebo after 1.5 to 2 years, further significant mean increases in BMD were seen at the lumbar spine, femoral neck and trochanter.

The results of four large, randomized, placebo-controlled trials (Studies 1 - 4) in women with postmenopausal osteoporosis separately and together demonstrate that ACTONEL 5 mg daily reverses the progression of disease, increasing BMD at the spine, hip, and wrist compared to the effects seen with placebo.

## Results of Study Number 5

Endpoints	ACTONEL 5 mg per day Mean Increase in BMD % (95% Confidence Interval)	ACTONEL 35 mg Once-a-Week Mean increase in BMD % (95% Confidence Interval)
	N=391	N=387
12 months Lumbar Spine	4.0 (3.7, 4.3)	3.9 (3.6, 4.3)

The results of the intent-to-treat analysis with the last observation carried forward were consistent with the primary efficacy analysis of completers. There were also no statistically significant differences between the two treatment groups at 1 year in regards to BMD increases from baseline at other skeletal sites (total proximal femur, femoral neck, and femoral trochanter). Based on these BMD outcomes, ACTONEL 35 mg Once-a-Week was concluded to be therapeutically equivalent to ACTONEL 5 mg daily.

In trials with ACTONEL 5 mg daily, changes in BMD of this magnitude were associated with a significant decrease in fracture incidence relative to placebo (see Table 6). This is further supported by the fact that within the 1-year study comparing ACTONEL 35 mg Once-a-Week to ACTONEL 5 mg daily, no statistically significant differences amongst these treatment groups were seen with respect to the number of patients with at least 1 new fractured vertebra at 1 year. ACTONEL 35 mg taken once a week is as safe and effective as ACTONEL 5 mg daily for the treatment of postmenopausal osteoporosis.

## Prevention of Osteoporosis in Postmenopausal Women

### Study Demographics and Trial Design

Study Number	Trial Design	Dosage	Duration	Patients N = number	Age Range (Age Mean)	Gender
6	R, PC, DB, MC, PG	2.5 mg/day 5 mg/day	2 years	383	42-63 (52.7)	Postmenopausal female
7	R, DB, PC, MC, PG	35 mg/week Placebo	1 year	280	44-64 (53.6)	Postmenopausal female

R: randomized; AC: active-controlled; PC: placebo-controlled; DB: double-blind; MC: multicentre; PG: parallel-group

Women in Study 6 were within 3 years of menopause and all patients in this study received supplemental calcium 1000 mg/day.

Study 7 included women who were 0.5 to 5 year postmenopausal without osteoporosis. All patients were supplemented with 1000 mg elemental calcium and 400 IU vitamin D per day.

## Study Results

### Results of Study Number 6

Table 10 Effect of ACTONEL 5 mg Daily on Bone Mineral Density in Postmenopausal Women without Osteoporosis				
Endpoints		ACTONEL 5 mg Mean increase in BMD %	Placebo Mean increase in BMD %	Mean Difference from Placebo %
24 months	Lumbar Spine	2.0	-2.5	4.5*
	Femoral Neck	1.0	-2.3	3.3*
	Trochanter	2.3	-2.0	4.3*

\* vs. placebo: p<0.001

Increases in BMD were observed as early as 3 months following initiation of ACTONEL treatment. Prevention of spinal bone loss was observed in the vast majority of women who received ACTONEL treatment. In contrast, most placebo-treated women experienced significant and progressive bone loss, despite receiving supplemental calcium 1000 mg/day. ACTONEL 5 mg daily was similarly effective in patients with lower baseline BMD (i.e., more than 1 SD below the premenopausal mean) and in those with higher BMD.

### Results of Study Number 7

Table 11 Effect of ACTONEL 35 mg Once-a-Week on Bone Mineral Density in Postmenopausal Women without Osteoporosis				
Endpoints		ACTONEL 35 mg Once-a-Week Mean Increase in BMD %	Placebo Mean Increase in BMD %	Mean Difference from Placebo %
6 months	Lumbar Spine	1.7	-0.5	2.2*
	Trochanter	1.0	-0.4	1.3*
	Femoral Neck	0.4	-1.0	1.4*
12 months	Lumbar Spine	1.9	-1.1	3.0*
	Trochanter	1.0	-0.7	1.7*
	Femoral Neck	0.3	-1.0	1.3**

\*vs. placebo: p≤0.0001; \*\* p=0.0041

**Histology/Histomorphometry:** Histomorphometric evaluation of 278 bone biopsy samples from 204 postmenopausal women who received ACTONEL 5 mg or placebo once daily for 2 to 3 years (including 74 pairs of biopsies, 43 from ACTONEL-treated patients) showed a moderate and expected decrease in bone turnover in ACTONEL-treated women.

Histologic assessment showed no osteomalacia, impaired bone mineralization, or other adverse effects on bone in ACTONEL-treated women. These findings demonstrate that the bone formed during ACTONEL administration is of normal quality.

## DETAILED PHARMACOLOGY

**ACTONEL:** There are extensive preclinical data to support that bone produced during ACTONEL treatment at therapeutic doses is of normal quality, consistent with clinical experience. Risedronate demonstrated potent anti-osteoclast, antiresorptive activity in ovariectomized animals, increasing bone mass and biomechanical strength dose-dependently. Risedronate treatment maintained the positive correlation between BMD and bone strength. In intact dogs, risedronate induced positive bone balance at the level of the basic multicellular unit.

Long-term oral administration of risedronate to ovariectomized rats (up to 2.5 mg/kg/day for 12 months) and ovariectomized minipigs (up to 2.5 mg/kg/day for 18 months) did not impair bone structure, mineralization, or biomechanical strength. These doses were 5 times the optimal antiresorptive dose for these species. Normal lamellar bone was formed in these animals. Risedronate treatment did not impair the normal healing of radial fractures in adult dogs. The Schenk rat assay, based on histologic examination of the epiphyses of growing rats after drug treatment, demonstrated that risedronate did not interfere with bone mineralization even at the highest dose tested (5 mg/kg/day, subcutaneously), which was > 3000 times the lowest antiresorptive dose (1.5 µg/kg/day).

### **Calcium:**

Published studies have demonstrated that changes in the dietary intake of calcium affect bone growth and skeletal development in intact animals, as well as bone loss in animal models of estrogen-depletion/ovariectomy and aging.

In young female rats, tibial BMD and trabecular bone volume were directly related to dietary calcium intake. The lower BMD and bone volume in the low calcium group were associated with higher bone resorption and lower bone formation. Peak bone mass remained low in the adult (8-month old) rats which had been fed low calcium diet from 1 to 3-months of age even if they were fed normal or high calcium diet from 3-months through 8-months.

In adult female rats (5-6 months), a low calcium diet for up to 9 months induced loss of BMD and bone volume, and potentiated the ovariectomy-induced loss of bone and bone strength in long bones and vertebra. In female dogs, a low calcium diet for 18 months induced loss of BMD in trabecular (vertebra) and cortical (forearm) bone but did not potentiate the ovariectomy induced bone loss. Bone loss with low calcium dietary intake was associated in both studies with increased bone turnover as measured by bone histomorphometry or turnover markers.

In rats fed a high calcium diet from 2-months through 24-months of age, the age-related loss of vertebral BMD and bone volume was reduced. This effect was associated with reduced bone turnover in the high calcium group.

## TOXICOLOGY

### **ACTONEL:**

**Acute Toxicity:** Lethality after single oral doses was seen in female rats at 903 mg/kg (5826 mg/m<sup>2</sup>) and male rats at 1703 mg/kg (10967 mg/m<sup>2</sup>). The minimum lethal dose in mice and rabbits was 4000 mg/kg (10909 mg/m<sup>2</sup>) and 1000 mg/kg (10870 mg/m<sup>2</sup>), respectively. These

values represent 320 to 620 times the human 30 mg dose based on surface area ( $\text{mg}/\text{m}^2$ ). There was no lethality in dogs at a dose of 100 mg/kg ( $2000 \text{ mg}/\text{m}^2$ ), the highest dose tested.

**Chronic Toxicity:** In a 1-year repeat dose toxicity study in dogs, the limiting toxicity of risedronate was observed at 8 mg/kg/day ( $160 \text{ mg}/\text{m}^2$ ) and consisted of liver, testicular, renal, and gastrointestinal changes. Gastrointestinal effects at 16 mg/kg ( $111 \text{ mg}/\text{m}^2$ ) were the first limiting toxicity in rats in a 26-week study. These doses are equivalent to approximately 6.25 to 9 times the human 30 mg dose based on surface area,  $\text{mg}/\text{m}^2$ .

**Carcinogenicity:** Three carcinogenicity studies in two species (mouse and rat) have been completed. All studies clearly showed dose-dependent bone pharmacologic effects. Risedronate was not carcinogenic in male or female rats dosed daily by gavage for 104 weeks at doses up to 24 mg/kg/day (12 times the human 30 mg dose based on surface area,  $\text{mg}/\text{m}^2$ ). Similarly, there was no evidence of a carcinogenic potential in male or female mice dosed daily by gavage for 80 weeks at doses up to 32 mg/kg/day (5 times the human 30 mg dose based on surface area,  $\text{mg}/\text{m}^2$ ).

**Mutagenesis:** In a series of seven *in vitro* and *in vivo* mutagenicity assays, risedronate was not genotoxic. An *in vitro* chromosomal aberration assay in Chinese hamster ovary cells was weakly positive at highly cytotoxic doses ( $> 675 \mu\text{g}/\text{mL}$ ). However, when the assay was repeated at doses exhibiting increased cell survival ( $300 \mu\text{g}/\text{mL}$ ), risedronate was negative.

**Reproduction:** Risedronate had no effect on fertility (male or female) in rats at doses up to 16 mg/kg/day (6.25 times the human 30 mg dose based on surface area,  $\text{mg}/\text{m}^2$ ).

Reproduction studies in rats showed decreased implantation at 7.1 mg/kg/day and increased body weights of neonates at 7.1 and 16 mg/kg/day. Sites of incomplete fetal ossification of sternebrae were statistically significantly decreased in rats at 3.2 mg/kg/day and increased in rats at 7.1 mg/kg/day. Unossified fetal sternebrae were statistically significantly decreased in rats at 3.2 mg/kg/day and 7.1 mg/kg/day. The above doses ranged from 1.25 times (3.2 mg/kg) to 6.25 times (16 mg/kg) the human 30 mg dose based on surface area,  $\text{mg}/\text{m}^2$ . No significant fetal ossification effects were seen when rabbits were treated at doses up to 10 mg/kg/day (6 times the human 30 mg dose based on surface area,  $\text{mg}/\text{m}^2$ ).

Similar to other bisphosphonates, treatment throughout mating and gestation with doses as low as 3.2 mg/kg/day has resulted in acute periparturient hypocalcemia and mortality in pregnant rats allowed to deliver.

#### **Calcium:**

**Acute Toxicity:** The  $\text{LD}_{50}$  in rats for calcium (as calcium gluconate) was found to be 930 mg calcium/kg.

**Chronic Toxicity:** Rats fed about 5 mg Ca/g as dibasic calcium phosphate for 20 days had significantly enlarged kidneys.

An elevated calcium diet can have deleterious effects on development and growth and in the adult animal.

**Carcinogenicity:** No carcinogenesis studies have been identified for calcium.

**Mutagenesis:** In a published report, calcium carbonate was negative in a *Salmonella typhimurium* (TA97 & TA102) assay for mutagenesis.

**Reproduction:** Combinations of calcium salts have been used widely and extensively in clinical practice worldwide for many years. Human experience generally supersedes previously documented nonclinical data in these situations.

In one published study, moderate increases in dietary calcium given to rats for six weeks prior to pregnancy, and during gestation had no deleterious impact on fertility, maintenance of pregnancy, nor was there any fetal toxicity or teratogenicity.

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**PART III: CONSUMER INFORMATION**

**ACTONEL PLUS CALCIUM**  
Risedronate Sodium 35 mg tablets and  
Calcium Carbonate 1250 mg tablets  
(equivalent to 500 mg elemental calcium)  
Film-coated tablets

This leaflet is Part III of a three-part “Product Monograph” published when ACTONEL PLUS CALCIUM was approved for sale in Canada. It is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about ACTONEL PLUS CALCIUM. Contact your doctor or pharmacist if you have any questions about the drug.

**ABOUT THIS MEDICATION****What the medication is used for:**

Treatment and prevention of postmenopausal osteoporosis.

**What it does:**

ACTONEL PLUS CALCIUM is a combination of ACTONEL (risedronate sodium hemi-pentahydrate) tablets and calcium carbonate tablets.

ACTONEL is a non-hormonal drug (i.e., not an estrogen) that builds and strengthens bones. In many people, ACTONEL actually rebuilds some of the bone that has already been lost. In osteoporosis, the body removes more bone than it replaces. This causes bones to get weaker and more likely to break or fracture (usually at the spine, wrist or hip). Spine fractures may result in a curved back, height loss or back pain. ACTONEL corrects this imbalance by decreasing the elevated rate of bone removal. ACTONEL can therefore help reduce the risk of spine and non-spine fractures.

ACTONEL is not a pain reliever. Your doctor may prescribe or recommend another medicine specifically for pain relief.

Calcium carbonate helps to provide the calcium that your body may need to harden new bone.

Since it is not known how long ACTONEL PLUS CALCIUM should be continued, you should discuss the need to stay on this medication with your doctor regularly to determine if ACTONEL PLUS CALCIUM is still right for you.

**When it should not be used:**

- If you have low blood calcium levels (hypocalcemia).
- If you have high blood calcium levels (hypercalcemia)
- If you are allergic to ACTONEL PLUS CALCIUM or any of its ingredients (see below).

**What the medicinal ingredients are:**

Risedronate sodium, calcium (as calcium carbonate).

**What the nonmedicinal ingredients are:**

**ACTONEL:** Crospovidone, ferric oxide, hypromellose, hydroxypropyl cellulose, lactose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, silicon dioxide, and titanium dioxide.

**Calcium:** FD&C Blue No. 2 aluminum lake hypromellose, hydroxypropyl cellulose, indigo carmine, magnesium stearate, polyethylene glycol, polysorbate, pregelatinized starch, sodium starch glycolate, and titanium dioxide.

**What dosage form it comes in:**

ACTONEL PLUS CALCIUM is a combination pack containing ACTONEL tablets and calcium carbonate tablets. It is supplied as a monthly (28 days) course of therapy. Each carton contains four strips of blister packaged weekly therapy. Each strip contains:

- One smaller orange ACTONEL 35 mg tablet
- Six larger blue calcium 500 mg tablets

**WARNINGS AND PRECAUTIONS**

Before you use ACTONEL PLUS CALCIUM, talk to your doctor or pharmacist if:

- You have had problems or disease in your kidneys, esophagus (i.e., the tube connecting the mouth and the stomach), stomach, or intestines.
- You are pregnant or nursing.
- You cannot carry out the dosing instructions (see PROPER USE OF THIS MEDICATION).
- You have one of the following risk factors: cancer, chemotherapy, radiotherapy of the head or neck, treatment with corticosteroids, or dental problems or dental infections. If so, a dental examination and any necessary dental procedures should be considered before you start treatment with ACTONEL.

Be sure to tell your health care providers, including doctors and dentists, about all medicines you are taking, including ACTONEL PLUS CALCIUM.

**INTERACTIONS WITH THIS MEDICATION**

Vitamin and mineral supplements, as well as antacids, may contain substances (e.g., calcium, magnesium, aluminum, and iron) which can stop your body from absorbing the ACTONEL in ACTONEL PLUS CALCIUM. These should be taken at a different time of day.

If taken with some other medicines, the effects of ACTONEL PLUS CALCIUM or the effects of other medicines may be changed. It is important to tell your doctor what other medications you are taking, even if the medicine does not require a prescription (including vitamins and herbal supplements).

Calcium products may interact with medications such as digoxin, certain antibiotics, iron supplements, phenytoin, thyroid hormones, steroid medications and thiazide diuretics.

Food, if taken with ACTONEL, may prevent your body from absorbing ACTONEL. Take ACTONEL on an empty stomach. (See “PROPER USE OF THIS MEDICATION” for instruction).

## PROPER USE OF THIS MEDICATION

### Recommended Dose:

- 1 ACTONEL 35 mg tablet (orange) one day per week, taken orally on an empty stomach and
- 1 calcium tablet (blue) daily on the other 6 days per week, taken orally with food.

ACTONEL PLUS CALCIUM provides 500 mg of elemental calcium for 6 days per week. It is intended to increase your calcium intake towards the recommended daily intake of 1200-1500 mg in elemental calcium from diet and supplementation. The amount of calcium in this product is not enough by itself to provide you with your daily requirements. Talk to your doctor about whether you are getting enough calcium from your diet and supplements. Other medications which may also contain calcium (e.g., multivitamins, antacids) should be taken at separate times of the day with food. All medications containing calcium should be taken at a different time of the day than your ACTONEL tablet.

ACTONEL PLUS CALCIUM does not contain vitamin D. Talk to your doctor or pharmacist about taking a vitamin D supplement.

### *ACTONEL tablets (orange)*

Choose a day of the week to take the orange ACTONEL tablet. On your chosen day take one ACTONEL tablet first thing in the morning with plain water before you have anything to eat or drink. Aside from plain water, do not eat or drink for at least 30 minutes after taking ACTONEL. Plain water is allowed at all times.

### *Instructions for all dosing options*

- Take with at least ½ cup (120 mL) of plain water. Do not take with coffee, tea, milk, or juice; they may prevent your body from absorbing ACTONEL.
- Swallow whole – do not chew or wait for it to dissolve.
- Do not lie down for at least 30 minutes after taking a dose. You may sit, stand or do normal activities like read the newspaper, take a walk, etc.

### *Calcium tablets (blue)*

- Take 1 blue tablet on each of the other 6 days per week that you don't take the orange ACTONEL tablets. Calcium tablets should be taken with food.

These recommendations help ACTONEL PLUS CALCIUM work correctly and help you avoid possible irritation of the esophagus (i.e., the tube connecting the mouth and the stomach).

### Missed Dose:

**ACTONEL tablet (orange):** If you forget to take your dose on the regularly scheduled day, simply take 1 tablet on the day you first remember having missed your dose. Do not take a calcium tablet on that day. Then resume your schedule by taking 1 tablet on the originally chosen day of the week, do not take 2 tablets on the same day. Simply take 1 tablet as you normally would have on this day and resume your weekly schedule.

**Calcium tablets (blue):** If you forget to take your dose, simply continue to take 1 tablet on the next day. Do not double your next dose (i.e., do not take more than 1 tablet on the same day). If the day that you remember is your regularly scheduled ACTONEL day, do not take the missed calcium tablet.

Discard any unused calcium tablets at the end of week.

### Overdose:

If you took too many orange ACTONEL tablets, drink a full glass of milk and contact your doctor or Poison Control Centre immediately. Do not induce vomiting. If you took a large number of blue calcium tablets, discontinue use and seek medical attention.

## SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Drugs like ACTONEL may cause problems in your stomach and esophagus (the tube connecting the mouth and the stomach), stomach and intestines, including ulcers. If you have trouble or pain upon swallowing, heartburn, chest pain and black or bloody stools, stop taking ACTONEL and tell your doctor right away. Remember to take ACTONEL PLUS CALCIUM as directed.

In clinical studies of osteoporosis with ACTONEL, the most commonly reported side effects were abdominal pain, heartburn and nausea.

ACTONEL may cause pain in bones, joints or muscles, rarely severe. Pain may start as soon as one day or up to several months after starting ACTONEL.

Calcium carbonate may cause constipation, flatulence, nausea, abdominal pain and bloating.

Very rarely patients have reported non-healing jaw wounds while receiving ACTONEL or other drugs in this class. Consult your doctor if you experience persistent pain in your mouth, teeth or jaw, or if your gums or mouth heal poorly.

Very rarely patients have reported unusual fractures in their thigh bone while receiving drugs in this class. Consult your doctor if you experience new or unusual pain in your hip, groin, or thigh.

<b>IMPORTANT SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM</b>			
Symptom / Effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
	Only if severe	In all cases	
<b>Common (more than 1 in 100)</b>			
Pain in bones, joints, or muscles	✓		
Abdominal pain			
<b>Uncommon (less than 1 in 100)</b>			
Eye pain, redness or inflammation; sensitivity to light, decreased vision			✓
<b>Rare (less than 1 in 1,000)</b>			
Painful tongue		✓	
<b>Very rare (less than 1 in 10,000)</b>			
Allergic reactions such as: hives; rash (with or without blisters); swelling of face, lips, tongue, or throat; difficult or painful swallowing; trouble breathing			✓
Jaw problems associated with delayed healing and infection, often following tooth extraction		✓	
New or unusual pain in hip, groin or thigh		✓	
Symptoms of low blood calcium level such as numbness, tingling, muscle spasms		✓	

*This is not a complete list of side effects. For any unexpected effects while taking ACTONEL PLUS CALCIUM, contact your doctor or pharmacist.*

### HOW TO STORE IT

- Keep ACTONEL PLUS CALCIUM and all other medications out of the reach of children.
- Keep the tablets in their original package and store at controlled room temperature (20°C – 25°C).
- Do not keep medicine that is out of date or that you no longer need.

### REPORTING SUSPECTED SIDE EFFECTS

**You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:**

- Report online at [www.healthcanada.gc.ca/medeffect](http://www.healthcanada.gc.ca/medeffect)
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: **Canada Vigilance Program  
Health Canada  
Postal Locator 0701D  
Ottawa, Ontario K1A 0K9**

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at [www.healthcanada.gc.ca/medeffect](http://www.healthcanada.gc.ca/medeffect).

*NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.*

### MORE INFORMATION

This document plus the full product monograph, prepared for health professionals, can be obtained by contacting Warner Chilcott Canada Co. at 1-800-565-0814.

This leaflet was prepared by Warner Chilcott Canada Co.

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