

ACTONEL - risedronate sodium tablet, film coated
Physicians Total Care, Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ACTONEL safely and effectively. See full prescribing information for ACTONEL.

ACTONEL® (risedronate sodium) tablets

Initial U.S. Approval: 1998

----- **RECENT MAJOR CHANGES** -----

Contraindications (4)	12/2009
Warnings and Precautions (5.1, 5.3)	12/2009

----- **INDICATIONS AND USAGE** -----

ACTONEL is a bisphosphonate indicated for:

- Treatment and prevention of postmenopausal osteoporosis (1.1),
- Treatment to increase bone mass in men with osteoporosis (1.2),
- Treatment and prevention of glucocorticoid-induced osteoporosis (1.3),
- Treatment of Paget's disease (1.4).

----- **DOSAGE AND ADMINISTRATION** -----

Must be taken with plain water (6 to 8 oz) at least 30 minutes before the first food or drink of the day; do not lie down for 30 minutes (2)

Treatment of Osteoporosis in Postmenopausal Women: 5 mg daily, 35 mg once a week, 75 mg taken on two consecutive days each month, or 150 mg once a month (2.1)

Prevention of Osteoporosis in Postmenopausal Women: 5 mg daily, or 35 mg once a week (2.2)

Men with Osteoporosis: 35 mg once a week (2.3)

Treatment and Prevention of Glucocorticoid-Induced Osteoporosis: 5 mg daily (2.4)

Paget's Disease: 30 mg daily for 2 months (2.5)

----- **DOSAGE FORMS AND STRENGTHS** -----

Tablets: 5, 30, 35, 75, and 150 mg (3)

----- **CONTRAINDICATIONS** -----

- Abnormalities of the esophagus which delay esophageal emptying such as stricture or achalasia (4, 5.1)
- Inability to stand or sit upright for at least 30 minutes (4, 5.1)
- Hypocalcemia (4, 5.2)
- Known hypersensitivity to any component of this product (4, 6.2)

----- **WARNINGS AND PRECAUTIONS** -----

- Severe irritation of the upper gastrointestinal (GI) mucosa can occur. Dosing instructions should be followed and caution should be used in patients with active upper GI disease. Discontinue use if new or worsening symptoms occur (5.1).
- Hypocalcemia may worsen and must be corrected prior to use (5.2).
- Osteonecrosis of the jaw has been reported rarely (5.3).
- Severe bone, joint, or muscle pain may occur. Consider discontinuing use if severe symptoms develop (5.4, 6.2).
- Before initiating treatment in patients with glucocorticoid-induced osteoporosis, sex steroid hormonal status of both men and women should be ascertained and appropriate replacement considered (5.6).
- Bisphosphonates may interfere with bone-imaging agents (5.7).

----- **ADVERSE REACTIONS** -----

Most common adverse reactions reported in >10% of patients treated with ACTONEL and with a higher frequency than placebo are: back pain, arthralgia, abdominal pain, and dyspepsia (6.1).

Hypersensitivity reactions (angioedema, generalized rash, bullous skin reactions), and eye inflammation (iritis, uveitis) have been reported rarely (6.2).

To report SUSPECTED ADVERSE REACTIONS, contact Warner Chilcott at 1-800-836-0658 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

----- **DRUG INTERACTIONS** -----

Calcium, antacids, or oral medications containing divalent cations interfere with the absorption of ACTONEL (7.1).

----- **USE IN SPECIFIC POPULATIONS** -----

ACTONEL is not recommended for use in patients with severe renal impairment (creatinine clearance <30 mL/min) (5.5, 8.6, 12.3).

ACTONEL is not indicated for use in pediatric patients (8.4).

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 12/2010

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE

- 1.1 Postmenopausal Osteoporosis
- 1.2 Osteoporosis in Men
- 1.3 Glucocorticoid-Induced Osteoporosis
- 1.4 Paget's Disease

2 DOSAGE AND ADMINISTRATION

- 2.1 Treatment of Postmenopausal Osteoporosis
- 2.2 Prevention of Postmenopausal Osteoporosis
- 2.3 Treatment to Increase Bone Mass in Men with Osteoporosis
- 2.4 Treatment and Prevention of Glucocorticoid-Induced Osteoporosis
- 2.5 Treatment of Paget's Disease

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Upper Gastrointestinal Adverse Reactions
- 5.2 Mineral Metabolism
- 5.3 Jaw Osteonecrosis
- 5.4 Musculoskeletal Pain
- 5.5 Renal Impairment
- 5.6 Glucocorticoid-Induced Osteoporosis
- 5.7 Laboratory Test Interactions

6 ADVERSE REACTIONS

- 6.1 Clinical Studies Experience
- 6.2 Postmarketing Experience

7 DRUG INTERACTIONS

- 7.1 Calcium Supplements/Antacids
- 7.2 Hormone Replacement Therapy
- 7.3 Aspirin/Nonsteroidal Anti-Inflammatory Drugs
- 7.4 H₂ Blockers and Proton Pump Inhibitors (PPIs)

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Renal Impairment
- 8.7 Hepatic Impairment

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

14.1 Treatment of Osteoporosis in Postmenopausal Women

14.2 Prevention of Osteoporosis in Postmenopausal Women

14.3 Men with Osteoporosis

14.4 Glucocorticoid-Induced Osteoporosis

14.5 Treatment of Paget's Disease

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

17.1 FDA-Approved Patient Labeling

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Postmenopausal Osteoporosis

ACTONEL is indicated for the treatment and prevention of osteoporosis in postmenopausal women. In postmenopausal women with osteoporosis, ACTONEL reduces the incidence of vertebral fractures and a composite endpoint of nonvertebral osteoporosis-related fractures [see *Clinical Studies (14.1, 14.2)*].

1.2 Osteoporosis in Men

ACTONEL is indicated for treatment to increase bone mass in men with osteoporosis.

1.3 Glucocorticoid-Induced Osteoporosis

ACTONEL is indicated for the treatment and prevention of glucocorticoid-induced osteoporosis in men and women who are either initiating or continuing systemic glucocorticoid treatment (daily dosage of \geq 7.5 mg prednisone or equivalent) for chronic diseases. Patients treated with glucocorticoids should receive adequate amounts of calcium and vitamin D.

1.4 Paget's Disease

ACTONEL is indicated for treatment of Paget's disease of bone in men and women.

2 DOSAGE AND ADMINISTRATION

ACTONEL should be taken at least 30 minutes before the first food or drink of the day other than water.

To facilitate delivery to the stomach, ACTONEL should be swallowed while the patient is in an upright position and with a full glass of plain water (6 to 8 oz). Patients should not lie down for 30 minutes after taking the medication [see *Warnings and Precautions (5.1)*].

Patients should receive supplemental calcium and vitamin D if dietary intake is inadequate [see *Warnings and Precautions (5.2)*]. Calcium supplements and calcium-, aluminum-, and magnesium-containing medications may interfere with the absorption of ACTONEL and should be taken at a different time of the day. ACTONEL is not recommended for use in patients with severe renal impairment (creatinine

clearance <30 mL/min). No dosage adjustment is necessary in patients with a creatinine clearance \geq 30 mL/min or in the elderly.

2.1 Treatment of Postmenopausal Osteoporosis

[see *Indications and Usage (1.1)*]

The recommended regimen is:

- one 5 mg tablet orally, taken daily

or

- one 35 mg tablet orally, taken once a week

or

- one 75 mg tablet orally, taken on two consecutive days for a total of two tablets each month

or

- one 150 mg tablet orally, taken once a month

2.2 Prevention of Postmenopausal Osteoporosis

[see *Indications and Usage (1.1)*]

The recommended regimen is:

- one 5 mg tablet orally, taken daily

or

- one 35 mg tablet orally, taken once a week

or

- alternatively, one 75 mg tablet orally, taken on two consecutive days for a total of two tablets each month may be considered

or

- alternatively, one 150 mg tablet orally, taken once a month may be considered

2.3 Treatment to Increase Bone Mass in Men with Osteoporosis

[see *Indications and Usage (1.2)*]

The recommended regimen is:

- one 35 mg tablet orally, taken once a week

2.4 Treatment and Prevention of Glucocorticoid-Induced Osteoporosis

[see *Indications and Usage (1.3)*]

The recommended regimen is:

- one 5 mg tablet orally, taken daily

2.5 Treatment of Paget's Disease

[see *Indications and Usage (1.4)*]

The recommended treatment regimen is 30 mg orally once daily for 2 months. Retreatment may be considered (following post-treatment observation of at least 2 months) if relapse occurs, or if treatment fails to normalize serum alkaline phosphatase. For retreatment, the dose and duration of therapy are the same as for initial treatment. No data are available on more than 1 course of retreatment.

3 DOSAGE FORMS AND STRENGTHS

- 5 mg film-coated, oval, yellow tablet with RSN on 1 face and 5 mg on the other.
- 30 mg film-coated, oval, white tablet with RSN on 1 face and 30 mg on the other.
- 35 mg film-coated, oval, orange tablet with RSN on 1 face and 35 mg on the other.
- 75 mg film-coated, oval, pink tablet with RSN on 1 face and 75 mg on the other.
- 150 mg film-coated, oval, blue tablet with RSN on 1 face and 150 mg on the other.

4 CONTRAINDICATIONS

- Abnormalities of the esophagus which delay esophageal emptying such as stricture or achalasia [see *Warnings and Precautions (5.1)*]
- Inability to stand or sit upright for at least 30 minutes [see *Dosage and Administration (2), Warnings and Precautions (5.1)*]
- Hypocalcemia [see *Warnings and Precautions (5.2)*]
- Known hypersensitivity to any component of this product [see *Adverse Reactions (6.2)*]

5 WARNINGS AND PRECAUTIONS

5.1 Upper Gastrointestinal Adverse Reactions

ACTONEL, like other bisphosphonates administered orally, may cause local irritation of the upper gastrointestinal mucosa. Because of these possible irritant effects and a potential for worsening of the underlying disease, caution should be used when ACTONEL is given to patients with active upper gastrointestinal problems (such as known Barrett's esophagus, dysphagia, other esophageal diseases, gastritis, duodenitis or ulcers) [see *Contraindications (4), Adverse Reactions (6.1), Information for Patients (17.1)*].

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

The risk of severe esophageal adverse experiences appears to be greater in patients who lie down after taking oral bisphosphonates and/or who fail to swallow it with the recommended full glass (6-8 oz) of water, and/or who continue to take oral bisphosphonates after developing symptoms suggestive of esophageal irritation. Therefore, it is very important that the full dosing instructions are provided to, and understood by, the patient [see *Dosage and Administration (2)*]. In patients who cannot comply with dosing instructions due to mental disability, therapy with ACTONEL should be used under appropriate supervision.

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

5.2 Mineral Metabolism

Hypocalcemia and other disturbances of bone and mineral metabolism should be effectively treated before starting ACTONEL therapy. Adequate intake of calcium and vitamin D is important in all patients, especially in patients with Paget's disease in whom bone turnover is significantly elevated [see *Contraindications (4), Adverse Reactions (6.1), Information for Patients (17.1)*].

5.3 Jaw Osteonecrosis

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

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

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

5.4 Musculoskeletal Pain

In postmarketing experience, there have been reports of severe and occasionally incapacitating bone, joint, and/or muscle pain in patients taking bisphosphonates [see *Adverse Reactions* (6.2)]. 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 medication. A subset had recurrence of symptoms when rechallenged with the same drug or another bisphosphonate. Consider discontinuing use if severe symptoms develop.

5.5 Renal Impairment

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

5.6 Glucocorticoid-Induced Osteoporosis

Before initiating ACTONEL treatment for the treatment and prevention of glucocorticoid-induced osteoporosis, the sex steroid hormonal status of both men and women should be ascertained and appropriate replacement considered.

5.7 Laboratory Test Interactions

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

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Treatment of Postmenopausal Osteoporosis

Daily Dosing

The safety of ACTONEL 5 mg once daily in the treatment of postmenopausal osteoporosis was assessed in four randomized, double-blind, placebo-controlled multinational trials of 3232 women aged 38 to 85 years with postmenopausal osteoporosis. The duration of the trials was up to three years, with 1619 patients exposed to placebo and 1613 patients exposed to ACTONEL 5 mg. Patients with pre-existing gastrointestinal disease and concomitant use of non-steroidal anti-inflammatory drugs, proton

pump inhibitors, and H₂ antagonists were included in these clinical trials. All women received 1000 mg of elemental calcium plus vitamin D supplementation up to 500 IU per day if their 25-hydroxyvitamin D₃ level was below normal at baseline.

The incidence of all-cause mortality was 2.0% in the placebo group and 1.7% in the ACTONEL 5 mg daily group. The incidence of serious adverse events was 24.6% in the placebo group and 27.2% in the ACTONEL 5 mg group. The percentage of patients who withdrew from the study due to adverse events was 15.6% in the placebo group and 14.8% in the ACTONEL 5 mg group. Table 1 lists adverse events from the Phase 3 postmenopausal osteoporosis trials reported in ≥5% of patients. Adverse events are shown without attribution of causality.

Table 1 Adverse Events Occurring at a Frequency ≥5% in Either Treatment Group Combined Phase 3 Postmenopausal Osteoporosis Treatment Trials

Body System	Placebo N = 1619 %	5 mg ACTONEL N = 1613 %
Body as a Whole		
Infection	29.9	31.1
Back Pain	26.1	28.0
Accidental Injury	16.8	16.9
Pain	14.0	14.1
Abdominal Pain	9.9	12.2
Flu Syndrome	11.6	10.5
Headache	10.8	9.9
Asthenia	4.5	5.4
Neck Pain	4.7	5.4
Chest Pain	5.1	5.0
Allergic Reaction	5.9	3.8
Cardiovascular System		
Hypertension	9.8	10.5
Digestive System		
Constipation	12.6	12.9
Diarrhea	10.0	10.8
Dyspepsia	10.6	10.8
Nausea	11.2	10.5
Metabolic & Nutritional Disorders		
Peripheral Edema	8.8	7.7
Musculoskeletal System		
Arthralgia	22.1	23.7
Arthritis	10.1	9.6
Traumatic Bone Fracture	12.3	9.3
Joint Disorder	5.3	7.0
Myalgia	6.2	6.7
Bone Pain	4.8	5.3
Nervous System		
Dizziness	5.7	7.1
Depression	6.1	6.8
Insomnia	4.6	5.0
Respiratory System		

Bronchitis	10.4	10.0
Sinusitis	9.1	8.7
Rhinitis	5.1	6.2
Pharyngitis	5.0	6.0
Increased Cough	6.3	5.9
Skin and Appendages		
Rash	7.1	7.9
Special Senses		
Cataract	5.7	6.5
Urogenital System		
Urinary Tract Infection	10.4	11.1

Gastrointestinal Adverse Events: The incidence of adverse events in the placebo and ACTONEL 5 mg daily groups were: abdominal pain (9.9% vs. 12.2%), diarrhea (10.0% vs. 10.8%), dyspepsia (10.6% vs. 10.8%), and gastritis (2.3% vs. 2.7%). Duodenitis and glossitis have been reported uncommonly in the ACTONEL 5 mg daily group (0.1% to 1%). In patients with active upper gastrointestinal disease at baseline, the incidence of upper gastrointestinal adverse events was similar between the placebo and ACTONEL 5 mg daily groups.

Musculoskeletal Adverse Events: The incidence of adverse events in the placebo and ACTONEL 5 mg daily groups were: back pain (26.1% vs. 28.0%), arthralgia (22.1% vs. 23.7%), myalgia (6.2% vs. 6.7%), and bone pain (4.8% vs. 5.3%).

Laboratory Test Findings: Throughout the Phase 3 studies, transient decreases from baseline in serum calcium (<1%) and serum phosphate (<3%) and compensatory increases in serum PTH levels (<30%) were observed within 6 months in patients in osteoporosis clinical trials treated with ACTONEL 5 mg once daily. There were no significant differences in serum calcium, phosphate, or PTH levels between placebo and ACTONEL 5 mg once daily at 3 years. Serum calcium levels below 8 mg/dL were observed in 18 patients, 9 (0.5%) in each treatment arm (placebo and ACTONEL 5 mg once daily). Serum phosphorus levels below 2 mg/dL were observed in 14 patients, 3 (0.2%) treated with placebo and 11 (0.6%) treated with ACTONEL 5 mg once daily. There have been rare reports (<0.1%) of abnormal liver function tests.

Endoscopic Findings: In the ACTONEL clinical trials, endoscopic evaluation was encouraged in any patient with moderate-to-severe gastrointestinal complaints, while maintaining the blind. Endoscopies were performed on equal numbers of patients between the placebo and treated groups [75 (14.5%) placebo; 75 (11.9%) ACTONEL]. Clinically important findings (perforations, ulcers, or bleeding) among this symptomatic population were similar between groups (51% placebo; 39% ACTONEL).

Once-a-Week Dosing

The safety of ACTONEL 35 mg once-a-week in the treatment of postmenopausal osteoporosis was assessed in a 1-year, double-blind, multicenter study comparing ACTONEL 5 mg daily and ACTONEL 35 mg once-a-week in postmenopausal women aged 50 to 95 years. The duration of the trials was one year, with 480 patients exposed to ACTONEL 5 mg daily and 485 exposed to ACTONEL 35 mg once-a-week. Patients with pre-existing gastrointestinal disease and concomitant use of non-steroidal anti-inflammatory drugs, proton pump inhibitors, and H₂ antagonists were included in these clinical trials. All women received 1000 mg of elemental calcium plus vitamin D supplementation up to 500 IU per day if their 25-hydroxyvitamin D₃ level was below normal at baseline.

The incidence of all-cause mortality was 0.4% in the ACTONEL 5 mg daily group and 1.0% in the ACTONEL 35 mg once-a-week group. The incidence of serious adverse events was 7.1% in the ACTONEL 5 mg daily group and 8.2% in the ACTONEL 35 mg once-a-week group. The percentage of patients who withdrew from the study due to adverse events was 11.9% in the ACTONEL 5 mg daily group and 11.5% in the ACTONEL 35 mg once-a-week group. The overall safety and tolerability

profiles of the two dosing regimens were similar.

Gastrointestinal Adverse Events: The incidence of gastrointestinal adverse events was similar between the ACTONEL 5 mg daily group and the ACTONEL 35 mg once-a-week group: dyspepsia (6.9% vs. 7.6%), diarrhea (6.3% vs. 4.9%), and abdominal pain (7.3% vs. 7.6%).

Musculoskeletal Adverse Events: Arthralgia was reported in 11.5% of patients in the ACTONEL 5 mg daily group and 14.2% of patients in the ACTONEL 35 mg once-a-week group. Myalgia was reported by 4.6% of patients in the ACTONEL 5 mg daily group and 6.2% of patients in the ACTONEL 35 mg once-a-week group.

Laboratory Test Findings: The mean percent changes from baseline at 12 months were similar between the ACTONEL 5 mg daily and ACTONEL 35 mg once-a-week groups, respectively, for serum calcium (0.4% vs. 0.7%), phosphate (-3.8% vs. -2.6%) and PTH (6.4% vs. 4.2%).

Monthly Dosing

Two Consecutive Days per Month

The safety of ACTONEL 75 mg administered on two consecutive days per month for the treatment of postmenopausal osteoporosis was assessed in a double-blind, multicenter study in postmenopausal women aged 50 to 86 years. The duration of the trial was two years; 613 patients were exposed to ACTONEL 5 mg daily and 616 were exposed to ACTONEL 75 mg two consecutive days per month. Patients with pre-existing gastrointestinal disease and concomitant use of non-steroidal anti-inflammatory drugs, proton pump inhibitors, and H₂ antagonists were included in this clinical trial. All women received 1000 mg of elemental calcium plus 400 to 800 IU of vitamin D supplementation per day.

The incidence of all-cause mortality was 1.0% for the ACTONEL 5 mg daily group and 0.5% for the ACTONEL 75 mg two consecutive days per month group. The incidence of serious adverse events was 10.8% in the ACTONEL 5 mg daily group and 14.4% in the ACTONEL 75 mg two consecutive days per month group. The percentage of patients who withdrew from treatment due to adverse events was 14.2% in the ACTONEL 5 mg daily group and 13.0% in the ACTONEL 75 mg two consecutive days per month group. The overall safety and tolerability profiles of the two dosing regimens were similar.

Acute Phase Reactions: Symptoms consistent with acute phase reaction have been reported with bisphosphonate use. The overall incidence of acute phase reaction was 3.6% of patients on ACTONEL 5 mg daily and 7.6% of patients on ACTONEL 75 mg two consecutive days per month. These incidence rates are based on reporting of any of 33 acute phase reaction-like symptoms within 5 days of the first dose. Fever or influenza-like illness with onset within the same period were reported by 0.0% of patients on ACTONEL 5 mg daily and 0.6% of patients on ACTONEL 75 mg two consecutive days per month.

Gastrointestinal Adverse Events: The ACTONEL 75 mg two consecutive days per month group resulted in a higher incidence of discontinuation due to vomiting (1.0% vs. 0.2%) and diarrhea (1.0% vs. 0.3%) compared to the ACTONEL 5 mg daily group. Most of these events occurred within a few days of dosing.

Ocular Adverse Events: None of the patients treated with ACTONEL 75 mg two consecutive days per month reported ocular inflammation such as uveitis, scleritis, or iritis; 1 patient treated with ACTONEL 5 mg daily reported uveitis.

Laboratory Test Findings: When ACTONEL 5 mg daily and ACTONEL 75 mg two consecutive days per month were compared in postmenopausal women with osteoporosis, the mean percent changes from baseline at 24 months were 0.2% and 0.8% for serum calcium, -1.9% and -1.3% for phosphate, and -10.4% and -17.2% for PTH, respectively. Compared to the ACTONEL 5 mg daily group, ACTONEL 75 mg two consecutive days per month resulted in a slightly higher incidence of hypocalcemia at the end of the first month of treatment (4.5% vs. 3.0%). Thereafter, the incidence of hypocalcemia with these regimens was similar at approximately 2%.

Once-a-Month

The safety of ACTONEL 150 mg administered once a month for the treatment of postmenopausal osteoporosis was assessed in a double-blind, multicenter study in postmenopausal women aged 50 to 88 years. The duration of the trial was one year, with 642 patients exposed to ACTONEL 5 mg daily and 650 exposed to ACTONEL 150 mg once-a-month. Patients with pre-existing gastrointestinal disease and concomitant use of non-steroidal anti-inflammatory drugs, proton pump inhibitors, and H₂ antagonists were included in this clinical trial. All women received 1000 mg of elemental calcium plus up to 1000 IU of vitamin D supplementation per day.

The incidence of all-cause mortality was 0.5% for the ACTONEL 5 mg daily group and 0.0% for the ACTONEL 150 mg once-a-month group. The incidence of serious adverse events was 4.2% in the ACTONEL 5 mg daily group and 6.2% in the ACTONEL 150 mg once-a-month group. The percentage of patients who withdrew from treatment due to adverse events was 9.5% in the ACTONEL 5 mg daily group and 8.6% in the ACTONEL 150 mg once-a-month group. The overall safety and tolerability profiles of the two dosing regimens were similar.

Acute Phase Reactions: Symptoms consistent with acute phase reaction have been reported with bisphosphonate use. The overall incidence of acute phase reaction was 1.1% in the ACTONEL 5 mg daily group and 5.2% in the ACTONEL 150 mg once-a-month group. These incidence rates are based on reporting of any of 33 acute phase reaction-like symptoms within 3 days of the first dose and for a duration of 7 days or less. Fever or influenza-like illness with onset within the same period were reported by 0.2% of patients on ACTONEL 5 mg daily and 1.4% of patients on ACTONEL 150 mg once-a-month.

Gastrointestinal Adverse Events: A greater percentage of patients experienced diarrhea with ACTONEL 150 mg once-a-month compared to 5 mg daily (8.2% vs. 4.7%, respectively). The ACTONEL 150 mg once-a-month group resulted in a higher incidence of discontinuation due to abdominal pain upper (2.5% vs. 1.4%) and diarrhea (0.8% vs. 0.0%) compared to the ACTONEL 5 mg daily regimen. All of these events occurred within a few days of the first dose. The incidence of vomiting that led to discontinuation was the same in both groups (0.3% vs. 0.3%).

Ocular Adverse Events: None of the patients treated with ACTONEL 150 mg once-a-month reported ocular inflammation such as uveitis, scleritis, or iritis; 2 patients treated with ACTONEL 5 mg daily reported iritis.

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

Prevention of Postmenopausal Osteoporosis

Daily Dosing

The safety of ACTONEL 5 mg daily in the prevention of postmenopausal osteoporosis was assessed in two randomized, double-blind, placebo-controlled trials. In one study of postmenopausal women aged 37 to 82 years without osteoporosis, the use of estrogen replacement therapy in both placebo- and ACTONEL-treated patients was included. The duration of the trial was one year, with 259 exposed to placebo and 261 patients exposed to ACTONEL 5 mg. The second study included postmenopausal women aged 44 to 63 years without osteoporosis. The duration of the trial was one year, with 125 exposed to placebo and 129 patients exposed to ACTONEL 5 mg. All women received 1000 mg of elemental calcium per day.

In the trial with estrogen replacement therapy, the incidence of all-cause mortality was 1.5% for the

placebo group and 0.4% for the ACTONEL 5 mg group. The incidence of serious adverse events was 8.9% in the placebo group and 5.4% in the ACTONEL 5 mg group. The percentage of patients who withdrew from treatment due to adverse events was 18.9% in the placebo group and 10.3% in the ACTONEL 5 mg group. Constipation was reported by 1.9% of the placebo group and 6.5% of ACTONEL 5 mg group.

In the second trial, the incidence of all-cause mortality was 0.0% for both groups. The incidence of serious adverse events was 17.6% in the placebo group and 9.3% in the ACTONEL 5 mg group. The percentage of patients who withdrew from treatment due to adverse events was 6.4% in the placebo group and 5.4% in the ACTONEL 5 mg group. Nausea was reported by 6.4% of patients in the placebo group and 13.2% of patients in the ACTONEL 5 mg group.

Once-a-Week Dosing

There were no deaths in a 1-year, double-blind, placebo-controlled study of ACTONEL 35 mg once a week for prevention of bone loss in 278 postmenopausal women without osteoporosis. More treated subjects on ACTONEL reported arthralgia (placebo 7.8%; ACTONEL 13.9%), myalgia (placebo 2.1%; ACTONEL 5.1%), and nausea (placebo 4.3%; ACTONEL 7.3%) than subjects on placebo.

Treatment to Increase Bone Mass in Men with Osteoporosis

In a 2-year, double-blind, multicenter study, 284 men with osteoporosis were treated with placebo (N = 93) or ACTONEL 35 mg once-a-week (N = 191). The overall safety and tolerability profile of ACTONEL in men with osteoporosis was similar to the adverse events reported in the ACTONEL postmenopausal osteoporosis clinical trials, with the addition of benign prostatic hyperplasia (placebo 3%; ACTONEL 35 mg 5%), nephrolithiasis (placebo 0%; ACTONEL 35 mg 3%), and arrhythmia (placebo 0%; ACTONEL 35 mg 2%).

Treatment and Prevention of Glucocorticoid-Induced Osteoporosis

The safety of ACTONEL 5 mg daily in the treatment and prevention of glucocorticoid-induced osteoporosis was assessed in two randomized, double-blind, placebo-controlled multinational trials of 344 patients [male (123) and female (221)] aged 18 to 85 years who had recently initiated oral glucocorticoid therapy (≤ 3 months, prevention study) or were on long-term oral glucocorticoid therapy (≥ 6 months, treatment study). The duration of the trials was one year, with 170 patients exposed to placebo and 174 patients exposed to ACTONEL 5 mg daily. Patients in one study received 1000 mg elemental calcium plus 400 IU of vitamin D supplementation per day; patients in the other study received 500 mg calcium supplementation per day.

The incidence of all-cause mortality was 2.9% in the placebo group and 1.1% in the ACTONEL 5 mg daily group. The incidence of serious adverse events was 33.5% in the placebo group and 30.5% in the ACTONEL 5 mg daily group. The percentage of patients who withdrew from the study due to adverse events was 8.8% in the placebo group and 7.5% in the ACTONEL 5 mg daily group. Back pain was reported in 8.8% of patients in the placebo group and 17.8% of patients in the ACTONEL 5 mg daily group. Arthralgia was reported in 14.7% of patients in the placebo group and 24.7% of patients in the ACTONEL 5 mg daily group.

Treatment of Paget's Disease

ACTONEL has been studied in 392 patients with Paget's disease of bone. As in trials of ACTONEL for other indications, the adverse experiences reported in the Paget's disease trials have generally been mild or moderate, have not required discontinuation of treatment, and have not appeared to be related to patient age, gender, or race.

The safety of ACTONEL was assessed in a randomized, double-blind, active-controlled study of 122 patients aged 34 to 85 years. The duration of the trial was 540 days, with 61 patients exposed to ACTONEL and 61 patients exposed to Didronel. The adverse event profile was similar for ACTONEL and Didronel: 6.6% (4/61) of patients treated with ACTONEL 30 mg daily for 2 months discontinued

treatment due to adverse events, compared to 8.2% (5/61) of patients treated with Didronel 400 mg daily for 6 months. Table 2 lists adverse events reported in $\geq 5\%$ of ACTONEL-treated patients in Phase 3 Paget's disease trials. Adverse events shown are considered to be possibly or probably causally related in at least one patient.

Table 2 Adverse Events Reported in $\geq 5\%$ of ACTONEL-Treated Patients* in Phase 3 Paget's Disease Trials

Body System	30 mg/day x 2 months ACTONEL % (N = 61)	400 mg/day x 6 months DIDRONEL % (N = 61)
Body as a Whole		
Flu Syndrome	9.8	1.6
Chest Pain	6.6	3.3
Gastrointestinal		
Diarrhea	19.7	14.8
Abdominal Pain	11.5	8.2
Nausea	9.8	9.8
Constipation	6.6	8.2
Metabolic and Nutritional Disorders		
Peripheral Edema	8.2	6.6
Musculoskeletal		
Arthralgia	32.8	29.5
Nervous		
Headache	18.0	16.4
Dizziness	6.6	4.9
Skin and Appendages		
Rash	11.5	8.2

*Considered to be possibly or probably causally related in at least one patient.

Gastrointestinal Adverse Events: During the first year of the study (treatment and nontreatment follow-up), the proportion of patients who reported upper gastrointestinal adverse events was similar between the treatment groups; no patients reported severe upper gastrointestinal adverse events. The incidence of diarrhea was 19.7% in the ACTONEL group and 14.8% in the Didronel group; none were serious or resulted in withdrawal.

Ocular Adverse Events: Three patients who received ACTONEL 30 mg daily experienced acute iritis in 1 supportive study. All 3 patients recovered from their events; however, in 1 of these patients, the event recurred during ACTONEL treatment and again during treatment with pamidronate. All patients were effectively treated with topical steroids.

6.2 Postmarketing Experience

Because these adverse reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Hypersensitivity Reactions

Hypersensitivity and skin reactions have been reported rarely, including angioedema, generalized rash and bullous skin reactions, some severe.

Gastrointestinal Adverse Events

Events involving upper gastrointestinal irritation, such as esophagitis and esophageal or gastric ulcers, have been reported [see *Warnings and Precautions (5.1)*].

Musculoskeletal Pain

Bone, joint, or muscle pain, described as severe or incapacitating, have been reported rarely [see *Warnings and Precautions (5.4)*].

Eye Inflammation

Reactions of eye inflammation including iritis and uveitis have been reported rarely.

Jaw Osteonecrosis

Osteonecrosis of the jaw has been reported rarely [see *Warnings and Precautions (5.3)*].

7 DRUG INTERACTIONS

No specific drug-drug interaction studies were performed. Risedronate is not metabolized and does not induce or inhibit hepatic microsomal drug-metabolizing enzymes (e.g. Cytochrome P450).

7.1 Calcium Supplements/Antacids

Co-administration of ACTONEL and calcium, antacids, or oral medications containing divalent cations will interfere with the absorption of ACTONEL.

7.2 Hormone Replacement Therapy

One study of about 500 early postmenopausal women has been conducted to date in which treatment with ACTONEL 5 mg daily plus estrogen replacement therapy was compared to estrogen replacement therapy alone. Exposure to study drugs was approximately 12 to 18 months and the primary endpoint was change in BMD. If considered appropriate, ACTONEL may be used concomitantly with hormone replacement therapy.

7.3 Aspirin/Nonsteroidal Anti-Inflammatory Drugs

Of over 5700 patients enrolled in the ACTONEL Phase 3 osteoporosis studies, aspirin use was reported by 31% of patients, 24% of whom were regular users (3 or more days per week). Forty-eight percent of patients reported NSAID use, 21% of whom were regular users. Among regular aspirin or NSAID users, the incidence of upper gastrointestinal adverse experiences in placebo-treated patients (24.8%) was similar to that in ACTONEL-treated patients (24.5%).

7.4 H₂ Blockers and Proton Pump Inhibitors (PPIs)

Of over 5700 patients enrolled in the ACTONEL Phase 3 osteoporosis studies, 21% used H₂ blockers and/or PPIs. Among these patients, the incidence of upper gastrointestinal adverse experiences in the placebo-treated patients was similar to that in ACTONEL-treated patients.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C: There are no adequate and well-controlled studies of ACTONEL in pregnant women. ACTONEL should be used during pregnancy only if the potential benefit justifies the potential risk to the mother and fetus.

Bisphosphonates are incorporated into the bone matrix, from which they are gradually released over periods of weeks to years. The amount of bisphosphonate incorporation into adult bone, and hence, the amount available for release back into the systemic circulation, is directly related to the dose and duration of bisphosphonate use. There are no data on fetal risk in humans. However, there is a

theoretical risk of fetal harm, predominantly skeletal, if a woman becomes pregnant after completing a course of bisphosphonate therapy. The impact of variables such as time between cessation of bisphosphonate therapy to conception, the particular bisphosphonate used, and the route of administration (intravenous versus oral) on this risk has not been studied.

In animal studies, pregnant rats received risedronate sodium during organogenesis at doses 1 to 26 times the human dose of 30 mg/day. Survival of neonates was decreased in rats treated during gestation with oral doses approximately 5 times the human dose and body weight was decreased in neonates from dams treated with approximately 26 times the human dose. The number of fetuses exhibiting incomplete ossification of sternebrae or skull from dams treated with approximately 2.5 times the human dose was significantly increased compared to controls. Both incomplete ossification and unossified sternebrae were increased in rats treated with oral doses approximately 5 times the human dose. A low incidence of cleft palate was observed in fetuses from female rats treated with oral doses approximately equal to the human dose. The relevance of this finding to human use of ACTONEL is unclear.

No significant fetal ossification effects were seen in rabbits treated with oral doses approximately 7 times the human dose (the highest dose tested). However, 1 of 14 litters were aborted and 1 of 14 litters were delivered prematurely.

Similar to other bisphosphonates, treatment during mating and gestation with doses of risedronate sodium approximately the same as the 30 mg/day human dose resulted in periparturient hypocalcemia and mortality in pregnant rats allowed to deliver.

Dosing multiples provided above are based on the recommended human dose of 30 mg/day and normalized using body surface area (mg/m^2). Actual animal doses were 3.2, 7.1 and 16 mg/kg/day in the rat and 10 mg/kg/day in the rabbit.

8.3 Nursing Mothers

Risedronate was detected in feeding pups exposed to lactating rats for a 24-hour period post-dosing, indicating a small degree of lacteal transfer. It is not known whether ACTONEL is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from ACTONEL, 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.

8.4 Pediatric Use

ACTONEL is not indicated for use in pediatric patients.

The safety and effectiveness of risedronate was assessed in a one-year, randomized, double-blind, placebo controlled study of 143 pediatric patients (94 received risedronate) with osteogenesis imperfecta (OI). The enrolled population was predominantly patients with mild osteogenesis imperfecta (85% Type-I), aged 4 to <16 years, 50% male and 82% Caucasian, with a mean lumbar spine BMD Z-score of -2.08 (2.08 standard deviations below the mean for age-matched controls). Patients received either a 2.5 mg (≤ 30 kg body weight) or 5 mg (> 30 kg body weight) daily oral dose. After one year, an increase in lumbar spine BMD in the risedronate group compared to the placebo group was observed. However, treatment with risedronate did not result in a reduction in the risk of fracture in pediatric patients with osteogenesis imperfecta. In ACTONEL-treated subjects, no mineralization defects were noted in paired bone biopsy specimens obtained at baseline and month 12.

The overall safety profile of risedronate in OI patients treated for up to 12 months was generally similar to that of adults with osteoporosis. However, there was an increased incidence of vomiting compared to placebo. In this study, vomiting was observed in 15% of children treated with risedronate and 6% of patients treated with placebo. Other adverse events reported in $\geq 10\%$ of patients treated with risedronate and with a higher frequency than placebo were: pain in the extremity (21% with risedronate versus 16% with placebo), headache (20% versus 8%), back pain (17% versus 10%), pain (15% versus 10%), upper abdominal pain (11% versus 8%), and bone pain (10% versus 4%).

8.5 Geriatric Use

Of the patients receiving ACTONEL in postmenopausal osteoporosis studies [*see Clinical Studies (14)*], 47% were between 65 and 75 years of age, and 17% were over 75. The corresponding proportions were 26% and 11% in glucocorticoid-induced osteoporosis trials, and 40% and 26% in Paget's disease trials. No overall differences in efficacy between geriatric and younger patients were observed in these studies. In the male osteoporosis trial, 28% of patients receiving ACTONEL were between 65 and 75 years of age and 9% were over 75. The lumbar spine BMD response for ACTONEL compared to placebo was 5.6% for subjects <65 years and 2.9% for subjects ≥65 years. No overall differences in safety between geriatric and younger patients were observed in the ACTONEL trials, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Renal Impairment

ACTONEL is not recommended for use in patients with severe renal impairment (creatinine clearance <30 mL/min) because of lack of clinical experience. No dosage adjustment is necessary in patients with a creatinine clearance ≥30 mL/min.

8.7 Hepatic Impairment

No studies have been performed to assess risedronate's safety or efficacy in patients with hepatic impairment. Risedronate is not metabolized in human liver preparations. Dosage adjustment is unlikely to be needed in patients with hepatic impairment.

10 OVERDOSAGE

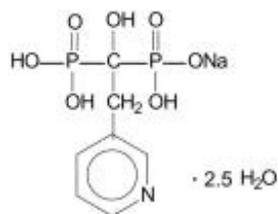
Decreases in serum calcium and phosphorus following substantial overdose may be expected in some patients. Signs and symptoms of hypocalcemia may also occur in some of these patients. Milk or antacids containing calcium should be given to bind ACTONEL and reduce absorption of the drug.

In cases of substantial overdose, gastric lavage may be considered to remove unabsorbed drug. 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.

Lethality after single oral doses was seen in female rats at 903 mg/kg and male rats at 1703 mg/kg. The minimum lethal dose in mice and rabbits was 4000 mg/kg and 1000 mg/kg, respectively. These values represent 320 to 620 times the 30 mg human dose based on surface area (mg/m²).

11 DESCRIPTION

ACTONEL (risedronate sodium) tablets is a pyridinyl bisphosphonate that inhibits osteoclast-mediated bone resorption and modulates bone metabolism. Each ACTONEL tablet for oral administration contains the equivalent of 5, 30, 35, 75, or 150 mg of anhydrous risedronate sodium in the form of the hemipentahydrate with small amounts of monohydrate. The empirical formula for risedronate sodium hemipentahydrate is C₇H₁₀NO₇P₂Na • 2.5 H₂O. The chemical name of risedronate sodium is [1-hydroxy-2-(3-pyridinyl)ethylidene]bis[phosphonic acid] monosodium salt. The chemical structure of risedronate sodium hemipentahydrate is the following:



Molecular Weight:
 Anhydrous: 305.10
 Hemi-pentahydrate: 350.13

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

Inactive Ingredients

All dose strengths contain: crospovidone, hydroxypropyl cellulose, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, silicon dioxide, titanium dioxide.

Dose strength-specific ingredients include: 5 mg—ferric oxide yellow, lactose monohydrate; 30 mg—lactose monohydrate; 35 mg—ferric oxide red, ferric oxide yellow, lactose monohydrate; 75 mg—ferric oxide red; 150 mg—FD&C blue #2 aluminum lake.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

ACTONEL has an affinity for hydroxyapatite crystals in bone and acts as an antiresorptive agent. At the cellular level, ACTONEL 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, and minipigs showed that ACTONEL treatment reduces bone turnover (activation frequency, i.e., the rate at which bone remodeling sites are activated) and bone resorption at remodeling sites.

12.2 Pharmacodynamics

ACTONEL treatment decreases the elevated rate of bone turnover that is typically seen in postmenopausal osteoporosis. In clinical trials, administration of ACTONEL to postmenopausal women resulted in decreases in biochemical markers of bone turnover, including urinary deoxypyridinoline/creatinine and urinary collagen cross-linked N-telopeptide (markers of bone resorption) and serum bone-specific alkaline phosphatase (a marker of bone formation). At the 5 mg dose, decreases in deoxypyridinoline/creatinine were evident within 14 days of treatment. Changes in bone formation markers were observed later than changes in resorption markers, as expected, due to the coupled nature of bone resorption and bone formation; decreases in bone-specific alkaline phosphatase of about 20% were evident within 3 months of treatment. Bone turnover markers 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. Bone turnover is decreased as early as 14 days and maximally within about 6 months of treatment, with achievement of a new steady-state that more nearly approximates the rate of bone turnover seen in premenopausal women. In a 1-year study comparing daily versus weekly oral dosing regimens of ACTONEL for the treatment of osteoporosis in postmenopausal women, ACTONEL 5 mg daily and ACTONEL 35 mg once-a-week decreased urinary collagen cross-linked N-telopeptide by 60% and 61%, respectively. In addition, serum bone-specific alkaline phosphatase was also reduced by 42% and 41% in the ACTONEL 5 mg daily and ACTONEL 35 mg once-a-week groups, respectively. When postmenopausal women with osteoporosis were treated for 1 year with ACTONEL 5 mg daily or ACTONEL 75 mg two consecutive days per month, urinary collagen cross-linked N-telopeptide was decreased by 54% and 52%, respectively, and serum bone-specific alkaline phosphatase was reduced by 36% and 35%, respectively. In a 1-year study comparing ACTONEL 5 mg

daily versus ACTONEL 150 mg once a month in women with postmenopausal osteoporosis, urinary collagen cross-linked N-telopeptide was decreased by 52% and 49%, respectively, and serum bone-specific alkaline phosphatase was reduced by 31% and 32%, respectively.

Osteoporosis in Men

In a 2-year study of men with osteoporosis, treatment with ACTONEL 35 mg once-a-week resulted in a mean decrease from baseline compared to placebo of 16% (placebo 20%; ACTONEL 35 mg 37%) for the bone resorption marker urinary collagen cross-linked N-telopeptide, 45% (placebo -6%; ACTONEL 35 mg 39%) for the bone resorption marker serum C-telopeptide, and 27% (placebo -2%; ACTONEL 35 mg 25%) for the bone formation marker serum bone-specific alkaline phosphatase.

Glucocorticoid-Induced Osteoporosis

Osteoporosis with glucocorticoid use occurs as a result of inhibited bone formation and increased bone resorption resulting in net bone loss. ACTONEL decreases bone resorption without directly inhibiting bone formation.

In two 1-year clinical trials in the treatment and prevention of glucocorticoid-induced osteoporosis, ACTONEL 5 mg decreased urinary collagen cross-linked N-telopeptide (a marker of bone resorption), and serum bone-specific alkaline phosphatase (a marker of bone formation) by 50% to 55% and 25% to 30%, respectively, within 3 to 6 months after initiation of therapy.

Paget's Disease

Paget's disease of bone is a chronic, focal skeletal disorder characterized by greatly increased and disordered bone remodeling. Excessive osteoclastic bone resorption is followed by osteoblastic new bone formation, leading to the replacement of the normal bone architecture by disorganized, enlarged, and weakened bone structure.

In pagetic patients treated with ACTONEL 30 mg daily for 2 months, bone turnover returned to normal in a majority of patients as evidenced by significant reductions in serum alkaline phosphatase (a marker of bone formation), and in urinary hydroxyproline/creatinine and deoxypyridinoline/creatinine (markers of bone resorption).

12.3 Pharmacokinetics

Absorption

Based on simultaneous modeling of serum and urine data, peak absorption after an oral dose is achieved at ~ 1 hour (T_{max}) and occurs throughout the upper gastrointestinal tract. The fraction of the dose absorbed is independent of dose over the range studied (single dose, from 2.5 mg to 30 mg; multiple dose, from 2.5 mg to 5 mg). Steady-state conditions in the serum are observed within 57 days of daily dosing. Mean absolute oral bioavailability of the 30 mg tablet is 0.63% (90% CI: 0.54% to 0.75%) and is comparable to a solution.

Food Effect

The extent of absorption of a 30 mg dose (three 10 mg tablets) when administered 0.5 hours before breakfast is reduced by 55% compared to dosing in the fasting state (no food or drink for 10 hours prior to or 4 hours after dosing). Dosing 1 hour prior to breakfast reduces the extent of absorption by 30% compared to dosing in the fasting state. Dosing either 0.5 hours prior to breakfast or 2 hours after dinner (evening meal) results in a similar extent of absorption. ACTONEL is effective when administered at least 30 minutes before breakfast.

Distribution

The mean steady-state volume of distribution for risedronate is 13.8 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 [¹⁴C] 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 in the range of 0.001% to 0.01%.

Metabolism

There is no evidence of systemic metabolism of risedronate.

Excretion

In young healthy subjects, approximately half of the absorbed dose of risedronate was excreted in urine within 24 hours, and 85% of an intravenous dose was recovered in the urine over 28 days. Based on simultaneous modeling of serum and urine data, mean renal clearance was 105 mL/min (CV = 34%) and mean total clearance was 122 mL/min (CV = 19%), with the difference primarily reflecting nonrenal 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. In osteopenic postmenopausal women, the terminal exponential half-life was 561 hours, mean renal clearance was 52 mL/min (CV=25%), and mean total clearance was 73 mL/min (CV=15%).

Specific Populations

Pediatric: ACTONEL is not indicated for use in pediatric patients (see *Pediatric Use [8.4]*).

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

Geriatric: Bioavailability and disposition are similar in elderly (>60 years of age) and younger subjects. No dosage adjustment is necessary.

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

Renal Impairment: Risedronate is excreted unchanged primarily via the kidney. As compared to persons with normal renal function, the renal clearance of risedronate was decreased by about 70% in patients with creatinine clearance of approximately 30 mL/min. ACTONEL is not recommended for use in patients with severe renal impairment (creatinine clearance <30 mL/min) because of lack of clinical experience. No dosage adjustment is necessary in patients with a creatinine clearance \geq 30 mL/min.

Hepatic Impairment: 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.

Drug Interactions: No specific drug-drug interaction studies were performed. Risedronate is not metabolized and does not induce or inhibit hepatic microsomal drug-metabolizing enzymes (Cytochrome P450) [see *Drug Interactions (7)*].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

In a 104-week carcinogenicity study, rats were administered daily oral doses up to approximately 8 times the maximum recommended human daily dose. There were no significant drug-induced tumor findings in male or female rats. The high dose male group was terminated early in the study (Week 93) due to excessive toxicity, and data from this group were not included in the statistical evaluation of the study results. In an 80-week carcinogenicity study, mice were administered daily oral doses approximately 6.5 times the human dose. There were no significant drug-induced tumor findings in male or female mice.

Mutagenesis

Risedronate did not exhibit genetic toxicity in the following assays: *In vitro* bacterial mutagenesis in *Salmonella* and *E. coli* (Ames assay), mammalian cell mutagenesis in CHO/HGPRT assay, unscheduled DNA synthesis in rat hepatocytes and an assessment of chromosomal aberrations *in vivo* in rat bone marrow. Risedronate was positive in a chromosomal aberration assay in CHO cells at highly cytotoxic concentrations (>675 mcg/mL, survival of 6% to 7%). When the assay was repeated at doses exhibiting appropriate cell survival (29%), there was no evidence of chromosomal damage.

Impairment of Fertility

In female rats, ovulation was inhibited at an oral dose approximately 5 times the human dose. Decreased implantation was noted in female rats treated with doses approximately 2.5 times the human dose. In male rats, testicular and epididymal atrophy and inflammation were noted at approximately 13 times the human dose. Testicular atrophy was also noted in male rats after 13 weeks of treatment at oral doses approximately 5 times the human dose. There was moderate-to-severe spermatid maturation block after 13 weeks in male dogs at an oral dose approximately 8 times the human dose. These findings tended to increase in severity with increased dose and exposure time.

Dosing multiples provided above are based on the recommended human dose of 30 mg/day and normalized using body surface area (mg/m²). Actual doses were 24 mg/kg/day in rats, 32 mg/kg/day in mice, and 8, 16 and 40 mg/kg/day in dogs.

13.2 Animal Toxicology and/or Pharmacology

Risedronate demonstrated potent anti-osteoclast, antiresorptive activity in ovariectomized rats and minipigs. Bone mass and biomechanical strength were increased dose-dependently at daily oral doses up to 4 and 25 times the human recommended oral dose of 5 mg for rats and minipigs, respectively. Risedronate treatment maintained the positive correlation between BMD and bone strength and did not have a negative effect on bone structure or mineralization. In intact dogs, risedronate induced positive bone balance at the level of the bone remodeling unit at oral doses ranging from 0.5 to 1.5 times the 5 mg/day human daily dose.

In dogs treated with an oral dose approximately 5 times the human daily dose, risedronate caused a delay in fracture healing of the radius. The observed delay in fracture healing is similar to other bisphosphonates. This effect did not occur at a dose approximately 0.5 times the human daily dose.

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, which was approximately 3500 times the lowest antiresorptive dose in this model (1.5 mcg/kg/day) and approximately 800 times the human daily dose of 5 mg. This indicates that ACTONEL administered at the therapeutic dose is unlikely to induce osteomalacia.

Dosing multiples provided above are based on the recommended human dose of 5 mg/day and normalized using body surface area (mg/m²).

14 CLINICAL STUDIES

14.1 Treatment of Osteoporosis in Postmenopausal Women

The fracture efficacy of ACTONEL 5 mg daily in the treatment of postmenopausal osteoporosis was demonstrated in 2 large, randomized, placebo-controlled, double-blind studies that enrolled a total of almost 4000 postmenopausal women under similar protocols. The Multinational study (VERT MN) (ACTONEL 5 mg, N = 408) was conducted primarily in Europe and Australia; a second study was conducted in North America (VERT NA) (ACTONEL 5 mg, N = 821). Patients were selected on the basis of radiographic evidence of previous vertebral fracture, and therefore, had established disease. The average number of prevalent vertebral fractures per patient at study entry was 4 in VERT MN, and 2.5 in VERT NA, with a broad range of baseline BMD levels. All patients in these studies received supplemental calcium 1000 mg/day. Patients with low 25-hydroxyvitamin D₃ levels (approximately 40

nmol/L or less) also received supplemental vitamin D 500 IU/day.

Effect on Vertebral Fractures

Fractures of previously undeformed vertebrae (new fractures) and worsening of pre-existing vertebral fractures were diagnosed radiographically; some of these fractures were also associated with symptoms (i.e., clinical fractures). Spinal radiographs were scheduled annually and prospectively planned analyses were based on the time to a patient's first diagnosed fracture. The primary endpoint for these studies was the incidence of new and worsening vertebral fractures across the period of 0 to 3 years. ACTONEL 5 mg daily significantly reduced the incidence of new and worsening vertebral fractures and of new vertebral fractures in both VERT NA and VERT MN at all time points (Table 3). The reduction in risk seen in the subgroup of patients who had 2 or more vertebral fractures at study entry was similar to that seen in the overall study population.

Table 3 The Effect of ACTONEL on the Risk of Vertebral Fractures

	Proportion of Patients with Fracture (%) ^a		Absolute Risk Reduction (%)	Relative Risk Reduction (%)
	Placebo N = 678	ACTONEL 5 mg N = 696		
VERT NA				
New and Worsening				
0 - 1 Year	7.2	3.9	3.3	49
0 - 2 Years	12.8	8.0	4.8	42
0 - 3 Years	18.5	13.9	4.6	33
New				
0 - 1 Year	6.4	2.4	4.0	65
0 - 2 Years	11.7	5.8	5.9	55
0 - 3 Years	16.3	11.3	5.0	41
VERT MN				
	Placebo N = 346	ACTONEL 5 mg N = 344	Absolute Risk Reduction (%)	Relative Risk Reduction (%)
New and Worsening				
0 - 1 Year	15.3	8.2	7.1	50
0 - 2 Years	28.3	13.9	14.4	56
0 - 3 Years	34.0	21.8	12.2	46
New				
0 - 1 Year	13.3	5.6	7.7	61
0 - 2 Years	24.7	11.6	13.1	59
0 - 3 Years	29.0	18.1	10.9	49

^a Calculated by Kaplan-Meier methodology.

Effect on Osteoporosis-Related Nonvertebral Fractures

In VERT MN and VERT NA, a prospectively planned efficacy endpoint was defined consisting of all radiographically confirmed fractures of skeletal sites accepted as associated with osteoporosis. Fractures at these sites were collectively referred to as osteoporosis-related nonvertebral fractures. ACTONEL 5 mg daily significantly reduced the incidence of nonvertebral osteoporosis-related fractures over 3 years in VERT NA (8% vs. 5%; relative risk reduction 39%) and reduced the fracture incidence in VERT MN from 16% to 11%. There was a significant reduction from 11% to 7% when the

studies were combined, with a corresponding 36% reduction in relative risk. Figure 1 shows the overall results as well as the results at the individual skeletal sites for the combined studies.

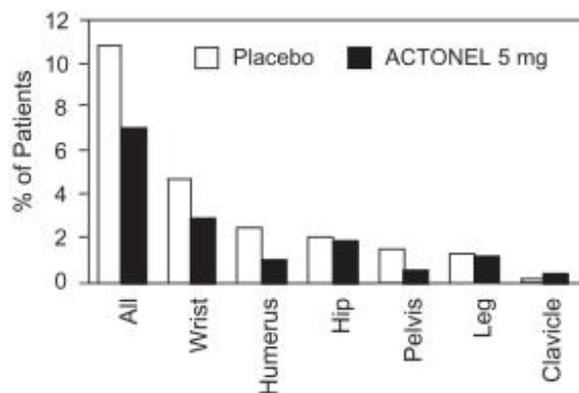


Figure 1 Nonvertebral Osteoporosis-Related Fractures Cumulative Incidence Over 3 Years Combined VERT MN and VERT NA

Effect on Bone Mineral Density

The results of 4 randomized, placebo-controlled trials in women with postmenopausal osteoporosis (VERT MN, VERT NA, BMD MN, BMD NA) demonstrate that ACTONEL 5 mg daily increases BMD at the spine, hip, and wrist compared to the effects seen with placebo. Table 4 displays the significant increases in BMD seen at the lumbar spine, femoral neck, femoral trochanter, and midshaft radius in these trials compared to placebo. Thus, overall ACTONEL reverses the loss of BMD, a central factor in the progression of osteoporosis. In both VERT studies (VERT MN and VERT NA), ACTONEL 5 mg daily produced increases in lumbar spine BMD that were progressive over the 3 years of treatment, and were statistically significant relative to baseline and to placebo at 6 months and at all later time points.

Table 4 Mean Percent Increase in BMD from Baseline in Patients Taking ACTONEL 5 mg or Placebo at Endpoint^a

	VERT MN ^b		VERT NA ^b		BMD MN ^c		BMD NA ^c	
	Placebo N = 323	5 mg N = 323	Placebo N = 599	5 mg N = 606	Placebo N = 161	5 mg N = 148	Placebo N = 191	5 mg N = 193
Lumbar Spine	1.0	6.6	0.8	5.0	0.0	4.0	0.2	4.8
Femoral Neck	-1.4	1.6	-1.0	1.4	-1.1	1.3	0.1	2.4
Femoral Trochanter	-1.9	3.9	-0.5	3.0	-0.6	2.5	1.3	4.0
Midshaft Radius	-1.5*	0.2*	-1.2*	0.1*	ND		ND	

^a The endpoint value is the value at the study's last time point for all patients who had BMD measured at that time; otherwise the last post-baseline BMD value prior to the study's last time point is used.

^b The duration of the studies was 3 years.

^c The duration of the studies was 1.5 to 2 years.

* BMD of the midshaft radius was measured in a subset of centers in VERT MN (placebo, N = 222; 5 mg, N = 214) and VERT NA (placebo, N = 310; 5 mg, N = 306).

ND = analysis not done

ACTONEL 35 mg once-a-week (N = 485) was shown to be non-inferior to ACTONEL 5 mg daily (N = 480) in a 1-year, double-blind, multicenter 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% confidence interval [CI]) in the 5 mg daily group (N = 391) and 3.9% (3.6, 4.3; 95% CI) in the 35 mg once-a-week group (N = 387) and the mean difference between 5 mg

daily and 35 mg once-a-week was 0.1% (-0.4, 0.6; 95% CI). The results of the intent-to-treat analysis with the last observation carried forward were consistent with the primary efficacy analysis of completers. The 2 treatment groups were also similar with regard to BMD increases at other skeletal sites.

In a double-blind, multicenter study of postmenopausal women with osteoporosis, treatment with ACTONEL 75 mg two consecutive days per month (N = 616) was shown to be non-inferior to ACTONEL 5 mg daily (N = 613). In the primary efficacy analysis of completers, the mean increases from baseline in lumbar spine BMD at 1 year were 3.6% (3.3, 3.9; 95% CI) in the 5 mg daily group (N = 527) and 3.4% (3.1, 3.7; 95% CI) in the 75 mg two days per month group (N = 524) with a mean difference between groups being 0.2% (-0.2, 0.6; 95% CI). The results of the intent-to-treat analysis with the last observation carried forward were consistent with the primary efficacy analysis of completers. The 2 treatment groups were also similar with regard to BMD increases at other skeletal sites.

ACTONEL 150 mg once-a-month (N = 650) was shown to be non-inferior to ACTONEL 5 mg daily (N = 642) in a 1-year, double-blind, multicenter study of postmenopausal women with osteoporosis. The primary efficacy analysis was conducted in all randomized patients with baseline and post-baseline lumbar spine BMD values (modified intent-to-treat population) using last observation carried forward. The mean increases from baseline in lumbar spine BMD at 1 year were 3.4% (3.0, 3.8; 95% CI) in the 5 mg daily group (N = 561), and 3.5% (3.1, 3.9; 95% CI) in the 150 mg once-a-month group (N = 578) with a mean difference between groups being -0.1% (-0.5, 0.3; 95% CI). The results of the completers analysis were consistent with the primary efficacy analysis. The 2 treatment groups were also similar with regard to BMD increases at other skeletal sites.

Histology/Histomorphometry

Bone biopsies from 110 postmenopausal women were obtained at endpoint. Patients had received placebo or daily ACTONEL (2.5 mg or 5 mg) for 2 to 3 years. Histologic evaluation (N = 103) showed no osteomalacia, impaired bone mineralization, or other adverse effects on bone in ACTONEL-treated women. These findings demonstrate that bone formed during ACTONEL administration is of normal quality. The histomorphometric parameter mineralizing surface, an index of bone turnover, was assessed based upon baseline and post-treatment biopsy samples from 21 treated with placebo and 23 patients treated with ACTONEL 5 mg. Mineralizing surface decreased moderately in ACTONEL-treated patients (median percent change: placebo, -21%; ACTONEL 5 mg, -74%), consistent with the known effects of treatment on bone turnover.

Effect on Height

In the two 3-year osteoporosis treatment studies, standing height was measured yearly by stadiometer. Both ACTONEL and placebo-treated groups lost height during the studies. Patients who received ACTONEL had a statistically significantly smaller loss of height than those who received placebo. In VERT MN, the median annual height change was -2.4 mm/yr in the placebo group compared to -1.3 mm/yr in the ACTONEL 5 mg daily group. In VERT NA, the median annual height change was -1.1 mm/yr in the placebo group compared to -0.7 mm/yr in the ACTONEL 5 mg daily group.

14.2 Prevention of Osteoporosis in Postmenopausal Women

ACTONEL 5 mg daily prevented bone loss in a majority of postmenopausal women (age range 42 to 63 years) within 3 years of menopause in a 2-year, double-blind, placebo-controlled study in 383 patients (ACTONEL 5 mg, N = 129). All patients in this study received supplemental calcium 1000 mg/day. Increases in BMD were observed as early as 3 months following initiation of ACTONEL treatment. ACTONEL 5 mg daily produced significant mean increases in BMD at the lumbar spine, femoral neck, and trochanter compared to placebo at the end of the study (Figure 2). ACTONEL 5 mg daily was also effective in patients with lower baseline lumbar spine BMD (more than 1 SD below the premenopausal mean) and in those with normal baseline lumbar spine BMD. Bone mineral density at the distal radius decreased in both ACTONEL and placebo-treated women following 1 year of treatment.

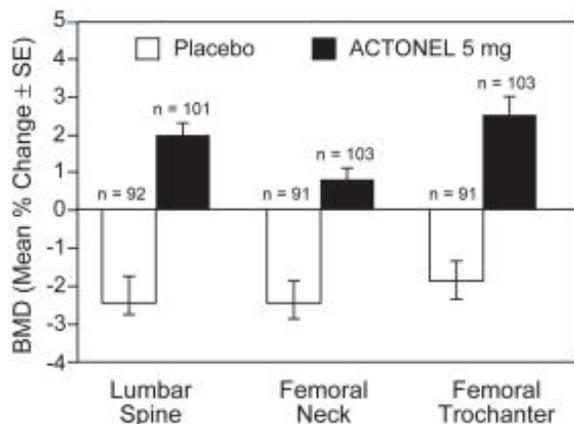


Figure 2 Change in BMD from Baseline 2-Year Prevention Study

ACTONEL 35 mg once-a-week prevented bone loss in postmenopausal women (age range 44 to 64 years) without osteoporosis in a 1-year, double-blind, placebo-controlled study in 278 patients (ACTONEL 35 mg, N = 136). All patients were supplemented with 1000 mg elemental calcium and 400 IU vitamin D per day. The primary efficacy measure was the percent change in lumbar spine BMD from baseline after 1 year of treatment using LOCF (last observation carried forward). ACTONEL 35 mg once-a-week resulted in a statistically significant mean difference from placebo in lumbar spine BMD of +2.9% (least square mean for placebo -1.05%; risedronate +1.83%). ACTONEL 35 mg once-a-week also showed a statistically significant mean difference from placebo in BMD at the total proximal femur of +1.5% (placebo -0.53%; risedronate +1.01%), femoral neck of +1.2% (placebo -1.00%; risedronate +0.22%), and trochanter of +1.8% (placebo -0.74%; risedronate +1.07%).

Combined Administration with Hormone Replacement Therapy

The effects of combining ACTONEL 5 mg daily with conjugated estrogen 0.625 mg daily (N = 263) were compared to the effects of conjugated estrogen alone (N = 261) in a 1-year, randomized, double-blind study of women ages 37 to 82 years, who were on average 14 years postmenopausal. The BMD results for this study are presented in Table 5.

Table 5 Percent Change from Baseline in BMD After 1 Year of Treatment

	Estrogen 0.625 mg N = 261	ACTONEL 5 mg + Estrogen 0.625 mg N = 263
Lumbar Spine	4.6 ± 0.20	5.2 ± 0.23
Femoral Neck	1.8 ± 0.25	2.7 ± 0.25
Femoral Trochanter	3.2 ± 0.28	3.7 ± 0.25
Midshaft Radius	0.4 ± 0.14	0.7 ± 0.17
Distal Radius	1.7 ± 0.24	1.6 ± 0.28

Values shown are mean (±SEM) percent change from baseline.

Histology/Histomorphometry

Bone biopsies from 53 postmenopausal women were obtained at endpoint. Patients had received ACTONEL 5 mg plus estrogen or estrogen alone once daily for 1 year. Histologic evaluation (N = 47) demonstrated that the bone of patients treated with ACTONEL plus estrogen was of normal lamellar structure and normal mineralization. The histomorphometric parameter mineralizing surface, a measure of bone turnover, was assessed based upon baseline and post-treatment biopsy samples from 12 patients treated with ACTONEL plus estrogen and 12 treated with estrogen alone. Mineralizing surface

decreased in both treatment groups (median percent change: ACTONEL plus estrogen, -79%; estrogen alone, -50%), consistent with the known effects of these agents on bone turnover.

14.3 Men with Osteoporosis

The effects of ACTONEL 35 mg once-a-week on BMD were examined in a 2-year, double-blind, placebo-controlled, multinational study in 285 men with osteoporosis (ACTONEL, N = 192). The patients had a mean age of 60.6 years (range 36 to 84 years) and 95% were Caucasian. At baseline, mean lumbar spine T-score was -3.2 and mean femoral neck T-score was -2.4. All patients in the study had either, 1) a BMD T-score ≤ -2 at the femoral neck and ≤ -1 at the lumbar spine, or 2) a BMD T-score ≤ -1 at the femoral neck and ≤ -2.5 at the lumbar spine. All patients were supplemented with calcium 1000 mg/day and vitamin D 400 to 500 IU/day. ACTONEL 35 mg once-a-week produced significant mean increases in BMD at the lumbar spine, femoral neck, trochanter, and total hip compared to placebo after 2 years of treatment (treatment difference: lumbar spine, 4.5%; femoral neck, 1.1%; trochanter, 2.2%; total proximal femur, 1.5%).

14.4 Glucocorticoid-Induced Osteoporosis

Bone Mineral Density

Two 1-year, double-blind, placebo-controlled trials in patients who were taking ≥ 7.5 mg/day of prednisone or equivalent demonstrated that ACTONEL 5 mg daily was effective in the prevention and treatment of glucocorticoid-induced osteoporosis in men and women who were either initiating or continuing glucocorticoid therapy. The efficacy of ACTONEL therapy for glucocorticoid-induced osteoporosis beyond one year has not been studied.

The prevention study enrolled 228 patients (ACTONEL 5 mg, N = 76) (18 to 85 years of age), each of whom had initiated glucocorticoid therapy (mean daily dose of prednisone 21 mg) within the previous 3 months (mean duration of use prior to study 1.8 months) for rheumatic, skin, and pulmonary diseases. The mean lumbar spine BMD was normal at baseline (average T-score -0.7). All patients in this study received supplemental calcium 500 mg/day. By the third month of treatment, and continuing through the year-long treatment, the placebo group experienced losses in BMD at the lumbar spine, femoral neck, and trochanter, while BMD was maintained or increased in the ACTONEL 5 mg group. At each skeletal site there were statistically significant differences between the placebo group and the ACTONEL 5 mg group at all timepoints (Months 3, 6, 9, and 12). The treatment differences increased with continued treatment. Although BMD increased at the distal radius in the ACTONEL 5 mg group compared to the placebo group, the difference was not statistically significant. The differences between placebo and ACTONEL 5 mg after 1 year were 3.8% at the lumbar spine, 4.1% at the femoral neck, and 4.6% at the trochanter, as shown in Figure 3. The results at these skeletal sites were similar to the overall results when the subgroups of men and postmenopausal women, but not premenopausal women, were analyzed separately. ACTONEL was effective at the lumbar spine, femoral neck, and trochanter regardless of age (<65 vs. ≥ 65), gender, prior and concomitant glucocorticoid dose, or baseline BMD. Positive treatment effects were also observed in patients taking glucocorticoids for a broad range of rheumatologic disorders, the most common of which were rheumatoid arthritis, temporal arteritis, and polymyalgia rheumatica.

The treatment study of similar design enrolled 290 patients (ACTONEL 5 mg, N = 100) (19 to 85 years of age) with continuing, long-term (≥ 6 months) use of glucocorticoids (mean duration of use prior to study 60 months; mean daily dose of prednisone 15 mg) for rheumatic, skin, and pulmonary diseases. The baseline mean lumbar spine BMD was low (1.63 SD below the young healthy population mean), with 28% of the patients more than 2.5 SD below the mean. All patients in this study received supplemental calcium 1000 mg/day and vitamin D 400 IU/day.

After 1 year of treatment, the BMD of the placebo group was within $\pm 1\%$ of baseline levels at the lumbar spine, femoral neck, and trochanter. ACTONEL 5 mg increased BMD at the lumbar spine (2.9%), femoral neck (1.8%), and trochanter (2.4%). The differences between ACTONEL and placebo were

2.7% at the lumbar spine, 1.9% at the femoral neck, and 1.6% at the trochanter as shown in Figure 4. The differences were statistically significant for the lumbar spine and femoral neck, but not at the femoral trochanter. ACTONEL was similarly effective on lumbar spine BMD regardless of age (<65 vs. ≥65), gender, or pre-study glucocorticoid dose. Positive treatment effects were also observed in patients taking glucocorticoids for a broad range of rheumatologic disorders, the most common of which were rheumatoid arthritis, temporal arteritis, and polymyalgia rheumatica.

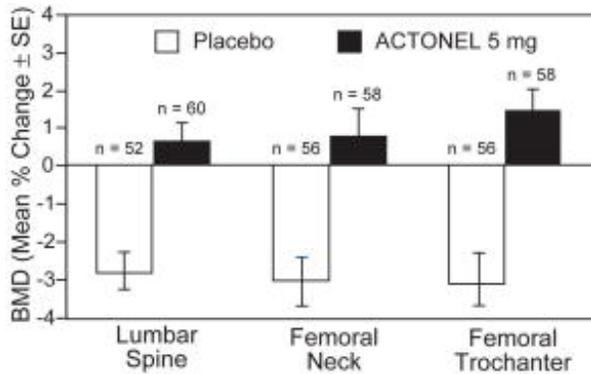


Figure 3 Change in BMD from Baseline Patients Recently Initiating Glucocorticoid Therapy

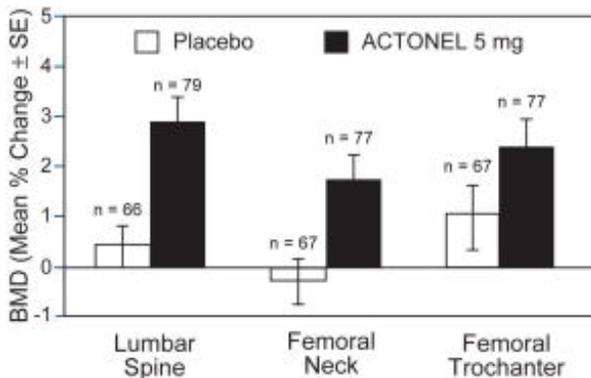


Figure 4 Change in BMD from Baseline Patients on Long-Term Glucocorticoid Therapy

Vertebral Fractures

In the prevention study of patients initiating glucocorticoids, the incidence of vertebral fractures at 1 year was reduced from 17% in the placebo group to 6% in the ACTONEL group. In the treatment study of patients continuing glucocorticoids, the incidence of vertebral fractures was reduced from 15% in the placebo group to 5% in the ACTONEL group (Figure 5). The statistically significant reduction in vertebral fracture incidence in the analysis of the combined studies corresponded to an absolute risk reduction of 11% and a relative risk reduction of 70%. All vertebral fractures were diagnosed radiographically; some of these fractures also were associated with symptoms (i.e., clinical fractures).

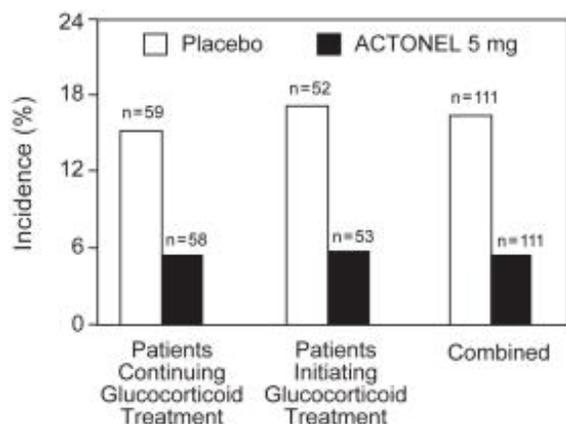


Figure 5 Incidence of Vertebral Fractures in Patients Initiating or Continuing Glucocorticoid Therapy

Histology/Histomorphometry

Bone biopsies from 40 patients on glucocorticoid therapy were obtained at endpoint. Patients had received placebo or daily ACTONEL (2.5 mg or 5 mg) for 1 year. Histologic evaluation (N = 33) showed that bone formed during treatment with ACTONEL was of normal lamellar structure and normal mineralization, with no bone or marrow abnormalities observed. The histomorphometric parameter mineralizing surface, a measure of bone turnover, was assessed based upon baseline and post-treatment biopsy samples from 10 patients treated with ACTONEL 5 mg. Mineralizing surface decreased 24% (median percent change) in these patients. Only a small number of placebo-treated patients had both baseline and post-treatment biopsy samples, precluding a meaningful quantitative assessment.

14.5 Treatment of Paget's Disease

The efficacy of ACTONEL was demonstrated in 2 clinical studies involving 120 men and 65 women. In a double-blind, active-controlled study of patients with moderate-to-severe Paget's disease (serum alkaline phosphatase levels of at least 2 times the upper limit of normal), patients were treated with ACTONEL 30 mg daily for 2 months or Didronel[®] (etidronate disodium) 400 mg daily for 6 months. At Day 180, 77% (43/56) of ACTONEL-treated patients achieved normalization of serum alkaline phosphatase levels, compared to 10.5% (6/57) of patients treated with Didronel (p<0.001). At Day 540, 16 months after discontinuation of therapy, 53% (17/32) of ACTONEL-treated patients and 14% (4/29) of Didronel-treated patients with available data remained in biochemical remission.

During the first 180 days of the active-controlled study, 85% (51/60) of ACTONEL-treated patients demonstrated a ≥75% reduction from baseline in serum alkaline phosphatase excess (difference between measured level and midpoint of the normal range) with 2 months of treatment compared to 20% (12/60) in the Didronel-treated group with 6 months of treatment (p<0.001). Changes in serum alkaline phosphatase excess over time (shown in Figure 6) were significant following only 30 days of treatment, with a 36% reduction in serum alkaline phosphatase excess at that time compared to only a 6% reduction seen with Didronel treatment at the same time point (p<0.01).

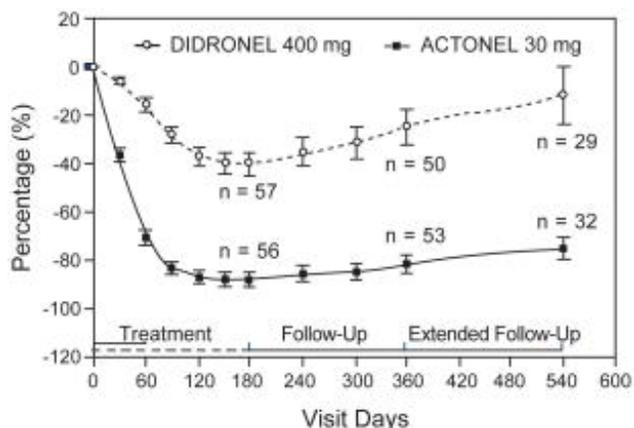


Figure 6 Mean Percent Change from Baseline in Serum Alkaline Phosphatase Excess by Visit

Response to ACTONEL therapy was similar in patients with mild to very severe Paget’s disease. Table 6 shows the mean percent reduction from baseline at Day 180 in excess serum alkaline phosphatase in patients with mild, moderate, or severe disease.

Table 6 Mean Percent Reduction from Baseline at Day 180 in Total Serum Alkaline Phosphatase Excess by Disease Severity

Subgroup: Baseline Disease Severity (AP)	ACTONEL 30 mg			DIDRONEL 400 mg		
	n	Baseline Serum AP (U/L)*	Mean % Reduction	n	Baseline Serum AP (U/L)*	Mean % Reduction
>2, <3x ULN	32	271.6 ± 5.3	-88.1	22	277.9 ± 7.45	-44.6
≥3, <7x ULN	14	475.3 ± 28.8	-87.5	25	480.5 ± 26.44	-35.0
≥7x ULN	8	1336.5 ± 134.19	-81.8	6	1331.5 ± 167.58	-47.2

*Values shown are mean ± SEM; ULN = upper limit of normal.

Response to ACTONEL therapy was similar between patients who had previously received anti-pagetic therapy and those who had not. In the active-controlled study, 4 patients previously non-responsive to 1 or more courses of anti-pagetic therapy (calcitonin, Didronel) responded to treatment with ACTONEL 30 mg daily (defined by at least a 30% change from baseline). Each of these patients achieved at least 90% reduction from baseline in serum alkaline phosphatase excess, with 3 patients achieving normalization of serum alkaline phosphatase levels.

Histomorphometry of the bone was studied in 14 patients with bone biopsies: 9 patients had biopsies from pagetic bone lesions and 5 patients from non-pagetic bone. Bone biopsy results in non-pagetic bone did not reveal osteomalacia, impairment of bone remodeling, or induction of a significant decline in bone turnover in patients treated with ACTONEL.

16 HOW SUPPLIED/STORAGE AND HANDLING

ACTONEL is available as follows:

5 mg film-coated, oval, yellow tablets with RSN on 1 face and 5 mg on the other.

Bottle of 30	NDC 54868-4386-0
Bottle of 60	NDC 54868-4386-1

35 mg film-coated, oval, orange tablets with RSN on 1 face and 35 mg on the other.

Dose pack of 4	NDC 54868- 4671-0
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150 mg film-coated, oval, blue tablets with RSN on 1 face and 150 mg on the other.

Dose pack of 1	NDC 54868- 6069-0
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Store at controlled room temperature 20° to 25°C (68° to 77°F) [see USP].

17 PATIENT COUNSELING INFORMATION

[See FDA-Approved Patient Labeling (17.1)]

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 at least 30 minutes before the first food or drink of the day other than water.

To facilitate delivery to the stomach, and thus reduce the potential for esophageal irritation, patients should take ACTONEL while in an upright position (sitting or standing) with a full glass of plain water (6 to 8 oz). Patients should not lie down for 30 minutes after taking the medication [see *Warnings and Precautions* (5.1)]. Patients should not chew or suck on the tablet because of a potential for oropharyngeal irritation.

Patients should be instructed that if they develop symptoms of esophageal disease (such as difficulty or pain upon swallowing, retrosternal pain or severe persistent or worsening heartburn) they should consult their physician before continuing ACTONEL.

Patients should be instructed that if they miss a dose of ACTONEL 35 mg 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. Patients should not take 2 tablets on the same day.

If one or both tablets of ACTONEL 75 mg on two consecutive days per month are missed, and the next month's scheduled doses are more than 7 days away, the patient should be instructed as follows:

- If both tablets are missed, take one ACTONEL 75 mg tablet in the morning after the day it is remembered and then the other tablet on the next consecutive morning.
- If only one ACTONEL 75 mg tablet is missed, take the missed tablet in the morning after the day it is remembered.

Patients should then return to taking their ACTONEL 75 mg on two consecutive days per month as originally scheduled. Patients should not take more than two 75 mg tablets within 7 days.

If one or both tablets of ACTONEL 75 mg on two consecutive days per month are missed, and the next month's scheduled doses are within 7 days, patients should wait until their next month's scheduled doses and then continue taking ACTONEL 75 mg on two consecutive days per month as originally scheduled.

If the dose of ACTONEL 150 mg once-a-month is missed, and the next month's scheduled dose is more than 7 days away, the patient should be instructed to take the missed tablet in the morning after the day it is remembered. Patients should then return to taking their ACTONEL 150 mg once-a-month as originally scheduled. Patients should not take more than one 150 mg tablet within 7 days.

If the dose of ACTONEL 150 mg once-a-month is missed, and the next month's scheduled dose is within 7 days, patients should wait until their next month's scheduled dose and then continue taking

ACTONEL 150 mg once-a-month as originally scheduled.

Patients should receive supplemental calcium and vitamin D if dietary intake is inadequate [*see Warnings and Precautions (5.2)*]. Calcium supplements or calcium-, aluminum-, and magnesium-containing medications may interfere with the absorption of ACTONEL and should be taken at a different time of the day, as with food.

Weight-bearing exercise should be considered along with the modification of certain behavioral factors, such as excessive cigarette smoking, and/or alcohol consumption, if these factors exist.

Physicians should instruct their patients to read the Patient Information before starting therapy with ACTONEL 5 mg, 35 mg, 75 mg, or 150 mg and to re-read it each time the prescription is renewed.

Patients should be reminded to give all of their health care providers an accurate medication history. Instruct patients to tell all of their health care providers that they are taking ACTONEL. Patients should be instructed that any time they have a medical problem they think may be from ACTONEL, they should talk to their doctor.

Covered under one or more of U.S. Patent Nos. 5,583,122; 5,994,329; 6,015,801; 6,096,342; 6,165,513; 6,410,520; 6,432,932; 6,465,443; and 6,562,974.

Mfg. by: Warner Chilcott Puerto Rico LLC,
Manati, Puerto Rico 00674

or

Norwich Pharmaceuticals, Inc.,
North Norwich, NY 13814

or

Chinoin Pharmaceutical and Chemical Works Private Co. Ltd
Veresegyhaz, Hungary

Mkt. by: Warner Chilcott Pharmaceuticals Inc.,
Mason, OH 45040



17.1 FDA-Approved Patient Labeling

Relabeling and Repackaging by:

Physicians Total Care, Inc.
Tulsa, OK 74146

Patient Information

ACTONEL[®] (AK-toh-nel) Tablets

**ACTONEL (risedronate sodium) tablets 5 mg,
ACTONEL (risedronate sodium) tablets 35 mg,
ACTONEL (risedronate sodium) tablets 75 mg, and
ACTONEL (risedronate sodium) tablets 150 mg for Osteoporosis**

Read this information carefully before you start to use your medicine. Read the information you get

every time you get more medicine. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or your treatment. If you have any questions or are not sure about something, ask your healthcare provider or pharmacist.

What is the most important information I should know about ACTONEL?

ACTONEL may cause problems in your stomach and esophagus (the tube that connects the mouth and the stomach), such as trouble swallowing (dysphagia), heartburn (esophagitis), and ulcers. You might feel pain in your bones, joints, or muscles (See “What are the Possible Side Effects of ACTONEL?”).

You must follow the instructions exactly for ACTONEL to work and to lower the chance of serious side effects. (See “How should I take ACTONEL?”).

What is ACTONEL?

ACTONEL is a prescription medicine used:

- to prevent and treat osteoporosis in postmenopausal women.
- to increase bone mass in men with osteoporosis.
- to prevent and treat osteoporosis in men and women that is caused by treatment with steroid medicines such as prednisone.
- to treat Paget’s disease of bone in men and women. The treatment for Paget’s disease is very different than for osteoporosis and uses a different dose of ACTONEL. This leaflet does not cover using ACTONEL for Paget’s disease. If you have Paget’s disease, ask your healthcare provider how to use ACTONEL.

ACTONEL may reverse bone loss by stopping more loss of bone and increasing bone strength in most people who take it, even though they won’t be able to see or feel a difference. ACTONEL helps lower the risk of breaking bones (fractures). Your healthcare provider may measure the thickness (density) of your bones or do other tests to check your progress.

Who should not take ACTONEL?

Do not take ACTONEL if you:

- have problems of the esophagus which delay emptying
- have low blood calcium (hypocalcemia)
- cannot sit or stand up for 30 minutes
- have kidneys that work poorly
- have an allergy to ACTONEL. The active ingredient in ACTONEL is risedronate sodium. (See the end of this leaflet for a list of all the ingredients in ACTONEL.)

Tell your doctor before using ACTONEL if:

- you are pregnant or may become pregnant. We do not know if ACTONEL can harm your unborn child.
- you are breast-feeding or plan to breast-feed. We do not know if ACTONEL can pass through your milk and if it can harm your baby.
- you have kidney problems. ACTONEL may not be right for you.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins and herbal supplements. ACTONEL can interact with other medicines. Keep a list of all the medicines you take. Show it to all your healthcare providers, including your dentist and pharmacist, each time you get a new medicine.

How should I take ACTONEL?

The following instructions apply to all patients taking ACTONEL:

- Take ACTONEL exactly as prescribed by your healthcare provider.
- Take ACTONEL first thing in the morning before you eat or drink anything except plain water.
- Take ACTONEL while you are sitting up or standing.
- Take ACTONEL with 6 to 8 ounces (about 1 cup) of plain water. Do **not** take it with any other drink besides plain water.
- Swallow ACTONEL whole. **Do not chew** the tablet or keep it in your mouth to melt or dissolve.
- After taking ACTONEL you must wait at least 30 minutes **BEFORE**:
 - lying down. You may sit, stand, or do normal activities like read the newspaper or take a walk.
 - eating or drinking anything except plain water.
 - taking vitamins, calcium, or antacids. Take vitamins, calcium, and antacids at a different time of the day from when you take ACTONEL.
- Keep taking ACTONEL for as long as your healthcare provider tells you.
- For ACTONEL to treat your osteoporosis or keep you from getting osteoporosis, you have to take it exactly as prescribed.
- If you miss a dose of ACTONEL, call your healthcare provider for instructions.
- If you take more than your prescribed dose of ACTONEL, call your healthcare provider right away.
- Your healthcare provider may tell you to take calcium and vitamin D supplements and to exercise.

What is my ACTONEL schedule?

ACTONEL tablets are made in 4 different dosages (amounts). How often you should take your tablet depends upon the dosage that your doctor has prescribed (recommended) for you.

- 5 mg tablets are yellow. One tablet should be taken every day in the morning.
- 35 mg tablets are orange. One tablet should be taken once a week in the morning.
- 75 mg tablets are pink. One tablet should be taken in the morning two days in a row every month.
- 150 mg tablets are blue. One tablet should be taken once a month in the morning.

If you miss your dose in the morning, do not take it later in the day. You should call your healthcare provider for instructions.

What should I avoid while taking ACTONEL?

- Do not eat or drink anything except water before you take ACTONEL and for at least 30 minutes after you take it. See “How should I take ACTONEL?”.
- Do not lie down for at least 30 minutes after you take ACTONEL.
- Foods and some vitamin supplements and medicines can stop your body from absorbing (using) ACTONEL. Therefore, do not take anything other than plain water at or near the time you take ACTONEL.

What are the possible side effects of ACTONEL?

Stop taking ACTONEL and tell your healthcare provider right away if:

- swallowing is difficult or painful
- you have chest pain
- you have very bad heartburn or it doesn't get better

Possible serious side effects may include:

- esophagus or stomach problems, including ulcers, pain, or trouble swallowing. Tell your healthcare

provider if you have pain or discomfort in your stomach or esophagus.

- low calcium and other mineral disturbances. If you already have one (or more) of these problems, it should be corrected before taking ACTONEL.
- pain in bones, joints or muscles, sometimes severe. Pain may start as soon as one day or up to several months after starting ACTONEL.
- jaw-bone problems in some people, which may include infection and slower healing after teeth are pulled. Tell your healthcare providers, including your dentist, right away if you have these symptoms.

Common side effects include the following:

- back and joint pain
- upset stomach and abdominal (stomach area) pain
- short-lasting, mild flu-like symptoms, which are reported with the monthly doses and usually get better after the first dose.

Other possible side effects may include:

- **Allergic and severe skin reactions.** Tell your healthcare provider if you develop any symptoms of an allergic reaction including: rash (with or without blisters), hives, or swelling of the face, lips, tongue, or throat. **Get medical help right away if you have trouble breathing or swallowing.**
- **Eye inflammation.** Tell your healthcare provider if you get any eye pain, redness, or if your eyes become more sensitive to light.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store ACTONEL?

- Store ACTONEL between 68°F to 77°F (20°C to 25°C).
- **Keep ACTONEL and all medicines out of the reach of children.**

General information about ACTONEL:

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use ACTONEL for a condition for which it was not prescribed. Do not give ACTONEL to other people, even if they have the same symptoms you have. It may harm them.

What if I have other questions about ACTONEL?

This leaflet summarizes the most important information about ACTONEL for osteoporosis. If you have more questions about ACTONEL, ask your healthcare provider or pharmacist. They can give you information written for healthcare professionals. For more information, call 1-877-ACTONEL (toll-free) or visit our web site at www.actonel.com.

What are the ingredients of ACTONEL?

ACTONEL (active ingredient): risedronate sodium.

ACTONEL (inactive ingredients):

All dose strengths contain: crospovidone, hydroxypropyl cellulose, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, silicon dioxide, titanium dioxide.

Dose-strength specific ingredients include: 5 mg—ferric oxide yellow, lactose monohydrate; 30 mg—lactose monohydrate; 35 mg—ferric oxide red, ferric oxide yellow, lactose monohydrate; 75 mg—

ferric oxide red; 150 mg—FD&C blue #2 aluminum lake.

ACTONEL[®] is marketed by:
Warner Chilcott Pharmaceuticals Inc.,
Mason, OH 45040

March 2010

To report SUSPECTED ADVERSE REACTIONS, contact Warner Chilcott at 1-800-836-0658 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.



PACKAGE/LABEL PRINCIPAL DISPLAY PANEL - 5 mg label

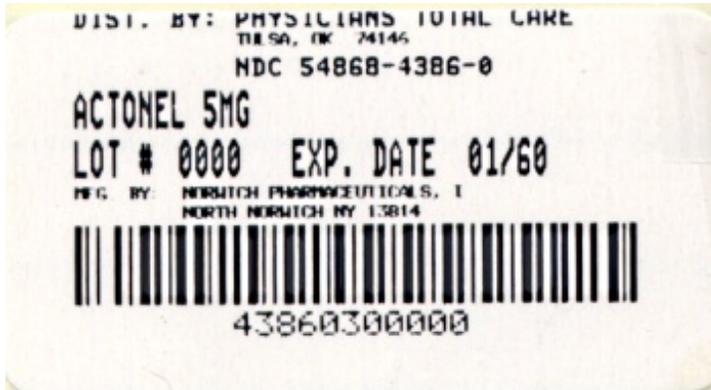
Important Patient Information

Actonel[®]

(risedronate sodium) tablets

5 mg

Rx Only



PACKAGE/LABEL PRINCIPAL DISPLAY PANEL - 35 MG

4 Week Supply

(4 tablets)

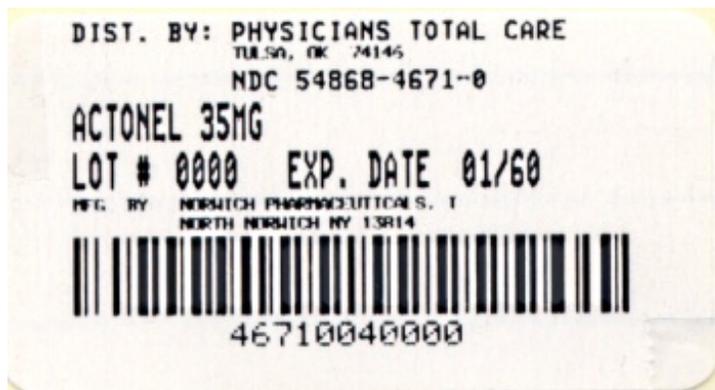
Actonel[®]

(risedronate sodium) tablets

35 mg

Rx Only

Once-a-Week



PACKAGE/LABEL PRINCIPAL DISPLAY PANEL - 150 MG

One Month Pack

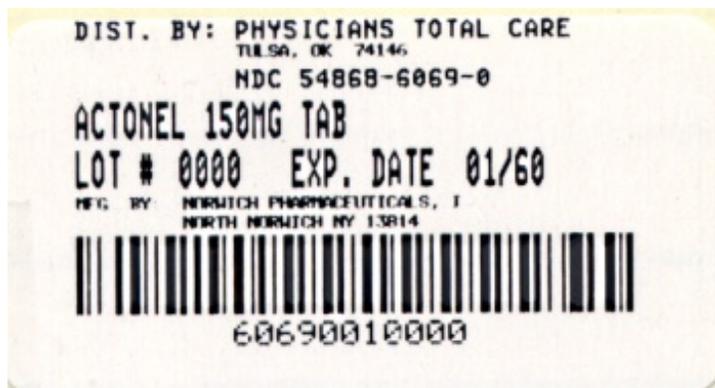
(1 tablet)

Actonel®

(risedronate sodium) tablets

150 mg

Rx Only



ACTONEL

risedronate sodium tablet, film coated

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:54868-4386 (NDC:0149-0471)
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
RISEDRO NATE SODIUM (UNII: OFG5EXG60L) (RISEDRONIC ACID - UNII:KM2Z91756Z)	RISEDRONATE SODIUM	5 mg

Inactive Ingredients

Ingredient Name	Strength
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CROSPVIDONE (UNII: 68401960MK)	
FERRIC OXIDE YELLOW (UNII: EX438O2MRT)	
HYDROXYPROPYL CELLULOSE (UNII: RFW2ET671P)	
HYPROMELLOSES (UNII: 3NXW29V3WO)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
POLYETHYLENE GLYCOL (UNII: 3WJQ0SDW1A)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	

Product Characteristics

Color	yellow	Score	no score
Shape	OVAL	Size	12mm
Flavor		Imprint Code	RSN;5;MG
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:54868-4386-0	30 in 1 BOTTLE		
2	NDC:54868-4386-1	60 in 1 BOTTLE, PLASTIC		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA020835	03/15/2002	

ACTONEL

risedronate sodium tablet, film coated

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:54868-4671(NDC:0149-0472)
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
RISEDRO NATE SODIUM (UNII: OFG5EXG60L) (RISEDRONIC ACID - UNII:KM2Z91756Z)	RISEDRO NATE SODIUM	35 mg

Inactive Ingredients

Ingredient Name	Strength
CROSPVIDONE (UNII: 68401960MK)	
FERRIC OXIDE RED (UNII: 1K09F3G675)	

FERRIC OXIDE YELLOW (UNII: EX438O2MRT)	
HYDROXYPROPYL CELLULOSE (UNII: RFW2ET671P)	
HYPROMELLOSES (UNII: 3NXW29V3WO)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
POLYETHYLENE GLYCOL (UNII: 3WJQ0SDW1A)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	

Product Characteristics

Color	orange	Score	no score
Shape	OVAL	Size	12mm
Flavor		Imprint Code	RSN;35;MG
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:54868-4671-0	1 in 1 DOSE PACK		
1		4 in 1 TRAY		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA020835	09/16/2002	

ACTONEL

risedronate sodium tablet, film coated

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:54868-6069(NDC:0149-0478)
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
RISEDRONATE SODIUM (UNII: OFG5EXG60L) (RISEDRONIC ACID - UNII:KM2Z91756Z)	RISEDRONATE SODIUM	150 mg

Inactive Ingredients

Ingredient Name	Strength
CROSPVIDONE (UNII: 68401960MK)	
HYDROXYPROPYL CELLULOSE (UNII: RFW2ET671P)	

HYPROMELLOSES (UNII: 3NXW29V3WO)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
POLYETHYLENE GLYCOL (UNII: 3WJQ0SDW1A)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
FD&C BLUE NO. 2 (UNII: L06K8R7DQK)	
ALUMINUM OXIDE (UNII: LM26O6933)	

Product Characteristics

Color	blue	Score	no score
Shape	OVAL	Size	12mm
Flavor		Imprint Code	RSN;150;MG
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:54868-6069-0	1 in 1 DOSE PACK		
1		1 in 1 TRAY		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA020835	10/05/2009	

Labeler - Physicians Total Care, Inc. (194123980)

Establishment

Name	Address	ID/FEI	Business Operations
Physicians Total Care, Inc.		194123980	relabel, repack