

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
022560Orig1s000

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Atelvia safely and effectively. See [Full Prescribing Information](#) for Atelvia.

Atelvia™ (risedronate sodium) delayed-release tablets
Initial U.S. Approval: 1998

RECENT MAJOR CHANGES

- Indications and Usage [(1.2) 01/2011]
- Warnings and Precautions [(5.6) 01/2011]

INDICATIONS AND USAGE

Atelvia is a bisphosphonate in a delayed-release formulation and is indicated for treatment of postmenopausal osteoporosis (1.1)
The optimal duration of use has not been determined. Patients should have the need for continued therapy re-evaluated on a periodic basis.

DOSAGE AND ADMINISTRATION

Take Atelvia in the morning immediately following breakfast with at least 4 oz. of plain water. Do not lie down for 30 minutes after taking Atelvia (2)
One 35 mg delayed-release tablet once a week (2.1)

DOSAGE FORMS AND STRENGTHS

Delayed-release tablets: 35 mg (3)

CONTRAINDICATIONS

- Abnormalities of the esophagus which delay esophageal emptying such as stricture or achalasia (4, 5.2)
- Inability to stand or sit upright for at least 30 minutes (4, 5.2)
- Hypocalcemia (4, 5.3)
- Known hypersensitivity to any component of this product (4, 6.2)

WARNINGS AND PRECAUTIONS

- Atelvia and Actonel contain the same active ingredient. Patients receiving Actonel should not be treated with Atelvia (5.1)

- 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 (5.2)
- Hypocalcemia may worsen and must be corrected prior to use (5.3)
- Osteonecrosis of the jaw has been reported rarely (5.4)
- Severe bone, joint, or muscle pain may occur. Consider discontinuing use if severe symptoms develop (5.5, 6.2)
- Atypical femur fractures have been reported. Patients with new thigh or groin pain should be evaluated to rule out a femoral fracture.

ADVERSE REACTIONS

Most common adverse reactions (>5%) include: diarrhea, influenza, arthralgia, back pain, and abdominal pain (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 1-800-521-8813 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Calcium supplements, antacids, magnesium-based supplements or laxatives, and iron preparations interfere with the absorption of Atelvia (7.1)

USE IN SPECIFIC POPULATIONS

Atelvia is not recommended for use in patients with severe renal impairment (creatinine clearance <30 mL/min) (5.6, 8.6, 12.3)
Atelvia is not indicated for use in pediatric patients (8.4)

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

Revised: 01/2011

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE

- 1.1 Postmenopausal Osteoporosis
- 1.2 Important Limitations of Use

2 DOSAGE AND ADMINISTRATION

- 2.1 Treatment of Postmenopausal Osteoporosis [see *Indications and Usage (1.1)*]

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Drug Products with the Same Active Ingredient
- 5.2 Upper Gastrointestinal Adverse Reactions
- 5.3 Mineral Metabolism
- 5.4 Jaw Osteonecrosis
- 5.5 Musculoskeletal Pain
- 5.7 Renal Impairment
- 5.8 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 Therapy
- 7.3 Aspirin/Nonsteroidal Anti-Inflammatory Drugs

- 7.4 Histamine 2 (H₂) Blockers, Proton Pump Inhibitors (PPIs), and Antacids

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

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the Full Prescribing Information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Postmenopausal Osteoporosis

Atelvia is indicated for the treatment of osteoporosis in postmenopausal women. Bone mineral density increases achieved at one year with Atelvia are non-inferior to increases seen with risedronate sodium 5 mg (immediate-release) daily. Daily risedronate sodium 5 mg (immediate-release) has been shown to reduce the incidence of vertebral fractures and a composite endpoint of nonvertebral osteoporosis-related fractures [[see Clinical Studies \(14.1\)](#)].

1.2 Important Limitations of Use

The safety and effectiveness of Atelvia for the treatment of osteoporosis are based on clinical data of one year duration. The optimal duration of use has not been determined. All patients on bisphosphonate therapy should have the need for continued therapy re-evaluated on a periodic basis.

2 DOSAGE AND ADMINISTRATION

Atelvia should be taken in the morning immediately following breakfast.

When compared with immediate-release risedronate, treatment with Atelvia resulted in a significantly higher incidence of abdominal pain when administered before breakfast under fasting conditions. Atelvia should be taken immediately following breakfast and not under fasting conditions.

To facilitate delivery to the stomach, Atelvia should be swallowed whole while the patient is in an upright position and with at least 4 ounces of plain water. Tablets should not be chewed, cut, or crushed. Patients should not lie down for 30 minutes after taking the medication [[see Warnings and Precautions \(5.2\)](#)].

Patients should receive supplemental calcium and vitamin D [[see Warnings and Precautions \(5.3\)](#)]. Calcium supplements, antacids, magnesium-based supplements or laxatives, and iron preparations interfere with the absorption of Atelvia and it is recommended they be taken at a different time of the day. Atelvia 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 or in the elderly.

2.1 Treatment of Postmenopausal Osteoporosis [[see Indications and Usage \(1.1\)](#)]

The recommended regimen is:

- one 35 mg delayed-release tablet orally, taken once-a-week

3 DOSAGE FORMS AND STRENGTHS

Delayed-release tablets: 35 mg, yellow, oval-shaped, and engraved with EC 35 on one side.

4 CONTRAINDICATIONS

- Abnormalities of the esophagus which delay esophageal emptying such as stricture or achalasia [[see Warnings and Precautions \(5.2\)](#)]
- Inability to stand or sit upright for at least 30 minutes [[see Dosage and Administration \(2\), Warnings and Precautions \(5.2\)](#)]
- Hypocalcemia [[see Warnings and Precautions \(5.3\)](#)]
- Known hypersensitivity to any component of this product [[see Adverse Reactions \(6.2\)](#)]

5 WARNINGS AND PRECAUTIONS

5.1 Drug Products with the Same Active Ingredient

Atelvia contains the same active ingredient found in Actonel[®]. A patient being treated with Actonel should not receive Atelvia.

5.2 Upper Gastrointestinal Adverse Reactions

Atelvia, 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 Atelvia 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 \(17\)](#)].

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 Atelvia 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 4 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 Atelvia 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.

5.3 Mineral Metabolism

Hypocalcemia and other disturbances of bone and mineral metabolism should be effectively treated before starting Atelvia therapy. Adequate intake of calcium and vitamin D is important in all patients [[see Contraindications \(4\)](#), [Adverse Reactions \(6.1\)](#), [Information for Patients \(17\)](#)].

5.4 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 risedronate. 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 ONJ 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 \(6.2\)](#)].

5.5 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.

5.6 Atypical Subtrochanteric and Diaphyseal Femoral Fractures

Atypical, low-energy, or low trauma fractures of the femoral shaft have been reported in bisphosphonate-treated patients. These fractures can occur anywhere in the femoral shaft from just below the lesser trochanter to above the supracondylar flare and are transverse or short oblique in orientation without evidence of comminution. Causality has not been established as these fractures also occur in osteoporotic patients who have not been treated with bisphosphonates.

Atypical femur fractures most commonly occur with minimal or no trauma to the affected area. They may be bilateral and many patients report prodromal pain in the affected area, usually presenting as dull, aching thigh pain, weeks to months before a complete fracture occurs. A number of reports note that patients were also receiving treatment with glucocorticoids (e.g. prednisone) at the time of fracture.

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

5.7 Renal Impairment

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

5.8 Laboratory Test Interactions

Bisphosphonates are known to interfere with the use of bone-imaging agents. Specific studies with Atelvia 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

Once-a-Week Dosing with Atelvia (risedronate sodium) delayed-release tablets

The safety of Atelvia 35 mg once-a-week in the treatment of postmenopausal osteoporosis was assessed in a 1-year, double-blind, multicenter study comparing Atelvia 35 mg once-a-week to risedronate sodium immediate-release 5 mg daily in postmenopausal women 50 years of age or older. Atelvia was administered either at least 30 minutes before (N = 308) or immediately following (N = 307) breakfast, and risedronate sodium immediate-release 5 mg daily (N = 307) was administered at least 30 minutes before breakfast. 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 daily supplementation with 1000 mg of elemental calcium plus 800 to 1000 IU vitamin D. As treatment with Atelvia resulted in a significantly higher incidence of abdominal pain when administered before breakfast under fasting conditions, safety results that follow refer only to Atelvia 35 mg once-a-week immediately following breakfast and risedronate sodium immediate-release 5 mg daily.

The incidence of all-cause mortality was 0.0% in the Atelvia 35 mg once-a-week group and 0.3% in the risedronate sodium immediate-release 5 mg daily group. The incidence of serious adverse reactions was 6.5% in the Atelvia 35 mg once-a-week group and 7.2% in the risedronate sodium immediate-release 5 mg daily group. The percentage of patients who withdrew from the study due to adverse reactions was 9.1% in the Atelvia 35 mg once-a-week group and 8.1% in the risedronate sodium immediate-release 5 mg daily group. The overall safety and tolerability profiles of the two dosing regimens were similar. Table 1 lists adverse reactions reported in $\geq 2\%$ of patients. Adverse reactions are shown without attribution of causality.

System Organ Class Preferred Term	35 mg Atelvia Weekly N = 307 %	5 mg Risedronate sodium Immediate- release Daily N = 307 %
Gastrointestinal disorders		
Diarrhea	8.8	4.9
Abdominal pain	5.2	2.9
Constipation	4.9	2.9
Vomiting	4.9	1.6
Dyspepsia	3.9	3.9
Nausea	3.6	3.9
Abdominal pain upper	2.9	2.3
Infections and infestations		
Influenza	7.2	6.2
Bronchitis	3.9	4.2
Upper respiratory tract infection	3.6	2.6
Musculoskeletal and connective tissue disorders		
Arthralgia	6.8	7.8
Back pain	6.8	5.9
Pain in extremity	3.9	2.3
Musculoskeletal pain	2.0	1.6
Muscle spasms	1.0	2.3
Nervous system disorders		
Dizziness	2.6	3.3
Headache	2.6	4.9

Acute Phase Reactions: Symptoms consistent with acute phase reaction have been reported with bisphosphonate use. The overall incidence of acute phase reaction was 2.3% in the Atelvia 35 mg once-a-week group and 1.3% in the risedronate sodium immediate-release 5 mg daily group. These incidence rates are based on reporting of one or more pre-specified acute phase reaction-like symptoms within 3 days of the first dose and for a duration of 7 days or less.

Gastrointestinal Adverse Reactions: Adverse reactions related to the upper gastrointestinal tract occurred in 16% of subjects treated with Atelvia 35 mg once-a-week and 15% of subjects treated with risedronate sodium immediate-release 5 mg daily. The incidence of upper gastrointestinal tract adverse reactions in the Atelvia 35 mg once-a-week and risedronate sodium immediate-release 5 mg daily groups were: abdominal pain (5.2% versus 2.9%), dyspepsia (3.9% versus 3.9%), upper abdominal pain (2.9% versus 2.3%), gastritis (1.0% versus 1.0%), and gastroesophageal reflux disease (1.0% versus 1.6%). Study discontinuation due to abdominal pain occurred in 1.3% of the Atelvia 35 mg once-a-week group and 0.7% of the risedronate sodium immediate-release 5 mg daily group.

Musculoskeletal Adverse Reactions: Selected musculoskeletal adverse reactions were reported in 16% of subjects treated with Atelvia 35 mg once-a-week and 15% of subjects treated with risedronate sodium immediate-release 5 mg daily. The incidence of musculoskeletal adverse reactions in the Atelvia 35 mg once-a-week and risedronate sodium immediate-release 5 mg daily groups were: arthralgia (6.8% versus 7.8%), back pain (6.8% versus 5.9%), musculoskeletal pain (2.0% versus 1.6%), and myalgia (1.3% versus 1.0%).

Laboratory Test Findings:

Parathyroid hormone: The effect of Atelvia 35 mg once-a-week and risedronate sodium immediate-release 5 mg daily on parathyroid hormone was evaluated in postmenopausal women with osteoporosis. At week 52, in subjects with normal levels at baseline, PTH levels greater than 65 pg/mL (upper limit of normal) were noted in 9% of subjects receiving Atelvia 35 mg once-a-week and 8% of subjects receiving risedronate sodium immediate-release 5 mg daily. In subjects with normal levels at baseline, PTH levels greater than 97 pg/mL (1.5 times the upper limit of normal) were seen in 2% of subjects receiving Atelvia 35 mg once-a-week and no subjects receiving risedronate sodium immediate-release 5 mg daily. There were no clinically significant differences between treatment groups for levels of calcium, phosphorus and magnesium.

Daily Dosing with risedronate sodium immediate-release 5 mg tablets

The safety of risedronate sodium immediate-release 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 risedronate sodium immediate-release 5 mg daily. Patients with pre-existing gastrointestinal disease and concomitant use of non-steroidal anti-inflammatory drugs, proton pump inhibitors (PPIs), 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 risedronate sodium immediate-release 5 mg daily group. The incidence of serious adverse reactions was 24.6% in the placebo group and 27.2% in the risedronate sodium immediate-release 5 mg daily group. The percentage of patients who withdrew from the study due to adverse reactions was 15.6% in the placebo group and 14.8% in the risedronate sodium immediate-release 5 mg daily group. The most common adverse reactions reported in >10% of subjects were: back pain, arthralgia, abdominal pain and dyspepsia.

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

Musculoskeletal Adverse Reactions: The incidence of adverse reactions in the placebo and risedronate sodium immediate-release 5 mg daily groups were: back pain (26.1% versus 28.0%), arthralgia (22.1% versus 23.7%), myalgia (6.2% versus 6.7%), and bone pain (4.8% versus 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 risedronate sodium immediate-release 5 mg daily. There were no significant differences in serum calcium, phosphate, or PTH levels between placebo and risedronate sodium immediate-release 5 mg 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 risedronate sodium immediate-release 5 mg 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 risedronate sodium immediate-release 5 mg daily. There have been rare reports (<0.1%) of abnormal liver function tests.

Endoscopic Findings: In the risedronate sodium immediate-release 5 mg daily 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%) risedronate sodium immediate-release 5 mg daily]. Clinically important findings (perforations, ulcers, or bleeding) among this symptomatic population were similar between groups (51% placebo; 39% risedronate sodium immediate-release 5 mg daily).

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.

The following adverse reactions have been reported with the use of risedronate sodium immediate-release.

Hypersensitivity Reactions

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

Gastrointestinal Adverse Reactions

Reactions involving upper gastrointestinal irritation, such as esophagitis and esophageal or gastric ulcers, have been reported [[see Warnings and Precautions \(5.2\)](#)].

Musculoskeletal Pain

Bone, joint, or muscle pain, described as severe or incapacitating, have been reported rarely [[see Warnings and Precautions \(5.5\)](#)].

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 \(5.4\)](#)].

7 DRUG INTERACTIONS

Risedronate is not metabolized and does not induce or inhibit hepatic microsomal drug-metabolizing enzymes (e.g., Cytochrome P450).

7.1 Calcium Supplements/Antacids

When Atelvia was administered following breakfast, the co-administration of a tablet containing 600 mg of elemental calcium and 400 IU vitamin D reduced risedronate bioavailability by approximately 38% [[see Clinical Pharmacology \(12.3\)](#)]. Calcium supplements, antacids, magnesium-based supplements or laxatives, and iron preparations may reduce the bioavailability of Atelvia and should not be taken together.

7.2 Hormone Therapy

Concomitant use of Atelvia with estrogens and estrogen agonist/antagonists has not been studied.

7.3 Aspirin/Nonsteroidal Anti-Inflammatory Drugs

In the Phase 3 study comparing Atelvia 35 mg once-a-week immediately following breakfast and risedronate sodium 5 mg daily, 18% of NSAID users (any use) in both groups developed upper gastrointestinal adverse reactions. Among non-users, 13% of patients taking Atelvia 35 mg once-a-week immediately following breakfast developed upper gastrointestinal adverse reactions, compared to 12% taking risedronate sodium 5 mg daily.

7.4 Histamine 2 (H₂) Blockers, Proton Pump Inhibitors (PPIs), and Antacids

Drugs that raise stomach pH (e.g., H₂ blockers, PPIs, or antacids) may affect the enteric coating on Atelvia tablets and thereby reduce bioavailability of Atelvia. The effects of concomitant administration of H₂ blockers, PPIs, and antacids on bioavailability of Atelvia have not been evaluated.

Atelvia should not be taken at the same time with antacids. Concomitant administration of Atelvia and H₂ blockers or PPIs is not recommended.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C: There are no adequate and well-controlled studies of Atelvia in pregnant women. Atelvia 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 Paget's disease 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 sternbrae or skull from dams treated with approximately 2.5 times the human dose was significantly increased compared to controls. Both incomplete ossification and unossified sternbrae 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 Atelvia 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 human Paget's disease dose of 30 mg/day resulted in periparturient hypocalcemia and mortality in pregnant rats allowed to deliver.

Dosing multiples provided above are based on the recommended human Paget's disease 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 Atelvia 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 Atelvia, 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

Atelvia is not indicated for use in pediatric patients.

The safety and effectiveness of risedronate sodium immediate-release 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 OI (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 sodium immediate-release group compared to the placebo group was observed. However, treatment with risedronate sodium immediate-release did not result in a reduction in the risk of fracture in pediatric patients with OI. In risedronate sodium immediate-release 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 sodium immediate-release and 6% of patients treated with placebo. Other adverse reactions reported in $\geq 10\%$ of patients treated with risedronate sodium immediate-release and with a higher frequency than placebo were: pain in the extremity (21% with risedronate sodium immediate-release 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 Atelvia in postmenopausal osteoporosis studies, 59% were 65 and over, while 13% were 75 and over. No overall differences in safety or effectiveness were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Renal Impairment

Atelvia 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 sodium'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. While milk or antacids containing calcium may be given to bind risedronate sodium immediate-release and reduce absorption of the drug, the impact of this intervention for Atelvia delayed-release tablets has not been evaluated.

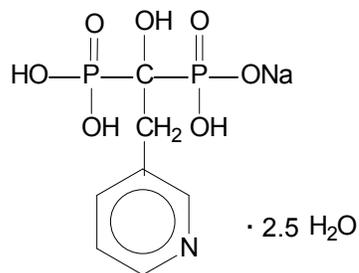
In cases of substantial overdose, gastric lavage may be considered to remove unabsorbed drug. Standard procedures that are effective for treating hypocalcemia, including the administration of calcium intravenously, would be expected to restore physiologic amounts of ionized calcium and to relieve signs and symptoms of hypocalcemia.

Lethality after single oral doses of risedronate 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 human Paget's disease dose of 30 mg/day based on surface area (mg/m^2).

11 DESCRIPTION

Atelvia (risedronate sodium) delayed-release tablets contain a pH-sensitive enteric coating and a chelating agent (EDTA).

Risedronate is a pyridinyl bisphosphonate that inhibits osteoclast-mediated bone resorption and modulates bone metabolism. Each Atelvia tablet for oral administration contains the equivalent of 35 mg of anhydrous risedronate sodium in the form of the hemi-pentahydrate with small amounts of monohydrate. The empirical formula for risedronate sodium hemi-pentahydrate is $\text{C}_7\text{H}_{10}\text{NO}_7\text{P}_2\text{Na} \cdot 2.5 \text{H}_2\text{O}$. The chemical name of risedronate sodium is [1-hydroxy-2-(3-pyridinyl)ethylidene]bis[phosphonic acid] monosodium salt. The chemical structure of risedronate sodium hemi-pentahydrate 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

Edetate disodium, ferric oxide yellow, magnesium stearate, methacrylic acid copolymer, polysorbate 80, silicified microcrystalline cellulose (ProSolv SMCC90), simethicone, sodium starch glycolate, stearic acid, talc, and triethyl citrate.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Risedronate has an affinity for hydroxyapatite crystals in bone and acts as an antiresorptive agent. At the cellular level, risedronate inhibits osteoclasts. The osteoclasts adhere normally to the bone surface, but show evidence of reduced active resorption (e.g., lack of ruffled border). Histomorphometry in rats, dogs, and minipigs showed that risedronate 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

Risedronate treatment decreases the elevated rate of bone turnover that is typically seen in postmenopausal osteoporosis. In clinical trials, administration of risedronate sodium immediate-release 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 daily 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 Atelvia 35 mg

weekly taken immediately after breakfast versus risedronate sodium immediate-release 5 mg daily oral dosing regimens in postmenopausal women, mean decreases from baseline at 1 year in urinary collagen cross-linked N-telopeptide were 47% in the Atelvia 35 mg once-a-week following breakfast group and 42% in the risedronate sodium immediate-release 5 mg daily group. In addition, serum bone-specific alkaline phosphatase at 1 year was reduced by 33% in the Atelvia 35 mg once-a-week following breakfast group and 32% in the risedronate sodium immediate-release 5 mg daily group.

12.3 Pharmacokinetics

Absorption

The mean absolute oral bioavailability of the 30 mg risedronate sodium immediate-release tablet taken 4 hours prior to a meal is 0.63% (90% confidence interval [CI]: 0.54% to 0.75%) and is similar to an oral solution. The time to peak concentration (T_{max}) for Atelvia tablet is ~3 hours when administered in the morning 4 hours prior to a meal.

Food Effect

In a crossover pharmacokinetic study, the bioavailability of Atelvia 35 mg delayed-release tablets decreased by ~30% when administered immediately after a high-fat breakfast compared to administration in the morning 4 hours before a meal.

The bioavailability of the 35 mg Atelvia tablet administered after a high-fat breakfast was similar to risedronate sodium 35 mg immediate-release tablet dosed 4 hours before a meal in one study and was approximately 2- to 4-fold greater than the immediate-release 35 mg tablet administered 30 minutes prior to a high-fat breakfast.

In a separate study, Atelvia administered after dinner exhibited approximately 87% increase in risedronate exposure compared to administration following a breakfast. The safety and efficacy of dosing Atelvia after dinner has not been evaluated [[see Dosage and Administration \(2\)](#)].

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 [^{14}C] risedronate indicate that approximately 60% of the dose is distributed to bone. The remainder of the dose is excreted in the urine. After multiple oral dosing in rats, the uptake of risedronate in soft tissues was 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 for the risedronate sodium immediate-release tablets, 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: Atelvia is not indicated for use in pediatric patients [[see Pediatric Use \(8.4\)](#)].

Geriatric: Effect of age on bioavailability of Atelvia has not been evaluated. Based on data from risedronate immediate-release tablet, bioavailability and disposition of risedronate 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. The clinical trial of Atelvia was conducted mostly in Caucasians.

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. Atelvia 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.

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: Risedronate is not metabolized and does not induce or inhibit hepatic microsomal drug-metabolizing enzymes (e.g., Cytochrome P450).

Calcium supplement: A Phase 1 single-dose, cross-over study in 101 postmenopausal women evaluated the relative bioavailability of Atelvia 35 mg delayed-release tablets taken after breakfast and following a 600 mg elemental calcium/400 IU vitamin D supplement, compared to Atelvia alone taken after breakfast without calcium or vitamin D supplementation. The addition of the calcium/vitamin D supplement following the meal resulted in an approximate 38% reduction in the amount of risedronate absorbed [[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 human Paget's disease dose of 30 mg/day. 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 Paget's disease 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 recommended human dose of 5 mg/day 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 human dose of 5 mg/day.

In dogs treated with an oral dose approximately 5 times the human dose of 5 mg/day, 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 dose of 5 mg/day. This indicates that Atelvia administered at the therapeutic dose is unlikely to induce osteomalacia.

Dosing multiples provided above are based on the recommended human osteoporosis 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 efficacy of Atelvia 35 mg once-a-week in the treatment of postmenopausal osteoporosis was demonstrated in a randomized, double-blind, active-control trial of approximately 900 subjects. All patients in this study received supplemental calcium (1000 mg/day) and vitamin D (800 to 1000 IU/day). The primary efficacy endpoint was percent change in lumbar spine bone mineral density at 1 year.

Atelvia 35 mg once-a-week administered after breakfast was shown to be non-inferior to risedronate sodium immediate-release 5 mg daily. Table 2 presents the primary efficacy analysis, percent change in lumbar spine BMD, in the intent-to-treat population with last observation carried forward (LOCF).

Table 2		
Lumbar Spine BMD - Percent Change from Baseline at Endpoint[a]		
	Risedronate sodium immediate-release 5 mg Daily	Atelvia 35 mg Once-a-Week Following Breakfast
	N = 307	N = 307
Primary Efficacy (LOCF)		
n	270	261
LS Mean (95% CI)	3.1* (2.7, 3.5)	3.3* (2.9, 3.7)
LS Mean Difference[b] (95% CI)		-0.2 (-0.8, 0.3)
N = number of intent-to-treat patients within specified treatment; n = number of patients with values at the visit. *Indicates a statistically significant difference from baseline determined from 95% CI unadjusted for multiple comparisons. LS = Least Squares [a] at 1 year LOCF [b] LS Mean Difference is 5 mg daily minus 35 mg weekly treatment.		

Fracture efficacy with risedronate sodium immediate-release 5 mg daily

The fracture efficacy of risedronate sodium immediate-release 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) (risedronate sodium immediate-release 5 mg daily, N = 408) was conducted primarily in Europe and Australia; a second study was conducted in North America (VERT NA) (risedronate sodium immediate-release 5 mg daily, 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 500 IU/day supplemental vitamin D.

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. Risedronate sodium immediate-release 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.

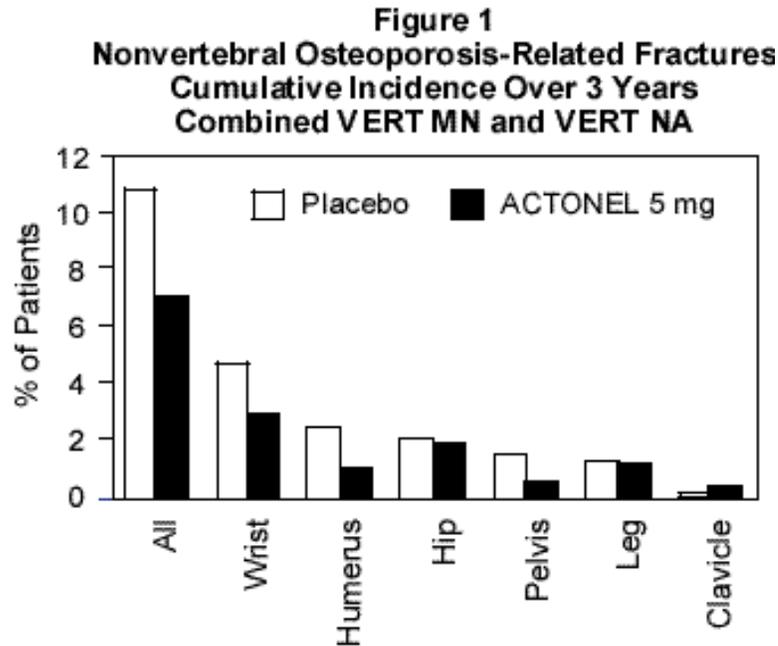
Table 3				
The Effect of Risedronate sodium 5 mg Immediate-Release Daily on the Risk of Vertebral Fractures				
VERT NA	Proportion of Patients with Fracture (%) ^a		Absolute Risk Reduction (%)	Relative Risk Reduction (%)
	Placebo N = 678	Risedronate sodium 5 mg N = 696		
New and Worsening				
0 to 1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

^aCalculated 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. Risedronate sodium immediate-release 5 mg daily significantly reduced the incidence of nonvertebral osteoporosis-related fractures over 3 years in VERT NA (8% versus 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.



Histology/Histomorphometry

Bone biopsies from 110 postmenopausal women were obtained at endpoint in the VERT NA study. Patients had received placebo or daily risedronate sodium immediate-release (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 risedronate sodium immediate-release treated women. These findings demonstrate that bone formed during risedronate sodium immediate-release 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 risedronate sodium immediate-release 5 mg daily. Mineralizing surface decreased moderately in risedronate sodium immediate-release treated patients (median percent change: placebo, -21%; risedronate sodium immediate-release 5 mg daily, -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 risedronate sodium immediate-release 5 mg daily and placebo-treated groups lost height during the studies. Patients who received risedronate sodium immediate-release 5 mg daily 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 risedronate sodium immediate-release 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 risedronate sodium immediate-release 5 mg daily group.

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 risedronate sodium immediate-release 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. In both VERT studies (VERT MN and VERT NA), risedronate sodium immediate-release 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.

	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	

^aThe 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.
^bThe duration of the studies was 3 years.
^cThe 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

16 HOW SUPPLIED/STORAGE AND HANDLING

AtelviaTM (risedronate sodium) delayed-release tablets are:

35 mg, yellow, oval-shaped, and engraved with EC 35 on one side.

NDC 0430-0979-03 Dosepak of 4 tablets

Store at controlled room temperature 20° to 25° C (68° to 77° F) [see USP].

17 PATIENT COUNSELING INFORMATION

[See FDA-Approved Patient Labeling]

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.

Patients should not take Atelvia if they have abnormalities of the esophagus which delay esophageal emptying such as stricture or achalasia, inability to stand or sit upright for at least 30 minutes, hypocalcemia, or known hypersensitivity to any component of this product [[see Contraindications \(4\)](#)].

Atelvia and Actonel contain the same active ingredient. Patients receiving Actonel should not receive Atelvia [[see Warnings and Precautions \(5.1\)](#)].

To facilitate delivery to the stomach, and thus reduce the potential for esophageal irritation, patients should take Atelvia in the morning, while in an upright position (sitting or standing) with at least 4 ounces of plain water immediately following breakfast. Atelvia should not be taken before breakfast. Patients must swallow Atelvia tablets whole. Patients should not chew, cut, or crush the tablet because of a potential for oropharyngeal irritation, and because the tablet coating is an important part of the delayed-release formulation. Patients should not lie down for 30 minutes after taking the medication

Severe irritation of the upper gastrointestinal (GI) mucosa can occur. Caution should be used in patients with active upper GI disease. 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 Atelvia [[see Warnings and Precautions \(5.2\)](#)].

Patients should receive supplemental calcium and vitamin D. Hypocalcemia may worsen and must be corrected prior to use [[see Warnings and Precautions \(5.3\)](#)]. Calcium supplements, antacids, magnesium-based supplements or laxatives, and iron preparations interfere with the absorption of Atelvia and should be taken at a different time of the day.

Osteonecrosis of the jaw has been reported rarely [[see Warnings and Precautions \(5.4\)](#)]. Severe bone, joint, or muscle pain may occur. Consider discontinuing use if severe symptoms develop [[see Warnings and Precautions \(5.5\)](#)]. Atelvia is not recommended for use in patients with severe renal impairment (creatinine clearance <30 mL/min) because of lack of clinical experience [[see Warnings and Precautions \(5.6\)](#)].

Most common adverse reactions while taking Atelvia include diarrhea, influenza, arthralgia, back pain, and abdominal pain [[see Adverse Reactions \(6.1\)](#)]. Hypersensitivity reactions (angioedema, generalized rash, bullous skin reactions), and eye inflammation (iritis, uveitis) have been reported rarely [[see Adverse Reactions \(6.2\)](#)].

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.

Patients should be instructed that if they miss a dose of Atelvia 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.

Physicians should instruct their patients to read the Medication Guide before starting therapy with Atelvia and to re-read it each time the prescription is renewed.

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

Medication Guide
Atelvia™ (uh-TEL-v-uh)
(risedronate sodium)
delayed-release tablets

Read this Medication Guide that comes with Atelvia™ before you start taking it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking with your doctor about your medical condition or your treatment. Talk to your doctor if you have any questions about Atelvia.

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

Atelvia can cause serious side effects including:

1. Esophagus problems
2. Low calcium levels in your blood (hypocalcemia)
3. Severe jaw bone problems (osteonecrosis)
4. Bone, joint, or muscle pain
5. Unusual thigh bone fractures

1. Esophagus problems.

Some people who take Atelvia may develop problems in the esophagus (the tube that connects the mouth and the stomach). These problems include irritation, inflammation, or ulcers of the esophagus which may sometimes bleed.

- **It is important that you take Atelvia exactly as prescribed to help lower your chance of getting esophagus problems. (See the section "How should I take Atelvia?")**
- **Stop taking Atelvia and call your doctor right away if you get chest pain, new or worsening heartburn, or have trouble or pain when you swallow.**

2. Low calcium levels in your blood (hypocalcemia).

Atelvia may lower the calcium levels in your blood. If you have low blood calcium before you start taking Atelvia, it may get worse during treatment. Your low blood calcium must be treated before you take Atelvia. Most people with low blood calcium levels do not have symptoms, but some people may have symptoms. Call your doctor right away if you have symptoms of low blood calcium such as:

- Spasms, twitches, or cramps in your muscles
- Numbness or tingling in your fingers, toes, or around your mouth

Your doctor may prescribe calcium and vitamin D to help prevent low calcium levels

in your blood, while you are taking Atelvia. Take calcium and vitamin D as your doctor tells you to.

3. Severe jaw bone problems (osteonecrosis).

Severe jaw bone problems may happen when you take Atelvia. Your doctor should examine your mouth before you start Atelvia. Your doctor may tell you to see your dentist before you start Atelvia. It is important for you to practice good mouth care during treatment with Atelvia.

4. Bone, joint, or muscle pain.

Some people who take Atelvia develop severe bone, joint, or muscle pain.

5. Unusual thigh bone fractures.

Some people have developed unusual fractures in their thigh bone. Symptoms of a fracture may include new or unusual pain in your hip, groin, or thigh.

Call your doctor right away if you have any of these side effects.

What is Atelvia?

Atelvia is a prescription medicine used to treat osteoporosis in women after menopause.

It is not known how long Atelvia works for the treatment and prevention of osteoporosis. You should see your doctor regularly to determine if Atelvia is still right for you.

Atelvia is not for use in children.

Who should not take Atelvia?

Do not take Atelvia if you:

- Have certain problems with your esophagus, the tube that connects your mouth and stomach
- Cannot sit or stand up for at least 30 minutes
- Have low blood calcium (hypocalcemia)
- Are allergic to any of the other ingredients in Atelvia. See the end of this leaflet for a complete list of ingredients in Atelvia.

What should I tell my healthcare provider before taking Atelvia?

Before you take Atelvia, tell your healthcare provider if you:

- Have problems swallowing
- Have stomach or digestive problems
- Have low blood calcium
- Plan to have dental surgery or teeth removed
- Have kidney problems

- Have been told you have trouble absorbing mineral in your stomach or intestines (malabsorption syndrome)
- Are pregnant or plan to become pregnant. It is not known if Atelvia can harm your unborn baby.
- Are breastfeeding or plan to breastfeed. It is not known if Atelvia passes into your breast milk and may harm your baby. You and your doctor should decide if you will take Atelvia or breastfeed. You should not do both.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins and herbal supplements. Certain medicines may affect how Atelvia works.

Especially tell your doctor if you take:

- Actonel[®] or other medicines to treat osteoporosis
- calcium supplements
- antacids
- laxatives
- iron supplements

Ask your doctor or pharmacist for a list of these medications, if you are not sure.

Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How should I take Atelvia?

- Take Atelvia exactly as your doctor tells you.
- Take Atelvia 1 time a week **right after breakfast**. Choose a day of the week to take Atelvia that best fits your schedule.
- Take Atelvia with at least 4 ounces (about 1-half cup) of plain water.
- Swallow Atelvia tablets whole. **Do not chew, cut, or crush** Atelvia tablets before swallowing. If you cannot swallow Atelvia tablets whole, tell your doctor. You may need a different medicine.

After swallowing Atelvia wait at least 30 minutes:

- Before you lie down. You may sit, stand or walk, and do normal activities like reading.
- Before you take other medicines, including antacids, calcium, and other supplements and vitamins.

Do not lie down for at least 30 minutes after you take Atelvia.

If you miss your weekly Atelvia dose, take Atelvia the morning after you remember then return to your normal schedule. Do not take 2 doses at the same time.

You should take calcium and vitamin D as directed by your doctor.

If you take too much Atelvia, call your doctor. Do not try to vomit. Do not lie down.

What are the possible side effects of Atelvia?

Atelvia may cause serious side effects:

- See **“What is the most important information I should know about Atelvia”**.

The most common side effects of Atelvia include:

- diarrhea
- flu-like symptoms
- muscle pain
- back and joint pain
- upset stomach
- stomach area (abdominal) pain

You may get allergic reactions, such as hives or, in rare cases, swelling of your face, lips, tongue, or throat.

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of Atelvia. For more information, ask your doctor or pharmacist.

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 Atelvia?

- Store Atelvia between 68° F to 77° F (20° C to 25° C).

Keep Atelvia and all medicines out of the reach of children.

General information about the safe and effective use of Atelvia

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information Leaflet. Do not use Atelvia for a condition for which it was not prescribed.

Do not give Atelvia to other people, even if they have the same symptoms you have. It may harm them.

This Medication Guide summarizes the most important information about Atelvia. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about Atelvia that is written for health professionals.

For more information, go to www.atelvia.com or call 1-800-521-8813.

What are the ingredients in Atelvia?

Active ingredient: risedronate sodium

Inactive ingredients: Edetate disodium, ferric oxide yellow, magnesium stearate, methacrylic acid copolymer, polysorbate 80, silicified microcrystalline cellulose (ProSolv SMCC90), simethicone, sodium starch glycolate, stearic acid, talc, and triethyl citrate.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Manufactured by:
Norwich Pharmaceuticals, Inc.
North Norwich, NY 13814
Marketed by:
Warner Chilcott (US), LLC
Rockaway, NJ 07866
1-800-521-8813

0979G016

Covered under one or more of U.S. Patent Nos. 5,583,122; 5,622,721; 7,645,459 B2 and 7,645,460 B2, and other patents pending.

Revised January 2011

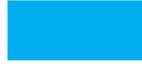




Yellow



Black



Cyan



PMS 287 Blue



PMS 485 Red



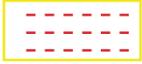
PMS 1585 Orange



Die line
not to be printed



Varnish Area



Glue Area



PMS 301 Blue

0979C024

N 0430-0979-03
Rx Only

Atelvia™ 35 mg

(risedronate sodium) delayed-release tablets

Dispense the enclosed Medication Guide to each patient.

Once-a-Week
4 tablets

NDC BARCODE
UPC VERSION A
PMS 287
304300979036
FOR POSITION ONLY

Lift to Open

Follow These Steps for Taking Atelvia

(risedronate sodium) delayed-release tablets

Pick a convenient day of the week to take your Atelvia 35 mg.

Please read the enclosed Medication Guide for full patient information.

Your Atelvia tablet should be taken on the **same day** every week.

- Take Atelvia in the morning immediately following breakfast with at least 4 ounces of plain water. Swallow the tablet whole.
- Do not** lie down for at least 30 minutes. **Do not** chew, cut, or crush the tablet. Take calcium supplements, antacids, magnesium-based supplements or laxatives and iron preparations at a different time of the day.

Press and Hold

Atelvia 35 mg (risedronate sodium) delayed-release tablets

APPLY PRESCRIPTION LABEL HERE

FOR POSITION ONLY
PMS 287
CODE 128
0979C024

Atelvia 35 mg (risedronate sodium) delayed-release tablets

WARRNER
CHILCOTT

Other patents pending.
Package Patent Nos. 6,047,829; 6,230,893;
6,412,636; 6,752,272.
Additional patents pending.
U.S. Patent Nos. 5,583,122; 5,622,721;
7,645,459 B2 and 7,645,460 B2.
1-800-521-8813
Rockaway, NJ 07866
Mkt. by: Warner Chilcott (US), LLC
North Norwich, NY 13814
Mfg. by: Norwich Pharmaceuticals, Inc.
Information:
See Package Insert for Full Prescribing
Take as directed by prescriber.
25° C (68° - 77° F) [See USP].
Store at controlled room temperature, 20° -

LOT AND EXP AREA

BARCODE



Yellow



Black



Cyan



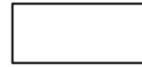
PMS 287 Blue



PMS 485 Red



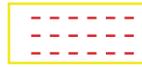
PMS 1585 Orange



Die line
not to be printed



Varnish Area



Glue Area



PMS 301 Blue

Sample - Not for Sale 0979C014

N 0430-0979-95
Rx Only

Atelvia™ 35 mg

(risedronate sodium) delayed-release tablets

Dispense the enclosed Medication Guide to each patient.

Once-a-Week
1 tablet

NDC BARCODE
UPC VERSION A
PMS 287
304300979951
FOR POSITION ONLY

Lift to Open

Follow These Steps for Taking Atelvia

(risedronate sodium) delayed-release tablets

Pick a convenient day of the week to take your Atelvia 35 mg.

Your Atelvia tablet should be taken on the **same day** every week.

Please read the enclosed Medication Guide for full patient information.

- Take Atelvia in the morning immediately following breakfast with at least 4 ounces of plain water. Swallow the tablet whole.
- Do not** lie down for at least 30 minutes. **Do not** chew, cut, or crush the tablet. Take calcium supplements, antacids, magnesium-based supplements or laxatives and iron preparations at a different time of the day.

Press and Hold

Atelvia 35 mg (risedronate sodium) delayed-release tablets

Sample - Not for Sale

APPLY PRESCRIPTION LABEL HERE

FOR POSITION ONLY
CODE 128
PMS 287
0979C014

LOT AND EXP AREA

Atelvia 35 mg (risedronate sodium) delayed-release tablets

Store at controlled room temperature, 20°-25° C (68°-77° F) [See USP].
Take as directed by prescriber.
See Package Insert for Full Prescribing Information.

Mfg. by: Norwich Pharmaceuticals, Inc.
North Norwich, NY 13814
Mkt. by: Warner Chilcott (US), LLC
Rockaway, NJ 07866
1-800-521-8813
U.S. Patent Nos. 5,583,122; 5,622,721;
7,645,459 B2 and 7,645,460 B2.
Additional patents pending.
Package Patent Nos.: 6,047,829; 6,230,893;
6,412,636; 6,752,272.
Other patents pending.

Warner Chilcott

BARCODE

NDA 22-560
Atelvia™ (risedronate sodium) Delayed-Release Tablets

Bisphosphonate Drug Class

Warner Chilcott (US), LLC
100 Enterprise Drive
Rockaway, NJ 07866
Phone: (973) 442-3200
Fax: (973) 442-3280

RISK EVALUATION AND MITIGATION STRATEGY (REMS):

I. GOAL

The goal of the REMS is to inform patients about the serious risks associated with the use of Atelvia including the possible risk of unusual thigh bone fractures.

II. REMS ELEMENTS

A. Medication Guide

Warner Chilcott (US), LLC will ensure that a Medication Guide will be dispensed with each Atelvia prescription and in accordance with 21 CFR 208.24.

B. Timetable for Submission of Assessments

Warner Chilcott (US), LLC will submit REMS Assessments to the FDA 18 months, 3 years and 7 years from the date of the approval of the REMS. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. Warner Chilcott (US), LLC will submit each assessment so that it will be received by FDA on or before the due date.