RIBONE 35

1. NAME OF THE MEDICINAL PRODUCT

RIBONE 35

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

RISEDRONATE 35mg tablets.

Excipients with known effect: each tablet contains 18mg lactose monohydrate.

For a full list of inactive ingredients see section 6.1.

3. PHARMACEUTICAL FORM

Round, biconvex, pale-yellow film-coated tablet.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

- Treatment of postmenopausal osteoporosis to reduce the risk of vertebral fractures.
- Treatment of established postmenopausal osteoporosis to reduce the risk of hip fractures.
- Prevention of osteoporosis in postmenopausal women with increased risk of osteoporosis.
- Treatment of osteoporosis in men at high risk of fracture.

4.2. Posology and method of Administration

The recommended dose in adults is one 35 mg tablet orally once a week.
The tablet should be taken on the same day each week.

The absorption of risedronate sodium is affected by food, thus to ensure adequate absorption patients should take RIBONE 35 at least 30 minutes before the first food, other medicinal product or drink (other than plain water) of the day.

Patients should be instructed that if a dose is missed, one RIBONE 35 tablet should be taken on the day that the tablet is remembered. Patients should then return to taking one tablet once a week on the day the tablet is normally taken. Two tablets should not be taken on the same day.

The tablet must be swallowed whole and not sucked or chewed. To aid delivery of the tablet to the stomach RIBONE 35 is to be taken while in an upright position with a glass of plain water (≥120 ml). Patients should not lie down for 30 minutes after taking the tablet *(see section 4.4 warnings and precautions).*
Supplemental calcium and vitamin D should be considered if the dietary intake is inadequate.

The optimal duration of bisphosphonate treatment for osteoporosis has not been established. The need for continued treatment should be re-evaluated periodically based on the benefits and potential risks of RIBONE 35 on an individual patient basis, particularly after 5 or more years of use.

Elderly: Since the target population is postmenopausal women, a specific dosage instruction for the elderly is not warranted. This has also been shown in the very elderly, 75 years old and above.

Renal Impairment: No dosage adjustment is required for those patients with mild to moderate renal impairment. The use of risedronate sodium is contraindicated in patients with severe renal impairment (creatinine clearance lower than 30ml/min), *(see sections 4.3 and 5.2).*

Children: Safety and efficacy of RIBONE 35 have not been established in children and adolescents

4.3. Contraindications

RIBONE 35 is contraindicated in patients with the following conditions:

- Abnormalities of the esophagus which delay esophageal emptying such as stricture or achalasia [*see Warnings and Precautions (4.4)*].
- Inability to stand or sit upright for at least 30 minutes [*see Posology and method of Administration (4.2)*, *Warnings and Precautions (4.4)*].
- Hypocalcemia [*see Warnings and Precautions (4.4)*].
- Hypersensitivity to active substance or to any of the excipients [*see Inactive Ingredients(6.1)].*

Angioedema, generalized rash, bullous skin reactions, Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported [*see Adverse Reactions (4.5)*].

4.4. Warnings And Precautions

Drug Products with the Same Active Ingredient

RIBONE 35 contains the same active ingredient found in RIBONE 150 tablets. A patient being treated with RIBONE 150 tablets should not receive RIBONE 35.

Upper Gastrointestinal Adverse Reactions

RIBONE 35, 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 RIBONE 35 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 (4.3), Adverse Reactions (4.5)*].

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 RIBONE 35 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 of plain 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 *Posology and method of Administration (4.2)].* In patients who cannot comply with dosing instructions due to mental disability, therapy with RIBONE 35 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.

Mineral Metabolism

Hypocalcemia has been reported in patients taking RIBONE 35. Treat hypocalcemia and other disturbances of bone and mineral metabolism before starting RIBONE 35 therapy. Instruct patients to take supplemental calcium and vitamin D if their dietary intake is inadequate. Adequate intake of calcium and vitamin D is important in all patients [*see Contraindications (4.3), Adverse Reactions (4.5)*].

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 RIBONE 35. Known risk factors for osteonecrosis of the jaw include invasive dental procedures (for example, tooth extraction, dental implants, boney surgery), diagnosis of cancer, concomitant therapies (for example, chemotherapy, corticosteroids, angiogenesis inhibitors), poor oral hygiene, and co-morbid disorders (for example, periodontal and/or other pre-existing dental disease, anemia, coagulopathy, infection, ill-fitting dentures). The risk of ONJ may increase with duration of exposure to bisphosphonates.

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 (4.5)].*

Musculoskeletal Pain

In post-marketing experience, there have been reports of severe and occasionally incapacitating bone, joint, and/or muscle pain in patients taking bisphosphonates [*see Adverse Reactions (4.5)*]. 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.

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 traverse 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 (for example, 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.

Renal Impairment

RIBONE 35 is not recommended for use in patients with severe renal impairment (creatinine clearance less than 30 mL/min).

Glucocorticoid-Induced Osteoporosis

Before initiating RIBONE 35 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.

Laboratory Test Interactions

Bisphosphonates are known to interfere with the use of bone-imaging agents. Specific studies with RIBONE 35 have not been performed.

4.5. Adverse Reactions

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 and Prevention of Postmenopausal Osteoporosis

Once-a-Week Dosing

The safety of Risedronate 35 mg once-a-week in the treatment of postmenopausal osteoporosis was assessed in a 1-year, double-blind, multicenter study comparing Risedronate 5 mg daily and Risedronate 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 Risedronate 5 mg daily and 485 exposed to Risedronate 35 mg once-a-week. Patients with pre-existing gastrointestinal disease and concomitant use of non-steroidal anti- inflammatory drugs, proton pump inhibitors, and H_2 antagonists were included in these clinical trials. All women received 1000 mg of elemental calcium plus vitamin D supplementation up to 500 international units per day if their 25-hydroxyvitamin D_3 level was below normal at baseline.

The incidence of all-cause mortality was 0.4% in the Risedronate 5 mg daily group and 1.0% in the Risedronate 35 mg once-a-week group. The incidence of serious adverse events was 7.1% in the Risedronate 5 mg daily group and 8.2% in the Risedronate 35 mg once-a-week group. The percentage of patients who withdrew from the study due to adverse events was 11.9% in the Risedronate 5 mg daily group and 11.5% in the Risedronate 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 Risedronate 5 mg daily group and the Risedronate 35 mg once-a-week group: dyspepsia (6.9% versus 7.6%), diarrhea (6.3% versus 4.9%), and abdominal pain
(7.3% versus 7.6%).

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

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

Prevention of Postmenopausal Osteoporosis

Once-a-Week Dosing

There were no deaths in a 1-year, double-blind, placebo-controlled study of

Risedronate 35 mg once-a-week for prevention of bone loss in 278 postmenopausal
women without osteoporosis. More treated subjects on Risedronate reported arthralgia (placebo 7.8%; Risedronate 13.9%), myalgia (placebo 2.1%; Risedronate 5.1%), and nausea (placebo 4.3%; Risedronate 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 Risedronate 35 mg once-a-week (N = 191). The overall safety and tolerability profile of Risedronate in men with osteoporosis was similar to the adverse events reported in the Risedronate postmenopausal osteoporosis clinical trials, with the addition of benign prostatic hyperplasia (placebo 3%; Risedronate 35 mg 5%), nephrolithiasis (placebo 0%; Risedronate 35 mg 3%), and arrhythmia (placebo 0%;
Risedronate 35 mg 2%).

Post-marketing 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, including angioedema, generalized rash, bullous skin reactions, Stevens-Johnson syndrome and toxic epidermal necrolysis.

Gastrointestinal Adverse Events

Events involving upper gastrointestinal irritation, such as esophagitis and esophageal or gastric ulcers, have been reported [*see Warnings and Precautions (4.4)*].

Musculoskeletal Pain

Bone, joint, or muscle pain, described as severe or incapacitating, have been reported rarely [*see Warnings and Precautions (4.4)*].

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 (4.4)*]

Pulmonary

Asthma exacerbations

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form.
https://www.gov.il/he/service/adverse_effects_reports
In addition, you can address "Unipharm Ltd.".

4.6. 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 (for example, Cytochrome P450).

Calcium Supplements/Antacids

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

Hormone Replacement Therapy

One study of about 500 early postmenopausal women has been conducted to date in which treatment with Risedronate 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, Risedronate may be used concomitantly with hormone replacement therapy.

Aspirin/Nonsteroidal Anti-Inflammatory Drugs

Of over 5700 patients enrolled in the Risedronate 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 Risedronate -treated patients (24.5%).

H_2 Blockers and Proton Pump Inhibitors (PPIs)

Of over 5700 patients enrolled in the Risedronate Phase 3 osteoporosis studies, 21% used H_2 blockers and/or PPIs. Among these patients, the incidence of upper gastrointestinal adverse experiences in the placebo-treated patients was similar to that in Risedronate - treated patients.

4.7. Use In Specific Populations

Pregnancy

Risk Summary

Available data on the use of Risedronate in pregnant women are insufficient to inform a drug-associated risk of adverse maternal or fetal outcomes. Discontinue Risedronate when pregnancy is recognized.

In animal reproduction studies, daily oral administration of risedronate to pregnant rats during organogenesis decreased neonatal survival and body weight at doses

approximately 5 and 26 times, respectively, the highest recommended human daily dose of 30 mg (based on body surface area, mg/m^2). A low incidence of cleft palate was observed in fetuses of dams treated at doses approximately equal to the 30 mg human daily dose. Delayed skeletal ossification was observed in fetuses of dams treated at approximately 2.5 to 5 times the 30 mg human daily dose. Periparturient mortality due to maternal hypocalcemia occurred in dams and neonates upon daily oral administration of risedronate to pregnant rats during mating and/or gestation starting at doses equivalent to the 30 mg daily human dose.

Bisphosphonates are incorporated into the bone matrix, from which they are gradually released over a period of years. The amount of bisphosphonate incorporated into adult bone and available for release into the systemic circulation is directly related to the dose and duration of bisphosphonate use. Consequently, based on the mechanism of action of bisphosphonates, there is a potential 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.

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of birth defects, loss, or other adverse outcomes. In the U.S. general population, the estimated background risks of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

In animal studies, pregnant rats received risedronate sodium during organogenesis at doses equivalent to 1 to 26 times the 30 mg human daily dose (based on body surface area, mg/m^2). Survival of neonates was decreased in dams treated during gestation with oral doses approximately 5 times the human dose, and body weight was decreased in neonates of dams treated with approximately 26 times the human dose. A low incidence of cleft palate was observed in fetuses of dams treated with oral doses approximately equal to the human dose. The number of fetuses exhibiting incomplete ossification of sternebrae or skull of 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 fetuses of dams treated with oral doses approximately 5 times the human dose.

No significant ossification effects were seen in fetuses of 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.

Periparturient mortality due to maternal hypocalcemia occurred in dams and neonates when pregnant rats were treated daily during mating and/or gestation with oral doses equivalent to the human dose or higher.

Lactation

Risk Summary

There are no data on the presence of risedronate in human milk, the effects on the breastfed infant, or the effects on milk production. A small degree of lacteal transfer occurred in nursing rats. The concentration of the drug in animal milk does not necessarily predict the concentration of drug in human milk. However, when a drug is present in animal milk, it is likely that the drug will be present in human milk. The developmental and health benefits of breast-feeding should be considered along with the mother's clinical need for Risedronate and any potential adverse effects on the breast-fed child from Risedronate or from the underlying maternal condition.

Data

Animal Data

Risedronate was detected in neonates of lactating rats given a single oral dose of risedronate at 24-hours post-dosing, indicating a small degree of lacteal transfer.

Pediatric Use

Risedronate 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 less than 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 (less than or equal to 30 kg body weight) or 5 mg (greater than 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 Risedronate -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 greater than or equal to 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%).

Geriatric Use

Of the patients receiving Risedronate in postmenopausal osteoporosis studies [*see Clinical Studies (5.4)*], 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 Risedronate were between 65 and 75 years of age and 9% were over 75. The lumbar spine BMD response for Risedronate compared to placebo was 5.6% for subjects less than 65 years and 2.9% for subjects greater than or equal to 65 years. No overall differences in safety between geriatric and younger patients were observed in the Risedronate trials, but greater sensitivity of some older individuals cannot be ruled out.

Renal Impairment

Risedronate is not recommended for use in patients with severe renal impairment (creatinine clearance less than 30 mL/min) because of lack of clinical experience. No dosage adjustment is necessary in patients with a creatinine clearance greater than or equal to 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 human liver preparations. Dosage adjustment is unlikely to be needed in patients with hepatic impairment.

4.8. 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 Risedronate 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/m^2).

5. CLINICAL PHARMACOLOGY

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 (for example, lack of ruffled border). Histomorphometry in rats, dogs, and minipigs showed that Risedronate treatment reduces bone turnover (activation frequency, that is, the rate at which bone remodeling sites are activated) and bone resorption at remodeling sites.

5.1. Pharmacodynamics

Risedronate treatment decreases the elevated rate of bone turnover that is typically seen in postmenopausal osteoporosis. In clinical trials, administration of Risedronate 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 Risedronate for the treatment of osteoporosis in postmenopausal women, Risedronate 5 mg daily and Risedronate 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 Risedronate 5 mg daily and Risedronate 35 mg once-a- week groups, respectively.

Osteoporosis in Men

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

5.2. Pharmacokinetics

Absorption

Based on simultaneous modeling of serum and urine data, peak absorption after an oral dose is achieved at approximately 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. Risedronate 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 [^{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, 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: Risedronate is not indicated for use in pediatric patients [see *Pediatric Use (4.8)*].

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

Geriatric: Bioavailability and disposition are similar in elderly (greater than 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. Risedronate is not recommended for use in patients with severe renal impairment (creatinine clearance less than 30 mL/min) because of lack of clinical experience. No dosage adjustment is necessary in patients with a creatinine clearance greater than or equal to 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 (less than 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 (4.7)*].

5.3. Nonclinical Toxicology

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 (greater than 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/m^2). 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.

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 Risedronate 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/m^2).

5.4. Clinical Studies

Treatment of Osteoporosis in Postmenopausal Women

The fracture efficacy of Risedronate 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 5 mg, N = 408) was conducted primarily in Europe and Australia; a second study was conducted in North America (VERT NA) (Risedronate 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 D_3 levels (approximately 40 nmol/L or less) also received supplemental vitamin D 500 international units/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 (that is, 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 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 on the Risk of Vertebral Fractures

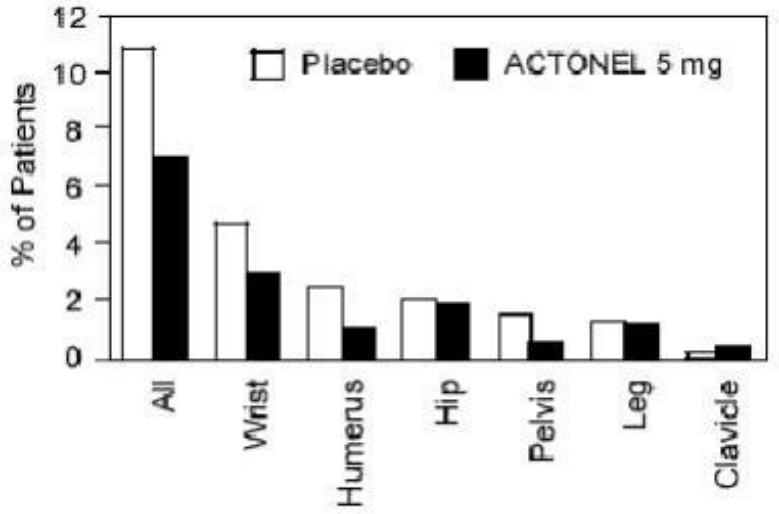
	Proportion of Patients with Fracture (%)[a]			
VERT NA	Placebo N = 678	Risedronate 5 mg N = 696	Absolute Risk Reduction (%)	Relative Risk Reduction (%)
New and Worsening				
0 - 1 Year	7.2	3.9	3.3	49
0 - 2 Years	12.8	8.0	4.8	42
0 - 3 Years	18.5	13.9	4.6	33
New				
0 - 1 Year	6.4	2.4	4.0	65
0 - 2 Years	11.7	5.8	5.9	55
0 - 3 Years	16.3	11.3	5.0	41
VERT MN	Placebo N = 346	Risedronate 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. Risedronate 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.

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 Risedronate 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 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 Risedronate 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

Risedronate 35 mg once-a-week (N = 485) was shown to be non-inferior to Risedronate 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.

Histology/Histomorphometry

Bone biopsies from 110 postmenopausal women were obtained at endpoint. Patients had received placebo or daily Risedronate (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 -treated women. These findings demonstrate that bone formed during Risedronate 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 5 mg. Mineralizing surface decreased moderately in Risedronate -treated patients (median percent change: placebo, -21%; Risedronate 5 mg, -74%), consistent with the known effects of treatment on bone turnover.

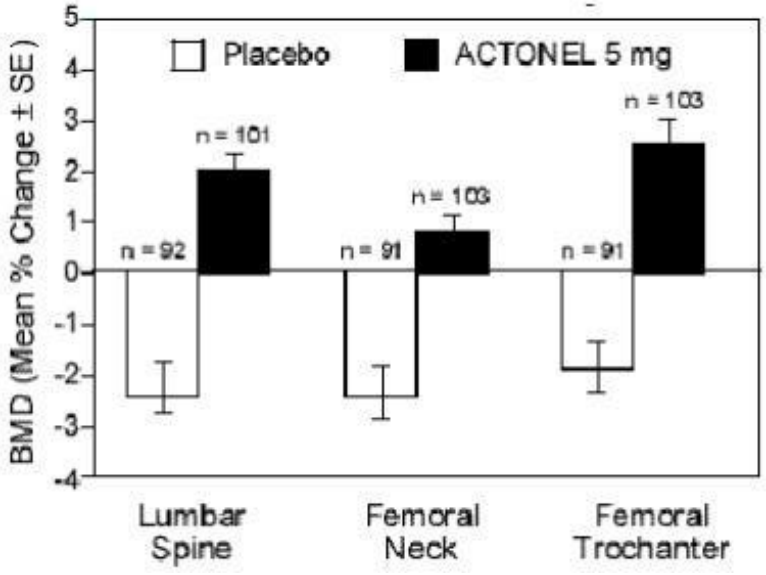
Effect on Height

In the two 3-year osteoporosis treatment studies, standing height was measured yearly by stadiometer. Both Risedronate and placebo-treated groups lost height during the studies. Patients who received Risedronate 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 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 5 mg daily group.

Prevention of Osteoporosis in Postmenopausal Women

The safety and effectiveness of Risedronate 5 mg daily for the prevention of postmenopausal osteoporosis were demonstrated in a 2-year, double-blind, placebo- controlled study of 383 postmenopausal women (age range 42 to 63 years) within three years of menopause (Risedronate 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 Risedronate treatment. Risedronate 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). Risedronate 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 Risedronate and placebo-treated women following 1 year of treatment.

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



The safety and effectiveness of Risedronate 35 mg once-a-week for the prevention postmenopausal osteoporosis were demonstrated in a 1-year, double-blind, placebo- controlled study of 278 patients (Risedronate 35 mg, N = 136). All patients were supplemented with 1000 mg elemental calcium and 400 international units 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).

Risedronate 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%). Risedronate 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 Risedronate 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 0.625mg N = 261	Risedronate 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 Risedronate 5 mg plus estrogen or estrogen-alone once daily for 1 year.
Histologic evaluation (N = 47) demonstrated that the bone of patients treated with Risedronate 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 Risedronate plus estrogen and 12 treated with estrogen-alone. Mineralizing surface decreased in both treatment groups (median percent change: Risedronate plus estrogen, -79%; estrogen-alone, -50%), consistent with the known effects of these agents on bone turnover.

Men with Osteoporosis

The effects of Risedronate 35 mg once-a-week on BMD were examined in a 2-year, double- blind, placebo-controlled, multinational study in 285 men with osteoporosis (Risedronate, N
= 192). The patients had a mean age of 61 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 less than or equal to -2 at the femoral neck and less than or equal to -1 at the lumbar spine, or 2) a BMD T- score less than or equal to -1 at the

femoral neck and less than or equal to -2.5 at the lumbar spine. All patients were supplemented with calcium 1000 mg/day and vitamin D 400 to 500 international units/day. Risedronate 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%).

6. PHARMACEUTICAL PARTICULARS

6.1. Inactive Ingredients

Microcrystalline cellulose, Lactose monohydrate, Crospovidone, Magnesium stearate, Colloidal silicon dioxide, Opadry white Y-1-7000, Opadry yellow OY-6478.

6.2. Incompatibilities

Not applicable.

6.3. Shelf-life

Do not use RIBONE 35 after the expiration date (the expiry date of the product is indicated on the package materials).
The expiration date refers to the last day of the specified month.

6.4. Storage

Store below 25ºC, in a dry place.

6.5. Nature and contents of container

Packed in Blister (PVC/Aluminium), which is inserted into a carton package with 1;2;4;5;7;10;15 tablets. Not all pack sizes may be marketed.

7. MARKETING AUTHORIZATION HOLDER

Unipharm Ltd. P.O.B.16545 Tel-Aviv 6116401.
Manufacturer: Unipharm Ltd. - "Mevo Carmel" Industrial Park.

8. REGISTRATION NUMBER ACCORDING TO MOH

145-61-33140-01

Revised in January 2026.