Dronel® 35

Risedronate Sodium 35mg

Once a Week

FORMS AND PRESENTATION

Dronel® 35: Film coated tablets: Box of 4.

COMPOSITION

Dronel® 35: Each film coated tablet contains Risedronate Sodium 35mg equivalent to Risedronic acid 32.5mg.

Excipients: microcrystalline cellulose, lactose, crospovidone, magnesium stearate, hypromellose, titanium dioxide, polyethylene glycol, yellow iron oxide , red iron oxide.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Therapeutic class: Drugs for treatment of bone diseases.

ATC code: M05BA07.

Risedronate Sodium is a pyridinyl bisphosphonate that binds to bone hydroxyapatite and inhibits osteoclast-mediated bone resorption. The bone turnover is reduced while the osteoblast activity and bone mineralization is preserved. In preclinical studies Risedronate Sodium demonstrated potent anti-osteoclast and antiresorptive activity, and dose dependently increased bone mass and biomechanical skeletal strength. The activity of Risedronate Sodium was confirmed by measuring biochemical markers for bone turnover during pharmacodynamic and clinical studies. In studies of post-menopausal women, decreases in biochemical markers of bone turnover were observed within 1 month and reached a maximum in 3-6 months. Decreases in biochemical markers of bone turnover were similar with Risedronate Sodium 35 mg and Risedronate Sodium 5 mg daily at 12 months.

Pharmacokinetic properties

Absorption

Absorption after an oral dose is relatively rapid (t_{max} ~1 hour) and is independent of dose over the range studied (single dose study, 2.5 to 30 mg; multiple dose studies, 2.5 to 5 mg daily and up to 50 mg dosed weekly). Mean oral bioavailability of the tablet is 0.63% and is decreased when Risedronate Sodium is administered with food. Bioavailability was similar in men and women.

Distribution

The mean steady state volume of distribution is 6.3 l/kg in humans. Plasma protein binding is about 24%.

Biotransformation

There is no evidence of systemic metabolism of Risedronate Sodium.

Elimination

Approximately half of the absorbed dose is excreted in urine within 24 hours, and 85% of an intravenous dose is recovered in the urine after 28 days. Mean renal clearance is 105 ml/min and mean total clearance is 122 ml/min, with the difference probably attributed to 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 Risedronate Sodium is eliminated unchanged in feces. After oral administration the concentration-time profile shows three elimination phases with a terminal half-life of 480 hours.

INDICATIONS

Dronel® 35 is indicated:

- In the treatment of postmenopausal osteoporosis, to reduce the risk of vertebral fractures.
- In the treatment of established postmenopausal osteoporosis, to reduce the risk of hip fractures.
- In the treatment of osteoporosis in men at high risk of fractures.

CONTRAINDICATIONS

- Hypersensitivity to Risedronate Sodium or to any of the excipients.
- Hypocalcemia.
- Pregnancy and lactation.
- Severe renal impairment (creatinine clearance <30ml/min).

PRECAUTIONS

- Foods, drinks (other than plain water) and medicinal products containing polyvalent cations (such as calcium, magnesium, iron and aluminium) interfere with the absorption of bisphosphonates and should not be taken at the same time as Risedronate Sodium. In order to achieve the intended efficacy, strict adherence to dosing recommendations is necessary .
- Efficacy of bisphosphonates in the treatment of postmenopausal osteoporosis is related to the presence of low bone mineral density (BMD T-score at hip or lumbar spine <-2.5 SD) and/or prevalent fracture.
- High age or clinical risk factors for fracture alone are not reasons to initiate treatment of osteoporosis with a bisphosphonate.
- The evidence to support efficacy of bisphosphonates including Risedronate Sodium in very elderly women (>80 years) is limited.
- Bisphosphonates have been associated with oesophagitis, gastritis, esophageal ulcerations and gastroduodenal ulcerations. Thus caution should be used: In patients who have a history of esophageal disorders which delay esophageal transit or emptying e.g. stricture or achalasia; in patients who are unable to stay in the upright position for at least 30 minutes after taking the tablet; if Risedronate is given to patients with active or recent esophageal or upper gastrointestinal problems.
- Prescribers should emphasize to patients the importance of paying attention to the dosing instructions and be alert to any signs or symptoms of possible esophageal reaction. The patients should be instructed to seek timely medical attention if they develop symptoms of esophageal irritation such as dysphagia, pain on swallowing, retrosternal pain or new/worsened heartburn.
- Hypocalcemia should be treated before starting Risedronate Sodium therapy. Other disturbances of bone and mineral metabolism (e.g. parathyroid dysfunction, hypovitaminosis D) should be treated at the time of starting Risedronate Sodium therapy.
- Osteonecrosis of the jaw, generally associated with tooth extraction and/or local infection (including osteomyelitis), has been reported in patients with cancer receiving treatment regimens including primarily intravenously administered bisphophonates. Many of these patients were also receiving chemotherapy and corticosteroids. Osteonecrosis of the jaw has also been reported in patients with osteoporosis receiving oral bisphosphonates.

A dental examination with appropriate preventive dentistry should be considered prior to treatment with bisphosphonates in patients with concomitant risk factors (e.g. cancer, chemotherapy, radiotherapy, corticosteroids, poor oral hygiene).

While on treatment, these patients should avoid invasive dental procedures if possible. For patients who develop osteonecrosis of the jaw while on bisphosphonate therapy, dental surgery may exacerbate the condition. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of osteonecrosis of the jaw.

- Clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit /risk assessment.
- Atypical fractures of the femur: Atypical subtrochanteric and diaphyseal femoral fractures have been reported with bisphosphonate therapy, primarily in patients receiving long-term treatment for osteoporosis. These transverse or short oblique fractures can occur anywhere along the femur from just below the lesser trochanter to just above the supracondylar flare. These fractures occur after minimal or no trauma and some patients experience thigh or groin pain, often associated with imaging features of stress fractures, weeks to months before presenting with a completed femoral fracture. Fractures are often bilateral; therefore the contralateral femur should be examined in bisphosphonate-treated patients who have sustained a femoral shaft fracture. Poor healing of these fractures has also been reported. Discontinuation of bisphosphonate therapy in patients suspected to have an atypical femur fracture should be considered pending evaluation of the patient, based on an individual benefit risk assessment.
- During bisphosphonate treatment patients should be advised to report any thigh, hip or groin pain and any patient presenting with such symptoms should be evaluated for an incomplete femur fracture.
- This medicine contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or

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glucose-galactose malabsorption should not take this medicine.

Ability to drive and use machines

No effects on ability to drive and use machines have been observed.

PREGNANCY AND LACTATION

There are no adequate data from the use of Risedronate Sodium in pregnant women. Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown. Studies in animal indicate that a small amount of Risedronate Sodium pass into breast milk.

Risedronate Sodium must not be used during pregnancy or by breast-feeding women.

DRUG INTERACTIONS

- No formal interaction studies have been performed, however no clinically relevant interactions with other medicinal products were found during clinical trials.
- In the Risedronate Sodium Phase III osteoporosis studies with daily dosing, acetyl salicylic acid or NSAID use was reported by 33% and 45% of patients respectively. In the Phase III once a week study in postmenopausal women, acetyl salicylic acid or NSAID use was reported by 57% and 40% of patients respectively. Among regular acetyl salicylic acid or NSAID users (3 or more days per week) the incidence of upper gastrointestinal adverse events in Risedronate Sodium treated patients was similar to that in control patients.
- If considered appropriate Risedronate Sodium may be used concomitantly with estrogen supplementation (for women only).
- Concomitant ingestion of medications containing polyvalent cations (e.g. calcium, magnesium, iron and aluminium) will interfere with the absorption of Risedronate Sodium.
- Risedronate Sodium is not systemically metabolized, does not induce cytochrome P450 enzymes, and has low protein binding.

ADVERSE EFFECTS

The majority of undesirable effects observed in clinical trials with Risedronate Sodium were mild to moderate in severity and usually did not require cessation of therapy.

Reported adverse experiences considered possibly or probably related to Risedronate Sodium are listed below using the following convention: Very common (≥1/10); common (≥1/100; <1/10); uncommon (≥1/1,000; <1/100); rare (≥1/10,000; <1/1,000); very rare (<1/10,000).

- Nervous system disorders: Headache (common).
- Eye disorders: Iritis (uncommon).
- Gastrointestinal disorders: Constipation, dyspepsia, nausea, abdominal pain, diarrhea (common); gastritis, esophagitis, dysphagia, duodenitis, esophageal ulcer (uncommon); glossitis, esophageal stricture (rare).
- Musculoskeletal and connective tissues disorders: Musculoskeletal pain (common).
- Investigations: Abnormal liver function tests (rare).
- Laboratory findings: Early, transient, asymptomatic and mild decreases in serum calcium and phosphate levels have been observed in some patients.

The following additional adverse reactions have been reported during post-marketing use (frequency unknown):

- Eye disorders: Iritis, uveitis.
- Muskuloskeletal and connective tissues disorders: Osteonecrosis of the jaw.
- Skin and subcutaneous tissue disorders: Hypersensitivity and skin reactions, including angioedema, generalized rash, urticaria and bullous skin reactions, some severe including isolated reports of Stevens Johnson syndrome, toxic epidermal necrolysis and leukocytoclastic vasculitis.
- Hair loss.
- Immune system disorders: Anaphylactic reaction.
- Hepatobiliary disorders: Serious hepatic disorders. In most of the reported cases the patients were also treated with other products known to cause hepatic disorders.

During post-marketing experience the following reactions have been reported (frequency rare):

- Atypical subtrochanteric and diaphyseal femoral fractures (bisphosphonate class adverse reaction).

DOSAGE AND ADMINISTRATION

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

The absorption of Dronel® 35 is affected by food, thus to ensure adequate absorption patients should take Dronel® 35:

- Before breakfast: At least 30 minutes before the first food, other medicinal product or drink (other than plain water) of the day.

In the particular instance that before breakfast dosing is not practical, Dronel® 35 can be taken between meals or in the evening at the same time every day, with strict adherence to the following instructions, to ensure Dronel® 35 is taken on an empty stomach:

- Between meals: Dronel® 35 should be taken at least 2 hours before and at least 2 hours after any food, medicinal product or drink (other than plain water).
- In the evening: Dronel® 35 should be taken at least 2 hours after the last food, medicinal product or drink (other than plain water) of the day. Dronel® 35 should be taken at least 30 minutes before going to bed.

If an occasional dose is missed, Dronel® 35 can be taken before breakfast, between meals, or in the evening according to the instructions above.

The tablet must be swallowed whole and not sucked or chewed. To aid delivery of the tablet to the stomach Dronel® 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.

Physicians should consider the administration of supplemental calcium and vitamin D if dietary intake is inadequate, especially as bone turnover is significantly elevated in Paget's disease.

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 Dronel® 35 on an individual patient basis, particularly after 5 or more years of use.

Elderly

No dosage adjustment is necessary since bioavailability, distribution and elimination were similar in elderly (>60 years of age) compared to younger subjects.

Renal impairment

No dosage adjustment is required for those patients with mild to moderate renal impairment. The use of Dronel® 35 is contraindicated in patients with severe renal impairment (creatinine clearance lower than 30 ml/min).

Pediatric population

Dronel® 35 is not recommended for use in children below age 18 due to insufficient data on safety and efficacy.

OVERDOSAGE

No specific information is available on the treatment of overdose with Risedronate Sodium.

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

Milk or antacids containing magnesium, calcium or aluminium should be given to bind Risedronate and reduce absorption of Risedronate Sodium. In cases of substantial overdose, gastric lavage may be considered to remove unabsorbed Risedronate Sodium.

STORAGE CONDITIONS

Store below 30˚C.

Keep in original pack in intact conditions.

Date of revision: February 2024.

This is a medicament

- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use, and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are experts in medicine, its benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed for you.
- Do not repeat the same prescription without consulting your doctor.
- Medicament: keep out of reach of children.

Council of Arab Health Ministers
Union of Arab Pharmacists

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