RISEDRONATE SODIUM

RESIDRON

35 mg Tablet

Bisphosphonate

FORMULATION:

Each film coated tablet contains:

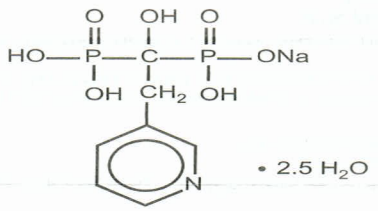
Risedronate Sodium hemipentahydrate	40.17 mg
Equivalent to Risedronate Sodium	35 mg

Excipients:

Starch Pregelatinised Ph.Eur, Microcrystalline cellulose Ph.Eur, Crospovidone Ph.Eur, Magnesium stearate Ph.Eur, *Opadry White IH (Titanium dioxide Ph.Eur, Lactose* monohydrate Ph.Eur, Macrogol 4000 Ph.Eur, Hypromellose Ph.Eur), Ethanol 96% Ph.Eur, Purified water Ph.Eur

DESCRIPTION:

Risedronate sodium tablet is a pyridinyl bisphosphonate that inhibits osteoclast-mediated bone resorption and modulates bone metabolism. The empirical formula for risedronate sodium hemi-pentahydrate is $C_7H_{10}NO_7P_2Na$ 2.5 H_2O. 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

MECHANISM OF ACTION:

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.

PHARMACOKINETICS :

Absorption: Absorption after an oral dose is relatively rapid (tmax ~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%.

Metabolism: 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:

Postmenopausal Osteoporosis

Risedronate is indicated for the treatment and prevention of osteoporosis in postmenopausal women. In postmenopausal women with osteoporosis, it reduces the incidence of vertebral fractures and a composite endpoint of nonvertebral osteoporosis-related fractures.

Osteoporosis in Men

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

DOSAGE AND 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 Risedronate:

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

If a patient forgets to take the 35mg risedronate tablet in the morning inform him/her not to take it later in the day. Take only 1 risedronate 35mg tablet the next morning & continue the usual schedule of 35mg (1 tablet on a chosen day of the week). 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 Risedronate is to be taken while in an upright (standing or sitting) position with a glass of plain water (≥ 120 ml). Patients should not lie down for 30 minutes after taking the tablet.

Supplemental calcium and vitamin D should be considered if the dietary intake is inadequate.

Elderly:

No dosage adjustment is necessary since bioavailability, distribution and elimination were similar in elderly (>60 years of age) compared to younger subjects. This has also been shown in the very elderly, 75 years old and above postmenopausal *population.*

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 30 ml/min).

Children:

Safety and efficacy of risedronate 35 mg have not been established in children and adolescents.

CONTRAINDICATIONS

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

WARNINGS & 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. In order to achieve the intended efficacy, strict adherence to dosing recommendations is necessary.

Efficacy of bisphosphonates in the treatment of osteoporosis is related to the presence of low bone mineral density and/or prevalent fracture.

High age or clinical risk factors for fracture alone are not sufficient reasons to initiate treatment of osteoporosis with a bisphosphonate. The evidence to support efficacy of bisphosphonates including risedronate in the very elderly (>80 years) is limited.

Bisphosphonates have been associated with oesophagitis, gastritis, oesophageal ulcerations and gastroduodenal ulcerations. Thus caution should be used:

- In patients who have a history of oesophageal disorders which delay oesophageal 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 oesophageal or upper gastrointestinal problems.

Prescribers should emphasize to patients the importance of paying attention to the dosing instructions and be alert to any signs and 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 therapy. Other disturbances of bone and mineral metabolism (i.e. parathyroid dysfunction, hypovitaminosis D) should be treated at the time of starting Risedronate 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.

This medicine contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency

or glucose-galactose malabsorption should not take this medicine.

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, acetylsalicylic 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.

Risedronate sodium is not systemically metabolized, does not induce cytochrome P450 enzymes, and has low protein binding.

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.

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

ADVERSE REACTIONS:
Risedronate sodium has been studied in phase III clinical trials involving more than 15,000 patients.

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

Adverse experiences reported in phase III clinical trials in postmenopausal women with osteoporosis treated for up to 36 months with risedronate sodium 5mg/day (n=5020) or placebo (n=5048) and considered possibly or probably related to risedronate sodium are listed below using the following convention (incidences versus placebo are shown in brackets):

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:
Common: headache (1.8% vs. 1.4%)

Eye disorders:
Uncommon: iritis*

Gastrointestinal disorders:
Common: constipation (5.0% vs. 4.8%), dyspepsia (4.5% vs. 4.1%),

nausea (4.3% vs. 4.0%), abdominal pain (3.5% vs. 3.3%), diarrhea (3.0% vs. 2.7%)

Uncommon: gastritis (0.9% vs. 0.7%), esophagitis (0.9% vs. 0.9%), dysphagia (0.4% vs. 0.2%), duodenitis (0.2% vs. 0.1%), esophageal ulcer (0.2% vs. 0.2%)

Rare: glossitis (<0.1% vs. 0.1%), esophageal stricture (<0.1% vs. 0.0%)

Musculoskeletal and connective tissues disorders:
Common: musculoskeletal pain (2.1% vs. 1.9%)

Investigations:

Rare: abnormal liver function tests*

* No relevant incidences from Phase III osteoporosis studies; frequency based on adverse event/laboratory/rechallenge findings in earlier clinical trials.

In a one-year, double-blind, multicentre study comparing risedronate sodium 5 mg daily (n=480) and risedronate sodium 35 mg weekly (n=485) in postmenopausal women with osteoporosis, the overall safety and tolerability profiles were similar. The following additional adverse experiences considered possibly or probably drug related by investigators have been reported (incidence greater in risedronate 35 mg than in risedronate sodium 5 mg group): gastrointestinal disorder (1.6% vs. 1.0%) and pain (1.2% vs. 0.8%).

In a 2-year study in men with osteoporosis, the overall safety and tolerability were similar between the treatment and the placebo groups. Adverse experiences were consistent with those previously observed in women.

Laboratory findings: Early, transient, asymptomatic and mild decreases in serum calcium and phosphate levels have been observed in some patients.

OVERDOSE:
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 at temperatures not exceeding 30°C, Protect from light and moisture.
Keep out of reach of children.

Availability:
1 Alu/PVC/PE/PVDC Blister Pack x 4's (Box of 4's)

Caution:
Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

DR-XY45055

MEGA We care

Manufactured by :
PHARMATHEN S.A.
6, Dervenakion Street, 153 51 Pallini, Attikis, Greece

For : **MEGA LIFESCIENCES (AUSTRALIA) PTY LTD**
60, National Avenue, Pakenham, Victoria 3810, Australia

Imported & Distributed by :
METRO DRUG, INC.
Mañalac Avenue, Bagumbayan, Taguig City, Philippines

For suspected adverse drug reaction, report to the FDA: **www.fda.gov.ph**

Date of First Authorization: 15 February 2016

Date of Revision of Package Insert: October 2018

2827084

I-R804-M25-00-00