

Risedronate

Core Safety Profile

4.2 Posology and method of administration*

The tablets must be swallowed whole and not sucked or chewed. To aid delivery of the tablet to the stomach risedronate sodium 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

Paediatric population: Risedronate sodium is not recommended for use in children below age 18 due to insufficient data on safety and efficacy.

*Only safety related information

4.3 Contraindications

Hypersensitivity to risedronate sodium or to any of the excipients.

Hypocalcaemia

Pregnancy and lactation.

Severe renal impairment (creatinine clearance < 30 ml/min).

4.4 Special warnings and precautions for use

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.

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 emphasise to patients the importance of paying attention to the dosing instructions and be alert to any signs or symptoms of possible oesophageal reaction. The patients should be instructed to seek timely medical attention if they develop symptoms of oesophageal irritation such as dysphagia, pain on swallowing, retrosternal pain or new/worsened heartburn.

Hypocalcaemia 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 bisphosphonates. 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. **

** Concerns only Risedronate 5 mg, 30 mg, 35 mg tablets

4.5 Interaction with other medicinal products and other forms of interaction

No formal interaction studies have been performed, however no clinically relevant interactions with other medicinal products were found during clinical trials.

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 metabolised, does not induce cytochrome P450 enzymes, and has low protein binding.

4.6 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.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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 5mg/day

(n=5020) or placebo (n=5048) and considered possibly or probably related to risedronate are listed below using the following convention (incidences versus placebo are shown in brackets): very common ($\geq 1/10$); common ($\geq 1/100$; $< 1/10$); uncommon ($\geq 1/1,000$; $< 1/100$); rare ($\geq 1/10,000$; $< 1/1,000$); 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%), diarrhoea (3.0% vs. 2.7%)

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

Rare: glossitis ($< 0.1\%$ vs. 0.1%), oesophageal 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.

For 75 mg only

In a 2-year, double-blind, multicentre study comparing risedronate sodium 5 mg daily (n= 613) and risedronate sodium 75 mg tablets on two consecutive days a month (n=616) in postmenopausal women with osteoporosis, the overall safety profiles were similar. The following additional adverse experiences considered possibly or probably drug related by investigators have been reported (incidence greater in risedronate sodium 75 mg than in risedronate sodium 5 mg group)

Gastrointestinal disorders:

Common: gastritis erosive (1.5% vs 0.8%), vomiting (1.3% vs 1.1%)

Musculoskeletal and connective tissues disorders:

Common: arthralgia (1.5% vs. 1.0%) bone pain (1.1% vs 0.5%) and pain in extremity (1.1% vs 0.5%).

General disorders:

Uncommon: acute phase reactions, such as fever and/or influenza-like illness (within 5 days of the first dose) (0.6% vs. 0.0%)

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

Musculoskeletal and connective tissues disorders:

osteonecrosis of the jaw

Skin and subcutaneous tissue disorders:

hypersensitivity and skin reactions, including angioedema, generalised 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.

4.9 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 hypocalcaemia 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.