PRESCRIBING INFORMATION

RISOBIS™ 35

(For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only)

1. QUALITATIVE & QUANTITATIVE COMPOSITION

Risedronate Sodium IP…..…… 35 mg

Excipients ……...……..……Q.S.

2. BRAND NAME

Risobis 35

3. DOSAGE FORM

Tablet for oral use

4. INDICATIONS

Postmenopausal Osteoporosis - Risedronate is indicated for the treatment and prevention of osteoporosis in postmenopausal women.

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

Glucocorticoid-Induced Osteoporosis - Risedronate is indicated for the treatment and prevention of glucocorticoid-induced osteoporosis in men and women who are either initiating or continuing systemic glucocorticoid treatment (daily dosage of ≥7.5 mg prednisone or equivalent) for chronic diseases.

Patients treated with glucocorticoids should receive adequate amounts of calcium and vitamin D.

Paget's Disease - Risedronate is indicated for treatment of Paget's disease of the bone in men and women.

Important Limitations of Use

The safety and effectiveness of risedronate for the treatment of osteoporosis are based on clinical data of 3 years 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.

Patients at low-risk for fracture should be considered for drug discontinuation after 3 to 5 years of use.

Patients who discontinue therapy should have their risk for fracture re-evaluated periodically.

5. DOSAGE AND ADMINISTRATION

5.1 Dosage

Treatment of Postmenopausal Osteoporosis

The recommended regimen is one 35 mg tablet orally, taken once-a-week.

Prevention of Postmenopausal Osteoporosis

The recommended regimen is one 35 mg tablet orally, taken once-a-week.

Treatment to Increase Bone Mass in Men with Osteoporosis

The recommended regimen is one 35 mg tablet orally, taken once-a-week.

Treatment and Prevention of Glucocorticoid-Induced Osteoporosis

The recommended regimen is one 35 mg tablet orally, taken weekly.

Paget's Disease

The recommended treatment regimen is 30 mg orally once daily for 2 months. Re-treatment may be considered (following post-treatment observation of at least 2 months) if relapse occurs, or if treatment fails to normalize serum alkaline phosphatase. For re-treatment, the dose and duration of therapy are the same as for initial treatment. No data are available on more than one course of re-treatment.

5.2 Missed Dose

Instruct patients about missing RISOBIS Tablets doses as follows:

If a dose of RISOBIS 35 once-a-week is missed:

- Take one tablet on the morning after they remember and return to taking one tablet once-a-week, as originally scheduled on their chosen day.

Do not take two tablets on the same day.

5.3 Administration

RISOBIS Tablets should be taken at least 30 minutes before the first food or drink of the day other than water and before taking any oral medication or supplementation, including calcium, antacids, or vitamins to maximize absorption and clinical benefit.

The use of water with supplements, including mineral water, should be avoided because they may have a higher concentration of calcium. To facilitate delivery to the stomach, RISOBIS Tablets should be swallowed while the patient is in an upright position and with a full glass of plain water (177 to 236 ml).

Patients should not lie down for 30 minutes after taking the medication. The tablet should not be chewed or sucked because of a potential for oropharyngeal ulceration. Patients should not eat or drink anything except plain water or take other medications for at least 30 minutes after taking RISOBIS Tablets. Patients should receive supplemental calcium

and vitamin D if dietary intake is inadequate. Calcium supplements and calcium-, aluminum-, iron- and magnesium-containing medications may interfere with the absorption of RISOBIS Tablets and should be taken at a different time of the day.

RISOBIS Tablets are 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 ≥30 mL/min or in the elderly (>60 years of age).

6. PHARMACOLOGY

6.1 Pharmacodynamics

Risedronate is a pyridinyl bisphosphonate that inhibits osteoclast-mediated bone resorption and modulates bone metabolism. Risedronate has an affinity for hydroxyapatite crystals in bone and acts as an anti-resorptive 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).

6.2 Pharmacokinetics

6.2.1 Absorption

Absorption after an oral dose is relatively rapid (Tmax ~1 hour) 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 to 30 mg; multiple doses from 2.5 to 5 mg daily and up to 50 mg dosed weekly).

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.

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 with 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. Bioavailability was similar in men and women.

6.2.2 Distribution

The mean steady-state volume of distribution is 13.8 L/kg in humans. Human plasma protein binding of drug is about 24%.

6.2.3 Metabolism

There is no evidence of systemic metabolism of risedronate.

6.2.4 Elimination

In young healthy subjects, approximately half of the absorbed dose is excreted in urine within 24 hours, and 85% of an intravenous dose is recovered in the urine over 28 days. Mean renal clearance is 105 mL/min (CV = 34%) and mean total clearance is 122 mL/min (CV = 19%), with the difference primarily reflecting non-renal 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 the faeces. 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%).

7. CONTRAINDICATIONS

- Hypocalcaemia.
- Known hypersensitivity to any component of this product.
- Inability to stand or sit upright for at least 30 minutes.
- Abnormalities of the esophagus, which delay esophageal emptying, such as stricture or achalasia.
- Severe renal impairment (creatinine clearance <30 mL/min).
- Pregnancy and lactation.

8. WARNINGS AND PRECAUTIONS

8.1 Warnings

Upper Gastrointestinal Adverse Reactions

Risedronate, 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 risedronate is given to patients with active upper gastrointestinal problems (such as known Barrett's esophagus, dysphagia, other esophageal diseases, gastritis, duodenitis or ulcers). 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 risedronate 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 (6 to 8 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. In patients who cannot comply with the dosing instructions due to mental disability, therapy with risedronate 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

Hypocalcaemia and other disturbances of bone and mineral metabolism (i.e. parathyroid dysfunction, hypovitaminosis D) should be effectively treated before starting therapy. Adequate intake of calcium and vitamin D is important in all patients, especially in patients with Paget`s disease in whom bone turnover is significantly elevated. Patients should take supplemental calcium and vitamin D if their dietary intake is inadequate.

Osteonecrosis of the Jaw

Osteonecrosis of the jaw (ONJ), which can occur spontaneously, is generally associated with tooth extraction and/or local infection (including osteomyelitis) with delayed healing, and has been reported in patients taking bisphosphonates, including risedronate. Known risk factors for ONJ include invasive dental procedures (e.g. tooth extraction, dental implants, boney surgery), diagnosis of cancer, concomitant therapies (e.g. chemotherapy, radiotherapy, corticosteroids, angiogenesis inhibitors), poor oral hygiene, and co-morbid disorders (e.g. 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 judgement 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.

Osteonecrosis of the External Auditory Canal

Osteonecrosis of the external auditory canal has been reported with bisphosphonates, mainly in association with long-term therapy. Possible risk factors for osteonecrosis of the external auditory canal include steroid use and chemotherapy and/or local risk factors such as infection or trauma. The possibility of osteonecrosis of the external auditory canal should be considered in patients receiving bisphosphonates who present with ear symptoms including chronic ear infections.

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. The time to onset of symptoms varied from 1 day to several months after starting the drug. Most

patients had relief of symptoms after stopping medication. A subset had recurrence of symptoms when re-challenged with the same drug or another bisphosphonate. Consider discontinuing use if severe symptoms develop.

Atypical Sub trochanteric and Diaphyseal Femoral Fractures

Atypical, low-energy or low-trauma fractures of the femoral shaft have been reported in bisphosphonate-treated patients, primarily in patients receiving long-term treatment for osteoporosis. 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 impact 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. Poor healing of these fractures has also been reported. Interruption of bisphosphonate therapy should be considered, pending a risk/benefit assessment, on an individual basis.

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.

Glucocorticoid-Induced Osteoporosis

Before initiating **risedronate** 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 risedronate have not been performed.

8.2 Precautions

Renal Impairment

Risedronate 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.

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.

Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies of risedronate in pregnant women. Risedronate should be used during pregnancy only if the potential benefit justifies the potential risk to the mother and foetus.

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.

Lactation

It is not known whether risedronate 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 bisphosphonates, 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.

Pediatric Use

Risedronate is not indicated for use in pediatric patients below age 18.

Geriatric Use

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 sodium in very elderly women (>80 years) is limited. Efficacy of bisphosphonates in the treatment of osteoporosis is related to the presence of low bone mineral density (BMD) [T-score at hip or lumbar spine ≤-2.5 standard deviations (SD)] and/or prevalent fracture.

No overall differences in safety and efficacy between geriatric and younger patients were observed in the risedronate trials, but the greater sensitivity of some older individuals cannot be ruled out.

9. DRUG INTERACTIONS

No specific drug–drug interaction studies have been performed. Risedronate is not metabolized and does not induce or inhibit hepatic microsomal drug-metabolizing enzymes (cytochrome P450) and has low protein binding.

Calcium Supplements/Antacids

Co-administration of risedronate and calcium, antacids, or oral medications containing polyvalent cations (e.g. calcium, magnesium, iron and aluminum) 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 the study drugs was approximately 12 to 18 months and the primary endpoint was change in bone mineral density (BMD). If considered appropriate, risedronate may be used concomitantly with hormone replacement therapy.

Aspirin/Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

Of over 5,700 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). NSAID use was reported by 48% of patients, 21% of whom were regular users. Among regular aspirin or NSAID users, the incidence of upper gastrointestinal adverse experiences in risedronate-treated patients (24.5%) was similar to that in placebo-treated patients (24.8%).

H2-Blockers and Proton-Pump Inhibitors (PPIs)

Of over 5,700 patients enrolled in the risedronate Phase 3 osteoporosis studies, 21% used H2-blockers and/or PPIs. Among these patients, the incidence of upper gastrointestinal adverse experiences in the risedronate-treated patients was similar to that in placebo-treated patients.

10. UNDESIRABLE EFFECTS

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 after risedronate treatment in Phase III clinical trials in postmenopausal women (12/36 months) and men (12 months) with osteoporosis, postmenopausal women without osteoporosis (12 months) and considered possibly or probably related to risedronate 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).

Body as a Whole

Common: Infection, back pain, accidental injury, pain, abdominal pain, flu syndrome, headache, asthenia, neck pain, chest pain, allergic reaction.

Cardiovascular System

Common: Hypertension, arrhythmia.

Metabolic and Nutritional Disorders

Common: Peripheral edema.

Musculoskeletal System

Common: Arthralgia, arthritis, traumatic bone fracture, joint disorder, myalgia, bone pain, musculoskeletal pain.

Very rare: Osteonecrosis of the external auditory canal (bisphosphonate class adverse reaction).

Respiratory System

Common: Bronchitis, sinusitis, rhinitis, pharyngitis, increased cough.

Special Senses

Common: Cataract.

Urogenital System

Common: Urinary tract infection, benign prostatic hyperplasia, nephrolithiasis.

Nervous System Disorders

Common: Headache, dizziness, depression, insomnia.

Eye Disorders

Uncommon: Iritis, uveitis, scleritis.

Gastrointestinal Disorders

Common: Constipation, dyspepsia, nausea, abdominal pain, diarrhea.

Uncommon: Gastritis, esophagitis, dysphagia, duodenitis, esophageal ulcer, vomiting.

Rare: Glossitis, esophageal stricture.

Skin and Appendages

Common: Rash

Acute Phase Reactions:

Common: Fever and influenza like illness

Laboratory Investigations

Early, transient, asymptomatic and mild decreases in serum calcium and phosphate levels and compensatory increases in serum PTH levels.

Common: Hypocalcemia

Rare: Abnormal liver function tests

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:

Skin and Subcutaneous Disorders

Hypersensitivity and skin reactions, including angioedema, generalized rash, urticarial, bullous skin reactions and leucocytoclastic vasculitis, some severe, including isolated reports of Stevens-Johnson syndrome and toxic epidermal necrolysis, hair loss.

Gastrointestinal Adverse Events

Events involving upper gastrointestinal irritation, such as esophagitis and esophageal or gastric ulcers, have been reported.

Musculoskeletal Pain

Bone, joint or muscle pain, described as severe or incapacitating, has been reported rarely.

Eye Inflammation

Reactions of eye inflammation, including iritis and uveitis, have been reported rarely.

ONJ

ONJ has been reported rarely.

Pulmonary

Asthma exacerbations.

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.

Atypical Sub trochanteric and Diaphyseal Femoral Fractures

Unusual fracture of the femur, particularly in patients on long-term treatment with bisphosphonates for osteoporosis, may occur rarely.

11. OVER DOSAGE

Decreases in serum calcium and phosphorus following substantial overdose may be expected in some patients. Signs and symptoms of hypocalcaemia 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 hypocalcaemia, including the administration of calcium intravenously, would be expected to restore physiologic amounts of ionized calcium and to relieve the signs and symptoms of hypocalcaemia.

12. STORAGE AND HANDLING INSTRUCTIONS

Store protected from light moisture, at temperature not exceeding $30^{o}C$.

13. PACKAGING INFORMATION

RISOBIS 35 is available in a blister pack of 4 tablets.

14. DETAILS OF MANUFACTURER

Manufactured in India by:

Mefro Organics Ltd.

Plot No. 4, Phase-1, Indl. Area, Tahliwal, Tehsil – Haroli, Dist. – Una (H.P.) – 174 507

Marketed By:

Zuci Pharma

123, FF, City Centre Arcade & Homes, Near SRP Camps, Krishnanagar NH-8, Naroda, Ahmedabad, Gujarat, India – 382345

zucipharmainfo@gmail.com

PATIENT INFORMATION

The patient should be informed to pay particular attention to the dosing instructions as clinical benefits might be compromised by failure to take the drug according to the instructions.

- Specifically, RISOBIS Tablets should be taken at least 30 minutes before the first food or drink of the day other than water.
- To facilitate delivery to the stomach and, thus, reduce the potential for esophageal irritation, patients should take RISOBIS Tablets while in an upright position (sitting or standing) with a full glass of plain water (177 to 236 ml).
- Patients should not lie down for 30 minutes after taking the medication.
- Patients should not chew or suck on the tablet because of a potential for oropharyngeal irritation.

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 RISOBIS Tablets.

Patients should be instructed that if they miss a dose of RISOBIS 35, they should take one tablet on the morning after they remember and return to taking one tablet once a week, as originally scheduled on their chosen day. Patients should not take two tablets on the same day.

Patients should receive supplemental calcium and vitamin D if dietary intake is inadequate. Calcium supplements or calcium-, aluminum-, iron- and magnesium-containing medications may interfere with the absorption of RISOBIS Tablets should be taken at a different time of

the day, as with food. 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 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 RISOBIS Tablets. Patients should be instructed that any time they have a medical problem that they think may be due to RISOBIS Tablets, they should talk to their doctor.

Last Updated: *April 2025*
Last Reviewed: *April 2025*