For the use of Gyneacologists only

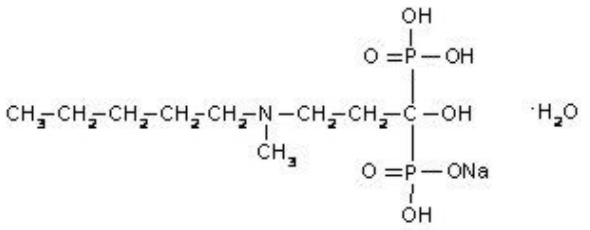
Ibandronate Sodium Tablets 150 mg

BONRISE

COMPOSITION
Each film-coated tablet contains:
Ibandronate Monosodium Monohydrate
equivalent to Ibandronic Acid.....150 mg
Excipients.....q.s.

COLOUR: Titanium Dioxide IP

DESCRIPTION
BONRISE (Ibandronate Sodium) is a nitrogen-containing bisphosphonate that inhibits osteoclast-mediated bone resorption. The chemical name for Ibandronate Sodium is 3-(N-methyl-N-pentyl) amino-1-hydroxypropane-1,1-diphosphonic acid, monosodium salt, monohydrate with the molecular formula $C_9H_{22}NO_7P_2NaH_2O$ and a molecular weight of 359.24.



DOSAGE FORM
Tablet

INDICATION
Treatment and Prevention of postmenopausal Osteoporosis: Ibandronic acid is indicated for the treatment and prevention of Osteoporosis in post-menopausal woman

DOSAGE AND ADMINISTRATION
One 150 mg tablet taken once monthly on the same date of each month.

Patient with Hepatic Impairment
No dose adjustment is necessary

Patient with Renal Impairment
No dose adjustment is necessary for patients with mild or moderate renal impairment where creatinine clearance is equal to or greater than 30 mL/min. Ibandronate sodium is not recommended for use in patients with severe renal impairment (creatinine clearance <30 mL/min).

Geriatric Patients
No dosage adjustment is necessary in the elderly.

CONTRAINDICATIONS
Known hypersensitivity to Ibandronate Sodium, Inability to stand or sit upright for at least 60 min , uncorrected Hypocalcemia

WARNINGS
Ibandronate Sodium, like other bisphosphonates administered orally may cause upper gastrointestinal disorders such as dysphagia, esophagitis, and esophageal or gastric ulcer

PRECAUTIONS
General
Mineral Metabolism: Hypocalcemia and other disturbances of bone and mineral metabolism should be effectively treated before starting BONRISE therapy. Adequate intake of calcium and vitamin D is important in all patients.
Upper Gastrointestinal Effects: Bisphosphonates administered orally have been associated with dysphagia, esophagitis, and esophageal or gastric ulcers. Therefore, patients should be advised to pay particular attention to and be able to comply with the dosing instructions to minimize the risk of these effects.
Severe Renal Impairment: BONRISE is not recommended for use in patients with severe renal impairment (creatinine clearance <30 mL/min).
Jaw Osteonecrosis: Osteonecrosis, primarily in the jaw, has been reported in patients treated with bisphosphonates. Most cases have been in cancer patients undergoing dental procedures, but some have occurred in patients with postmenopausal osteoporosis or other diagnoses. Known risk factors for osteonecrosis include a diagnosis of cancer, concomitant therapies (eg, chemotherapy, radiotherapy, corticosteroids), and co-morbid disorders (eg, anemia, coagulopathy, infection, pre-existing dental disease). Most reported cases have been in patients treated with bisphosphonates intravenously but some have been in patients treated orally.
For patients who develop osteonecrosis of the jaw (ONJ) 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 ONJ. Clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.
Musculoskeletal Pain: In postmarketing experience, severe and occasionally incapacitating bone, joint, and/or muscle pain has been reported in patients taking bisphosphonates that are approved for the prevention and treatment of osteoporosis. However, such reports have been infrequent. Most of the patients were postmenopausal women. 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. A subset had recurrence of symptoms when rechallenged with the same drug or another bisphosphonate.
In placebo-controlled studies with Ibandronate Sodium, the percentages of patients with these symptoms were similar in the Ibandronate Sodium and placebo groups.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

CARCINOGENESIS: In a 104-week carcinogenicity study, there were no significant drug-related tumor findings in male or female rats.. In a 90-week carcinogenicity study, a dose-related increased incidence of adrenal subcapsular adenoma/carcinoma was observed in female mice, which was statistically significant at 80 mg/kg/day (220 to 400 times human exposure at the recommended daily oral dose of 2.5 mg and 115 times human exposure at the recommended once-monthly oral dose of 150 mg, based on AUC comparison). The relevance of these findings to humans is unknown.
MUTAGENESIS : There was no evidence for a mutagenic or clastogenic potential of ibandronate in the following assays: in vitro bacterial mutagenesis assay in Salmonella typhimurium and Escherichia coli (Ames test), mammalian cell mutagenesis assay in Chinese hamster V79 cells, and chromosomal aberration test in human peripheral lymphocytes, each with and without metabolic activation. Ibandronate was not genotoxic in the in vivo mouse micronucleus tests for chromosomal damage.
IMPAIRMENT OF FERTILITY: In female rats treated from 14 days prior to mating through gestation, decreases in fertility, corpora lutea, and implantation sites were observed

PREGNANCY AND LACTATION
Pregnancy Category C
There are no adequate and well-controlled studies in pregnant women. Ibandronate sodium should be used during pregnancy only if the potential benefit justifies the potential risk to the mother and fetus.

Nursing Mothers
It is not known whether Ibandronate Sodium is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Ibandronate Sodium is administered to a nursing woman.

SPECIAL POPULATIONS
Pediatric Use: Safety and effectiveness in pediatric patients(<18 years)have not been established
Geriatric Use:
Of the patients receiving Ibandronate Sodium 150 mg once monthly in the post menopausal osteoporosis 1-year study, 52% were over 65 years of age & 9% were over 75 years of age. No overall differences in effectiveness or safety were observed between these patients and younger patients but greater sensitivity in some older individuals cannot be ruled out .Since Ibandronate is not known to be metabolized, the only difference in Ibandronate elimination for geriatric patients versus younger patients is expected to relate to progressive age-related changes in renal function.
Renal Impairment:
Renal clearance of Ibandronate in patients with vasrious degrees of renal impairment is linearly related to creatinine clearance (CLcr). Following a single dose of 0.5 mg Ibandronate by intravenous administration, patients with CLcr 40 to 70 mL/min had 55% higher exposure (AUC_{∞}) than the exposure observed in subjects with CLcr >90 mL/min. Patients with CLcr <30 mL/min had more than a two-fold increase in exposure compared to the exposure for healthy subjects.

Hepatic Impairment:
No studies have been performed to assess the pharmacokinetics of Ibandronate in patients with hepatic impairment since Ibandronate is not metabolized in the human liver. No dose adjustment is necessary in patients with hepatic impairment.

DRUG INTERACTIONS:
Ibandronate does not undergo hepatic metabolism and does not inhibit the hepatic cytocrome P 450 system.
Calcium Supplements/Antacids: Products containing calcium and other multivalent cations (such as aluminum, magnesium, iron) are likely to interfere with absorption of Ibandronate Sodium. BONRISE should be taken at least 60 minutes before any oral medications, including medication containing multivalent cations (such as antacids, supplements or vitamins) Also, patients should wait at least 60 minutes after dosing before taking any other oral medications

Aspirin/Nonsteroidal Antiinflammatory Drugs (NSAIDs): Because aspirin, NSAIDs, and bisphosphonates are all associated with gastrointestinal irritation, caution should be exercised in the concomitant use of aspirin or NSAIDs with BONRISE.

H2 Blockers: In healthy volunteers, co administration with ranitidine resulted in a 20 % increased bioavailability of Ibandronate which was not considered to be clinically relevant.

DRUG/LABORATORY TEST INTERACTONS: Bisphosphonates are known to interfere with the use of bone-imaging agents. Specific studies with Ibandronate have not been performed.

SIDE EFFECTS:
The most possible side effects are Back Pain, Pain in Extremity, Infection, Asthenia, Allergic reaction, Dyspepsia, Diarrhea, Tooth Disorder, Vomiting, Gastritis, Hypercholesterolemia, Myalgia, Joint Disorder, Arthritis, Headache, Dizziness, Vertigo, Nerve Root lesion, Upper Respiratory Infection, Bronchitis, Pneumonia, Pharyngitis, and Urinary Tract Infection. Hypertension Nausea, Constipation, ABDOMINAL Pain, Arthralgia, Localized Osteoarthritis, Muscle Cramp, Influenza, Influenza- like Illness, Nasopharyngitis, Fatigue, Flatulence, Gastro esophageal Reflux Disease, Musculoskeletal Pain, Fever Chills, Loss of appetite, Bone Pain, Dizziness, Rash, Insomnia were also possible, Reports in the medical literature indicate that bisphosphonates may be associated with ocular inflammation such as uveitis and scleritis.

OVERDOSE
No specific information is available on the treatment of overdosage with Bonrise. However based on knowledge of this class of compounds, oral overdosage may result in hypocalcemia, hypophosphatemia, and upper gastrointestinal adverse events, such as upset stomach, dyspepsia, esophagitis, gastritis, or ulcer. Milk or antacid should be given to bind Bonrise. Due to the risk of esophageal irritation, vomiting should not been induced, and the patient should remain fully upright. Dialysis would not be beneficial.

CLINICAL PHARMACOLOGY
Mechanism of Action
The action of Ibandronate on bone tissue is based on its affinity for hydroxyapatite, which is part of the mineral matrix of bone. Ibandronate inhibits osteoclast activity and reduces bone resorption and turnover. In postmenopausal women, it reduces the elevated rate of bone turnover, leading to, on average, a net gain in bone mass.

Pharmacokinetics
Absorption: The absorption of oral Ibandronate occurs in the upper gastrointestinal tract. Plasma concentrations increase in a dose-linear manner up to 50 mg oral intake and increases nonlinearly above this dose. Following oral dosing, the time to maximum observed plasma Ibandronate concentrations ranged from 0.5 to 2 hours (median 1 hour) in fasted healthy postmenopausal women. The mean oral bioavailability of 2.5 mg Ibandronate was about 0.6% compared to intravenous dosing. The extent of absorption is impaired by food or beverages (other than plain water). The oral bioavailability of Ibandronate is reduced by about 90% when BONRISE is administered concomitantly with a standard breakfast in comparison with bioavailability observed in fasted subjects. There is no meaningful reduction in bioavailability when Ibandronate is taken at least 60 minutes before a meal. However, both bioavailability and the effect on bone mineral density (BMD) are reduced when food or beverages are taken less than 60 minutes following an Ibandronate dose.

Distribution: After absorption, Ibandronate either rapidly binds to bone or is excreted into urine. In humans, the apparent terminal volume of distribution is at least 90 L, and the amount of dose removed from the circulation via the bone is estimated to be 40% to 50% of the circulating dose. In vitro protein binding in human serum was 99.5% to 90.9% over an Ibandronate concentration range of 2 to 10 ng/mL in one study and approximately 85.7% over a concentration range of 0.5 to 10 ng/mL in another study.

Metabolism: There is no evidence that Ibandronate is metabolized in humans.
Elimination: The portion of Ibandronate that is not removed from the circulation via bone absorption is eliminated unchanged by the kidney (approximately 50% to 60% of the absorbed dose). Unabsorbed Ibandronate is eliminated unchanged in the feces.
The plasma elimination of Ibandronate is multiphasic. Its renal clearance and distribution into bone accounts for a rapid and early decline in plasma concentrations, reaching 10% of the Cmax within 3 or 8 hours after intravenous or oral administration, respectively. This is followed by a slower clearance phase as Ibandronate redistributes back into the blood from bone. The observed apparent terminal half-life for Ibandronate is generally dependent on the dose studied and on assay sensitivity. The observed apparent terminal half-life for the 150 mg Ibandronate tablet upon oral administration to healthy postmenopausal women ranges from 37 to 157 hours.
Total clearance of Ibandronate is low; with average values in the range 84 to 160 mL/min. Renal clearance (about 60 mL/min in healthy postmenopausal females) accounts for 50% to 60% of total clearance and is related to creatinine clearance. The difference between the apparent total and renal clearances likely reflects bone uptake of the drug.

STORAGE : Store in a cool & dry place. Protect from light.

PRESENTATION : Strip of one tablet

KEEP OUT OF REACH OF CHILDREN

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torrent PHARMA
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Ahmedabad-380 009, INDIA

IN/BONRISE 150mg/Jul-15/01/PI