Bondronat®

ATNAHS

Ibandronic acid

1. Pharmaceutical Form

Tablets 50mg

Film-coated tablets of oblong shape and white to off-white in colour, engraved L2/IT.

2. Qualitative and Quantitative Composition

Ibandronic acid, monosodium salt, monohydrate.

Tablets 50mg

One film-coated tablet contains 56.25 mg of ibandronic acid, monosodium salt, monohydrate corresponding to 50 mg ibandronic acid.

3. Clinical Particulars

3.1 Therapeutic Indications

Bondronat is indicated for the prevention of skeletal events associated with metastatic bone disease due to breast cancer.

3.2 Dosage and Method of Administration

The recommended dose is one 50 mg film-coated tablet daily.

Bondronat should be taken after an overnight fast and before the first food or drink of the day. Medications and supplements (including calcium) should similarly be avoided prior to taking Bondronat tablets. Fasting should be continued for at least 60 minutes after taking the tablet. Plain water may be taken at any time during the course of Bondronat treatment.

- The tablets should be swallowed whole with a full glass of plain water (180 to 240 ml) while the patient is standing or sitting in an upright position.
- Patients should not chew or suck the tablet because of a potential for oropharyngeal ulceration.
- Plain water is the only drink that should be taken with Bondronat. Please note that some mineral waters may have a higher concentration of calcium and therefore should not be used.
- Patients should not lie down for 60 minutes after taking Bondronat.

Patients with hepatic impairment

No dosage adjustment is expected to be necessary (see 4.2.5 Pharmacokinetics in Special Populations).

Patients with renal impairment

For patients with mild renal impairment (CLcr ≥50 and <80 mL/min) no dosage adjustment is necessary. For patients with moderate renal impairment (CLcr ≥30 and <50 mL/min) a dosage adjustment to one 50 mg film-coated tablet every second day is recommended. For patients with severe renal impairment (CLcr <30 mL/min) the recommended dose is one 50 mg film-coated tablet once weekly *(see section* 4.2.5*)*

Elderly

No dose adjustment is necessary.

Children

Safety and efficacy have not been established in patients less than 18 years old.

3.3 Contraindications

Bondronat film-coated tablets is contraindicated in patients with:

- hypocalcemia
- known hypersensitivity to ibandronic acid or to any of its excipients.
- abnormalities of the esophagus which delay esophageal emptying such as stricture or achalasia
- inability to stand or sit upright for at least 60 minutes

3.4 Warnings and Precautions for Use

Caution is indicated in patients with known hypersensitivity to other bisphosphonates.

Hypocalcemia and other disturbances of bone and mineral metabolism should be effectively treated before starting Bondronat therapy. Adequate intake of calcium and vitamin D is important in all patients. Patients should receive supplemental calcium and/or vitamin D if dietary intake is inadequate.

Orally administered bisphosphonates 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 Bondronat is given to patients with active upper gastrointestinal problems (e.g. known Barrett's esophagus, dysphagia, other esophageal diseases, gastritis, duodenitis or ulcers).

Adverse experiences such as esophagitis, esophageal ulcers and esophageal erosions, in some cases severe and requiring hospitalization, rarely with bleeding or followed by esophageal stricture or perforation, have been reported in patients receiving treatment with oral bisphosphonates. The risk of severe esophageal adverse experiences appears to be greater in patients who do not comply with the dosing instruction and/or who continue to take oral bisphosphonates after developing symptoms suggestive of esophageal irritation. Patients should pay particular attention and be able to comply with the dosing instructions *(see section 3.2)*.

Physicians should be alert to any signs or symptoms signaling a possible esophageal reaction and patients should be instructed to discontinue Bondronat and seek medical attention if they develop dysphagia, odynophagia, retrosternal pain or new or worsening heartburn.

While no increased risk was observed in controlled clinical trials there have been post-marketing reports of gastric and duodenal ulcers with oral bisphosphonate use, some severe and with complications.

Since NSAIDS are associated with gastrointestinal irritation, caution should be taken during concomitant oral medication with Bondronat.

Clinical placebo-controlled, randomized studies in patients with metastatic bone disease due to breast cancer have not shown any evidence of deterioration in renal function with long term Bondronat therapy. Nevertheless, according to clinical assessment of the individual patient, it is recommended that renal function, serum calcium, phosphate and magnesium should be monitored in patients treated with Bondronat.

Bondronat tablets contain lactose and should not be administered to patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption.

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 including angiogenesis inhibitors, 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 judgement of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

Cases of osteonecrosis of other oro-facial sites including the external auditory canal have also been reported in patients treated with bisphosphonates including IBN [91, 92]. Risk factors are similar as for ONJ. Other risk factors may include repetitive minor trauma (e.g., habitual cotton bud use). 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.

3.5 Interactions with other Medical Products and other Forms of Interaction

Drug-Food Interactions

Products containing calcium and other multivalent cations (such as aluminium, magnesium, iron), including milk and food, are likely to interfere with absorption of Bondronat tablets. Therefore, with such products, food intake must be delayed at least 60 minutes following oral administration.

Bioavailability was reduced by approximately 75% when Bondronat tablets were administered 2 hours after a standard meal. Therefore, it is recommended that the tablets should be taken after an overnight fast (at least 6 hours) and fasting should continue at least 60 minutes following oral administration.

Drug-Drug Interactions

When co-administered with melphalan/prednisolone in patients with multiple myeloma, no interaction was observed.

Other interaction studies in postmenopausal women have demonstrated the absence of any interaction potential with tamoxifen or hormone replacement therapy (estrogen).

In healthy male volunteers and postmenopausal women, i.v. ranitidine caused an increase in ibandronic acid bioavailability of about 20% (which is within the normal range of the bioavailability of ibandronic acid), probably as a result of reduced gastric acidity. However, no dosage adjustment is required when Bondronat is administered with H_2-antagonists or other drugs that increase gastric pH.

In relation to disposition, no drug interactions of clinical significance are likely. Ibandronic acid is eliminated by renal secretion only and does not undergo any biotransformation. The secretory pathway does not appear to include known acidic or basic transport systems involved in the excretion of other drugs. In addition, ibandronic acid does not inhibit the major human hepatic P450 isoenzymes and does not induce the hepatic cytochrome P450 system in rats. Plasma protein binding is low at therapeutic concentrations and ibandronic acid is therefore unlikely to displace other drugs.

Caution is advised when bisphosphonates are administered with aminoglycosides, since both agents can lower serum calcium levels for prolonged periods. Attention should also be paid to the possible existence of simultaneous hypomagnesaemia.

In clinical studies, Bondronat has been administered concomitantly with commonly used anticancer agents, diuretics, antibiotics and analgesics without clinically apparent interactions occurring.

3.6 Pregnancy and Lactation

Bondronat should not be used during pregnancy and lactation.

There are no adequate data from the use of ibandronic acid in pregnant women. Studies in rats have shown some reproductive toxicity (see 4.2.6, Reproductive toxicity). The potential risk for humans is unknown.

It is not known whether ibandronic acid is excreted in human milk. Studies in lactating rats have demonstrated the presence of low levels of ibandronic acid in the milk following intravenous administration.

3.7 Effects on Ability to Drive and Use Machines

No studies on the effects on the ability to drive and use machines have been performed.

3.8 Undesirable Effects

The safety profile of Bondronat is derived from controlled clinical trials in the approved indication and after the oral administration of Bondronat at the recommended dose.

In the pooled database from the 2 pivotal phase III trials (286 patients treated with Bondronat 50 mg), the proportion of patients who experienced an adverse reaction with a possible or probable relationship to Bondronat was 27%.

Adverse reactions are ranked under heading of frequency, the most frequent first, using the following convention: very common (≥10%), common (≥1% and <10%), uncommon (≥0.1% and <1%), rare (≥0.01% and <0.1%), very rare (≤0.01%).

Table 1 lists common adverse reactions from the pooled phase III trials. Adverse reactions that are equally frequent in both active and placebo or more frequent in placebo-treated patients are excluded.

Table 1 Adverse Reactions Reported Commonly and Greater than Placebo

Adverse Reaction	Placebo p. o. daily (n=277 patients) No. (%)	Bondronat 50 mg p.o. daily (n=286 patients) No. (%)
Metabolism and Nutrition Disorders		
Hypocalcaemia	14 (5.1)	27 (9.4)
Gastrointestinal Disorders		
Dyspepsia	13 (4.7)	20 (7.0)
Nausea	4 (1.4)	10 (3.5)
Abdominal Pain	2 (0.7)	6 (2.1)
Oesophagitis	2 (0.7)	6 (2.1)
General Disorders		
Asthenia	2 (0.7)	4 (1.4)

Adverse drug reactions occurring at a frequency <1%:

The following list provides information on adverse drug reactions reported in study MF 4414 and MF 4434 occurring more frequently with Bondronat 50 mg than with placebo:

Uncommon:

Blood and Lymphatic System Disorders
Anaemia
Nervous System Disorders
Paraesthesia, dysgeusia (taste perversion)
Gastrointestinal Disorders
Haemorrage, duodenal ulcer, gastritis, dysphagia, abdominal pain, dry mouth
Skin and Subcutaneous Tissue Disorders
Pruritus
Renal and Urinary Disorders
Azotaemia (uraemia)
General Disorders
Chest pain, influenza-like illness, malaise, pain
Investigations
Blood parathyroid hormone increased

Post-Marketing

Musculoskeletal and connective tissue disorders:
Osteonecrosis of the jaw and of other oro-facial sites, including the external auditory canal, has been reported in patients treated by bisphosphonates. The majority of the reports refer to cancer patients, but such cases have also been reported in patients treated for osteoporosis. Osteonecrosis of the jaw is generally associated with tooth extraction and / or local infection (including osteomyelitis). Diagnosis of cancer, chemotherapy, radiotherapy, corticosteroids and poor oral hygiene are also deemed as risk factors.

In post marketing experience, severe and occasionally incapacitating bone, joint, and/or muscle pain has been reported in patients taking bisphosphonates. However, such reports have been infrequent. 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.

Eye disorders:
Ocular inflammation events such as uveitis, episcleritis and scleritis have been reported with bisphosphonates, including ibandronic acid. In some cases, these events did not resolve until the bisphosphonate was discontinued.

Gastrointestinal disorders:
Stomatitis has been reported in patients receiving bisphosphonates.

Immune system disorders:
Cases of anaphylactic reaction/shock, including fatal events, have been reported in patients treated with ibandronic acid.

Allergic reactions including asthma exacerbation have been reported.

Severe Cutaneous Adverse Reactions including Stevens-Johnson Syndrome, Erythema Multiforme, and Bullous Dermatitis, have been reported.

Injury, Poisoning and Procedural complications:
Atypical subtrochanteric and diaphyseal femoral fractures have been reported with bisphosphonate therapy, including ibandronate, however causality has not been established.

3.9 Overdose

So far, no case of overdosing with Bondronat film-coated tablets has been reported.

No specific information is available on the treatment of overdosage with Bondronat. However, oral overdosage may result in upper gastrointestinal events, such as upset stomach, heartburn, esophagitis, gastritis or ulcer. Milk or antacids should be given to bind Bondronat. Owing to the risk of esophageal irritation, vomiting should not be induced and the patient should remain fully upright.

4. Pharmacological Properties & Effects

4.1 Pharmacodynamic Properties

Pharmaco-therapeutic group: Bisphosphonate, ATC Code: M05B A 06

Ibandronic acid belongs to the bisphosphonate group of compounds which act specifically on bone. Their selective action on bone tissue is based on the high affinity of bisphosphonates for bone mineral. Bisphosphonates act by inhibiting osteoclast activity, although the precise mechanism is still not clear.

In vivo, ibandronic acid prevents experimentally-induced bone destruction caused by cessation of gonadal function, retinoids, tumours or tumour extracts. The inhibition of endogenous bone resorption has also been documented by ^{45}Ca kinetic studies and by the release of radioactive tetracycline previously incorporated into the skeleton.

At doses that were considerably higher than the pharmacologically effective doses, ibandronic acid did not have any effect on bone mineralisation.

Bone resorption due to malignant disease is characterised by excessive bone resorption that is not balanced with appropriate bone formation. Ibandronate selectively inhibits osteoclast activity, reducing bone resorption and thereby reducing skeletal complications of the malignant disease.

Clinical studies in patients with metastatic bone disease have shown that there is a dose dependent inhibitory effect on bone osteolysis, expressed by markers of bone resorption, and a dose dependent effect on skeletal events.

In metastatic bone disease, a statistically and clinically relevant decrease in the incidence of skeletal related events, as measured by the time-adjusted Skeletal Morbidity Period Rate (SMPR), was shown in patients treated with Bondronat compared to patients treated with placebo. There was also a statistically significant decrease in events requiring radiotherapy or surgery to bone. In a multivariate analysis the risk for a skeletal event was statistically and clinically significantly reduced in comparison to placebo. Statistically significant improvements in global quality of life, bone pain score and analgesic score were also noted. WHO performance status deteriorated more in placebo patients than in patients treated with Bondronat, and the difference was statistically significant. There was a marked depression of uCTx, a marker of bone resorption, which was statistically significant compared to placebo.

4.2 Pharmacokinetic Properties

4.2.1 Absorption

The absorption of ibandronic acid in the upper gastrointestinal tract is rapid after oral administration. Maximum observed plasma concentrations were reached within 0.5 to 2 hours (median 1 hour) in the fasted state and absolute bioavailability was about 0.6%. The extent of absorption is impaired when taken together with food or beverages (other than plain water). Bioavailability is reduced by about 90% when ibandronic acid is administered with a standard breakfast in comparison with bioavailability

seen in fasted subjects. When taken 30 minutes before a meal, the reduction in bioavailability is approximately 30%. There is no meaningful reduction in bioavailability provided ibandronic acid is taken 60 minutes before a meal.

Bioavailability was reduced by approximately 75% when Bondronat tablets were administered 2 hours after a standard meal. Therefore, it is recommended that the tablets should be taken after an overnight fast (minimum 6 hours) and fasting should continue for at least 60 minutes after the dose has been taken.

Plasma concentrations of ibandronic acid increase in a dose-proportional manner after oral administration up to 50 mg.

4.2.2 Distribution

After initial systemic exposure, ibandronic acid 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 reaching the bone is estimated to be 40-50% of the circulating dose. Protein binding in human plasma is low (approximately 85% bound at therapeutic concentrations), and thus drug-drug interaction due to displacement is unlikely.

4.2.3 Metabolism

There is no evidence that ibandronic acid is metabolized in animals or humans.

4.2.4 Elimination

The absorbed fraction of ibandronic acid is removed from the circulation via bone absorption (40-50%) and the remainder is eliminated unchanged by the kidney. The unabsorbed fraction of ibandronic acid is eliminated unchanged in the feces.

The range of observed apparent half-lives is broad and dependent on dose and assay sensitivity, but the apparent terminal half-life is generally in the range of 10-60 hours. However, early plasma levels fall quickly, reaching 10% of peak values within 3 and 8 hours after intravenous or oral administration respectively.

Total clearance of ibandronic acid is low with average values in the range 84-160 ml/min. Renal clearance (about 60 ml/min in healthy postmenopausal females) accounts for 50-60% of total clearance and is related to creatinine clearance. The difference between the apparent total and renal clearances is considered to reflect the uptake by bone.

4.2.5 Pharmacokinetics in Special Populations

Gender

Bioavailability and pharmacokinetics of ibandronic acid are similar in both men and women.

Race

There is no evidence for clinically relevant interethnic differences between Asians and Caucasians in ibandronic acid disposition. There are only very few data available on patients with African origin.

Patients with renal impairment

Patients with severe renal impairment (CLcr <30 mL/min) receiving oral administration of 10 mg ibandronic acid daily for 21 days, had 2 - 3 fold higher plasma concentrations than patients with normal renal function (CLcr ≥80 mL/min). Total clearance of ibandronic acid was reduced to 44 mL/min in patients with severe renal impairment compared with 129 mL/min in patients with normal renal function. For patients with mild renal impairment (CLcr ≥50 and <80 mL/min) no dosage adjustment is necessary. For patients with moderate renal impairment (CLcr ≥30 and <50 mL/min) or severe renal impairment (CLcr <30 mL/min) an adjustment in the dose is recommended.

Approximately 37% of ibandronate was cleared from the body during a standard 4-hour hemodialysis procedure.

Patients with hepatic impairment

There are no pharmacokinetic data for ibandronic acid in patients who have hepatic impairment. The liver has no significant role in the clearance of ibandronic acid since it is not metabolised but is cleared by renal excretion and by uptake into bone. Therefore dosage adjustment is not necessary in patients with hepatic impairment. Further, as protein binding of ibandronic acid is low at therapeutic concentrations (85%), hypoproteinemia in severe liver disease is unlikely to lead to clinically significant increases in free plasma concentration.

Elderly

In a multivariate analysis, age was not found to be an independent factor of any of the pharmacokinetic parameters studied. As renal function decreases with age, this is the only factor to take into consideration.

Children

There are no data on the use of Bondronat in patients less than 18 years old.

4.2.6 Preclinical Safety

As with other bisphosphonates, the kidney was identified to be the primary target organ of systemic toxicity. Toxic effects in animals were observed only at exposures sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

Mutagenicity/Carcinogenicity

No indication of carcinogenic potential was observed. Tests for genotoxicity revealed no evidence of genetic activity for ibandronic acid.

Reproductive toxicity

There was no evidence for a direct fetal toxic or teratogenic effect of ibandronic acid in orally treated rats and rabbits and there were no adverse effects on the development in F1 offspring in rats at an extrapolated exposure well above that expected in humans. Adverse effects of ibandronic acid in reproductive toxicity studies in the rat were those observed with bisphosphonates as a class. They include a decreased number of implantation sites, interference with natural delivery (dystocia), and an increase in visceral variations (renal pelvis ureter syndrome).

5. PHARMACEUTICAL PARTICULARS

5.1 List of Excipients

Tablet core: lactose monohydrate, povidone, cellulose microcrystalline, crospovidone, stearic acid, silica, anhydrous colloidal

Tablet coat: hypromellose, titanium dioxide E171, talc, macrogol 6000

5.2 Stability

5.2.1 Special Precautions for Storage

No special precautions for storage.

This medicine should not be used after the expiry date (EXP) shown on the pack.

Disposal of unused/expired medicines

The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Use established “collection systems”, if available in your location.

6. PACKS

Tablets 50mg 28, 84

Medicine: keep out of reach of children

ATNAHS

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Made for Atnahs Pharma UK Ltd., Sovereign House, Miles Gray Road, Basildon, Essex, SS14 3FR, United Kingdom
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