Australian Product Information - BONDRONAT® (ibandronic acid)

1. NAME OF THE MEDICINE

Ibandronic acid (as the monosodium salt monohydrate)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

BONDRONAT is available as a concentrated injection for intravenous (IV) infusion containing 6 mg ibandronic acid (as the monosodium salt monohydrate 6.75 mg).

BONDRONAT is also available as film-coated tablets containing 50 mg ibandronic acid (as the monosodium salt monohydrate 56.25 mg).The tablets also contain lactose.

Ibandronate sodium is a white to off-white powder and is freely soluble in water.

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

BONDRONAT is a sterile, clear and colourless concentrated injection for intravenous (IV) infusion.

BONDRONAT 50 mg tablets are white to off-white, oblong, film-coated tablets, engraved with “IT” on one side and “L2” on the other side.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

BONDRONAT Injection and Tablets are indicated for the treatment of metastatic bone disease in patients with breast cancer.

BONDRONAT Injection is indicated for the treatment of tumour-induced hypercalcaemia with or without metastases.

4.2 DOSE AND METHOD OF ADMINISTRATION

Standard Dosage

A temporary drug discontinuation after 3 to 5 years of bisphosphonate therapy may be appropriate in patients at low risk of fracture (see Sections 4.4 Special warnings and precautions and 4.8 Adverse effects (undesirable effects)).

Treatment of Metastatic Bone Disease

BONDRONAT is intended for long-term administration unless clinically inappropriate.

Intravenous

The recommended dose is 6 mg IV given every 4 weeks. The dose should be infused over 1 - 2 hours. For infusion, the contents of the vial should be added to 500 mL isotonic sodium chloride solution (or 500 mL 5% glucose solution).

Oral

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

BONDRONAT should be taken 30 minutes before the first food or drink of the day (other than plain water) or any other oral medication or supplement (including calcium).

- Tablets should be swallowed whole with a full glass of plain water (180 - 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 30 minutes after taking BONDRONAT tablets.

Treatment of Tumour-Induced Hypercalcaemia

Prior to treatment with BONDRONAT the patient should be adequately rehydrated with 0.9 % sodium chloride. Consideration should be given to the severity of the hypercalcaemia as well as the tumour type. In general, patients with osteolytic bone metastases require lower doses than patients with the humoral type of hypercalcaemia. In most patients with severe hypercalcaemia (albumin-corrected serum calcium* ≥ 3 mmol/L or ≥ 12 mg/dL) 4 mg will be an adequate single dosage. In patients with moderate hypercalcaemia (albumin-corrected serum calcium < 3 mmol/L or < 2 mg/dL) 2 mg is an effective dose. The highest dose used in clinical trials was 6 mg but this dose does not add any further benefit in terms of efficacy.

* Note: Albumin-corrected serum calcium (mmol/L)

= serum calcium (mmol/L) - [0.02 x albumin (g/L)] + 0.8

or

Albumin-corrected serum calcium (mg/dL)

= serum calcium (mg/dL) + 0.8 x [4 - albumin (g/dL)]

To convert the albumin-corrected serum calcium in mmol/L value to mg/dL, multiply by 4.

In most cases a raised serum calcium level can be reduced to the normal range within 7 days. The median time to relapse (re-increase of albumin corrected serum calcium above 3 mmol/L) was 18 – 19 days for the 2 mg and 4 mg doses. The median time to relapse was 26 days with a dose of 6 mg.

A limited number of patients (*n* = 50) have received a second infusion for hypercalcaemia. Repeated treatment may be considered in case of recurrent hypercalcaemia or insufficient efficacy.

BONDRONAT concentrate for infusion should be administered as an IV infusion. For this purpose, the contents of the vial should be added to 500 mL isotonic sodium chloride solution (or 500 mL 5% glucose solution) and infused over 1 – 2 hours. BONDRONAT concentrate should not be mixed with calcium containing solutions.

To avoid potential incompatibilities, BONDRONAT concentrated solution for infusion should only be diluted with isotonic sodium chloride solution or 5% dextrose solution.

As the inadvertent intra-arterial administration of preparations not expressly recommended for this purpose as well as paravenous administration can lead to tissue damage, care must be taken to ensure that BONDRONAT concentrate for infusion is administered intravenously.

Special Patient Groups (see Section 5.2 Pharmacokinetics in Special Populations)

Patients with renal impairment

IV Infusion for Metastatic Bone Disease

For patients with mild renal impairment (CLcr ≥ 50 and < 80 mL/min) no dosage adjustment is necessary. For breast cancer patients with moderate renal impairment (CLcr ≥ 30 and < 50 mL/min) or severe renal impairment (CLcr < 30 mL/min) being treated for metastatic bone disease the following dosing recommendations should be followed (see Section 5.2 *Pharmacokinetics in Special Populations – Patients with Renal Impairment*).

Creatinine Clearance (mL/min)	Dosage/Infusion Time[1]	Infusion Volume[2]
≥ 50 CLcr < 80	6 mg/1 - 2 hours	500 mL
≥ 30 CLcr < 50	4 mg/1 - 2 hours	500 mL
< 30	2 mg/1 - 2 hours	500 mL

1. Administration every 4 weeks
2. 0.9% Sodium chloride solution or 5% glucose solution

Film-coated Tablets

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 50 mg once weekly (see Section 5.2 *Pharmacokinetics in Special Populations – Patients with Renal Impairment)*.

Patients with hepatic impairment

No dosage adjustment is necessary.

Elderly

No dosage adjustment is necessary.

4.3 CONTRAINDICATIONS

BONDRONAT Injection and Tablets must not be used in patients with:

- hypocalcaemia (see Section 4.4)
- a known hypersensitivity to ibandronic acid, other bisphosphonates or any of the excipients.

BONDRONAT Tablets must not be used in patients:

- with abnormalities of the oesophagus which delay oesophageal emptying such as stricture or achalasia (see Section 4.4)
- who are unable to stand or sit upright for at least 30 minutes (see Section 4.4 and Section 4.2).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

General

As the inadvertent intra-arterial administration of preparations not expressly recommended for this purpose as well as paravenous administration can lead to tissue damage, care must be taken to ensure that BONDRONAT infusion solution is administered IV.

Clinical placebo-controlled, randomised 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, it is recommended that renal function, serum calcium, phosphate and magnesium should be monitored in patients treated with BONDRONAT.

In patients treated for hypercalcaemia, the onset of action of BONDRONAT is not immediate, so all patients should be adequately hydrated with normal saline and their urine output should be maintained. Over-hydration should be avoided in patients at risk of cardiac failure.

Since non-steroidal anti-inflammatory drugs (NSAIDs) and bisphosphonates are both associated with gastrointestinal irritation, caution should be taken during concomitant medication with BONDRONAT.

Products containing calcium and other multivalent cations (such as aluminium, magnesium, iron), including milk and food, are likely to interfere with the absorption of BONDRONAT tablets. Therefore, with such products, including food, intake must be delayed at least 30 minutes following oral administration.

Anaphylactic reaction/shock

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

Appropriate medical support and monitoring measures should be readily available when BONDRONAT is administered intravenously. If anaphylactic or other severe hypersensitivity/allergic reactions occur, immediately discontinue the infusion and initiate appropriate treatment.

Gastrointestinal irritation

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 oesophagus, dysphagia, other oesophageal diseases, gastritis, duodenitis or ulcers).

Adverse experiences such as oesophagitis, oesophageal ulcers and oesophageal erosions, in some cases severe and requiring hospitalisation, rarely with bleeding or followed by oesophageal stricture or perforation, have been reported in patients receiving treatment with oral bisphosphonates. The risk of severe oesophageal 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 oesophageal irritation. Patients should pay particular attention to the dosing instructions and be able to comply with these instructions (see Section 4.2).

Physicians should be alert to any signs or symptoms signalling a possible oesophageal 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.

Hypocalcaemia

Hypocalcaemia 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.

Infusion of BONDRONAT may present a risk of hypocalcaemia. In most cases, plasma calcium concentrations remain within the normal range during the administration of recommended doses of BONDRONAT. Hypocalcaemia was reported in about 2% of patients treated with doses up to 4 mg. If plasma calcium falls into the hypocalcaemic range, the patients usually remain asymptomatic. In severe or symptomatic cases of hypocalcaemia, oral or parenteral calcium supplementation may be required.

Osteonecrosis

Osteonecrosis of the jaw, generally associated with tooth extraction and/or local infection (including osteomyelitis), has been reported in patients treated with bisphosphonates. Most cases have been reported in patients being treated with IV bisphosphonates. Some cases of osteonecrosis of the jaw have occurred after treatment with oral bisphosphonates for osteoporosis.

A dental examination with appropriate preventive dentistry should be considered prior to treatment with BONDRONAT, particularly in patients with concomitant risk factors (e.g. cancer, chemotherapy including angiogenesis inhibitors, radiotherapy, corticosteroids, poor oral hygiene). While on treatment, patients should avoid invasive dental procedures if possible.

For patients who develop osteonecrosis of the jaw while on bisphosphonate therapy, treatment should be discontinued. Dental surgery for these patients may exacerbate the condition. For patients requiring dental procedures, there are no data available to suggest whether the 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 BONDRONAT. Risk factors are similar as for osteonecrosis of the jaw. 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.

Atypical fractures of the femur

Atypical subtrochanteric and diaphyseal femoral fractures have been reported with bisphosphonate therapy, primarily in patients receiving long-term treatment for osteoporosis. These transverse or short oblique fractures can occur anywhere along the femur from just below the lesser trochanter to just above the supracondylar flare. These fractures occur after minimal or no trauma and some patients experience thigh or groin pain, often associated with imaging features of stress fractures, weeks to months before presenting with a completed femoral fracture. Fractures are often bilateral; therefore the contralateral femur should be examined in bisphosphonate-treated patients who have sustained a femoral shaft fracture. Poor healing of these fractures has also been reported.

Discontinuation of bisphosphonate therapy in patients suspected to have an atypical femur fracture should be considered pending evaluation of the patient, based on an individual benefit risk assessment.

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.

Atypical fractures of other long bones

Atypical fractures of other long bones, such as the ulna and tibia have also been reported in patients receiving long-term treatment. As with atypical femoral fractures, these fractures occur after minimal, or no trauma and some patients experience prodromal pain prior to presenting with a completed fracture. In cases of ulna fracture, this may be associated with repetitive stress loading associated with the long-term use of walking aids (See section 4.8 Adverse effects (undesirable effects)).

A temporary discontinuation after 3-5 years of bisphosphonate therapy may be appropriate in patients at low risk of fracture (see section 4.2 Dose and method of administration).Paediatric use

The safety and efficacy of BONDRONAT in paediatric patients have not been established.

Use in the Elderly

No overall differences in efficacy or safety were observed between the elderly patients and younger patients.

Effects on laboratory tests

Bisphosphonates are known to interfere with the use of bone-imaging agents. Specific studies with BONDRONAT have not been performed.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No drug interactions of clinical significance are likely since BONDRONAT does not inhibit the major human hepatic P450 isoenzymes and has been shown not to induce the hepatic cytochrome P450 system in rats. BONDRONAT is eliminated by renal secretion only and does not undergo any biotransformation. In rats, there was no evidence for renal secretion of ibandronic acid by known acidic and basic transport systems involved in the excretion of other drugs.

General

In clinical studies, BONDRONAT has been administered concomitantly with commonly used anti-cancer agents, diuretics, antibiotics and analgesics without clinically apparent interactions occurring.

Aminoglycosides

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.

Calcium Supplements/Antacids

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, which is consistent with findings in animal studies. Therefore, with such products, including food, intake must be delayed for 30 minutes following oral administration of BONDRONAT.

H_2 Blockers

In healthy male volunteers and postmenopausal women, IV 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.

Hormone Replacement Therapy

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

Melphalan/Prednisolone

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

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

Rat fertility was unaffected by an oral ibandronic acid dose of 16 mg/kg/day. Females were treated from 14 days prior to mating to the end of gestation, and pre-implantation losses were increased at oral doses of 1 - 16 mg/kg/day. Fertility and sperm concentrations in rats were reduced following IV doses of 0.3 and 1 mg/kg/day given to males for 28 days prior to and during mating. Females were treated from 14 days prior to mating to gestation day 7, and decreased corpora lutea and increased post-implantation loss were observed with a dose of 1.2 mg/kg/day. Animal:human exposure comparisons are not valid because of differences in frequency of dosing.

Use in Pregnancy

Category B3

BONDRONAT should not be used during pregnancy.

There was no evidence for a direct foetal toxic or teratogenic effect of ibandronic acid in orally treated rats (30 mg/kg/day) and rabbits (20 mg/kg/day). No teratogenicity was observed in rats treated with IV doses of 0.1 - 1.5 mg/kg/day or in rabbits treated with IV doses of 0.03 - 0.20 mg/kg/day. Animal:human exposure comparisons are not valid because of differences in frequency of dosing.

Adverse effects of ibandronic acid in reproductive toxicity studies in the rat were those observed with bisphosphonates as a class. There was an increase in foetal visceral variations (renal pelvis ureter syndrome) and ibandronic acid interfered with natural delivery (dystocia). Dystocia could be partially reversed by calcium supplementation.

There is no clinical experience with BONDRONAT in pregnant women.

Use in Lactation

BONDRONAT should not be used during lactation.

It is not known whether BONDRONAT is excreted in human milk. After IV administration ibandronic acid was excreted in the milk of lactating rats.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Experience from Clinical Trials

Treatment of Metastatic Bone Disease

Adverse reactions from the phase III trial, reported as remotely, possibly, or probably related to study medication at a frequency ≥ 2% in patients treated intravenously, at 4 week intervals, with BONDRONAT 6 mg are listed in Table1. Adverse reactions that are equally frequent in both active and placebo or more frequent in placebo-treated patients are excluded.

Table 1 Related Adverse Reactions Reported at a Frequency ≥ 2% and Greater than Placebo

	Placebo ***n*** **= 157** **(%)**	**BONDRONAT 6 mg** ***n*** **= 152** **(%)**
Body as a Whole		
Asthenia	8 (5.1)	10 (6.6)
Flu Syndrome	2 (1.3)	8 (5.3)
Digestive System		

	Placebo ***n* = 157** **(%)**	**BONDRONAT 6 mg** ***n* = 152** **(%)**
Diarrhoea	1 (0.6)	8 (5.3)
Dyspepsia	5 (3.2)	6 (3.9)
Vomiting	2 (1.3)	5 (3.3)
Gastrointestinal Pain	2 (1.3)	4 (2.6)
Sore Throat	-	3 (2.0)
Tooth Disorder	-	3 (2.0)
Musculoskeletal System		
Myalgia	6 (3.8)	8 (5.3)
Nervous System		
Headache	4 (2.5)	9 (5.9)
Dizziness	2 (1.3)	4 (2.6)
Metabolic and Nutritional Disorders		
Peripheral Oedema	2 (1.3)	3 (2.0)
Gamma-GT increased	1 (0.6)	4 (2.6)
Creatinine increased	1 (0.6)	3 (2.0)

Adverse reactions from pooled oral phase III trials, reported as remotely, possibly, or probably related to study medication, at a frequency ≥ 2% in patients treated with BONDRONAT 50 mg once daily are listed in Table 2. Adverse reactions that are equally frequent in both active and placebo or more frequent in placebo-treated patients are excluded.

Table 2 Related Adverse Reactions Reported at a Frequency ≥ 2% and Greater than Placebo

	Placebo ***n* = 277** **(%)**	**BONDRONAT 50 mg** ***n* = 286** **(%)**
Digestive System		
Dyspepsia	13 (4.7)	20 (7.0)
Nausea	4 (1.4)	10 (3.5)
Abdominal pain	2 (0.7)	6 (2.1)

	Placebo ***n* = 277** **(%)**	**BONDRONAT 50 mg** ***n* = 286** **(%)**
Oesophagitis	2 (0.7)	6 (2.1)
Metabolic and Nutritional Disorders Hypocalcaemia	 14 (5.1)	 27 (9.4)
General Disorders Asthenia	 2 (0.7)	 4 (1.4)

The following adverse reactions occurred < 1% in patients receiving BONDRONAT 50 mg once daily:

Blood and Lymphatic System Disorders: anaemia

Nervous System Disorders: dysgeusia, paraesthesia

Gastrointestinal Disorders: abdominal pain, dry mouth, duodenal ulcer, haemorrhage, dysphagia, gastritis

Skin and Subcutaneous Tissue Disorders: pruritus

Renal and Urinary Disorders: uraemia

General Disorders: chest pain, influenza-like illness, malaise, pain NOS

Investigations: increased blood parathyroid hormone

Treatment of Tumour-Induced Hypercalcaemia

The most common adverse reaction associated with IV infusion of BONDRONAT is a rise in body temperature, which occurred in up to 9% of patients. Occasionally, this was combined with one or more of the following symptoms: fever, chills, headache, heat sensation, sweating, bone and/or muscle ache-like pain (2 - 3% of all patients). In most cases no specific treatment was required and the symptoms subsided after a couple of hours/days.

Serum calcium may fall to hypocalcaemic values in about 2% of patients treated with doses up to 4 mg (see Section 4.4).

Frequently, the decreased renal calcium excretion is accompanied by a fall in serum phosphate levels not requiring therapeutic measures. Clinically relevant hypophosphataemia and hypomagnesaemia were reported in less than 1% of patients.

Gastrointestinal intolerability has been reported in isolated cases.

Administration of other bisphosphonates has been associated with broncho-constriction in aspirin-sensitive asthmatic patients.

Post Marketing Experience

System Organ Class	Very rare	Unknown
Musculoskeletal and connective tissue disorders:	Osteonecrosis of the jaw	Atypical subtrochanteric and diaphyseal fractures
Eye disorders:		Ocular inflammation
Immune system disorders:		Anaphylactic reaction/shock, Allergic reactions, Stevens-Johnson Syndrome, Erythema Multiforme, Bullous Dermatitis

Musculoskeletal and connective tissue disorders:

Osteonecrosis of the jaw and of other oro-facial sites, including the external auditory canal, has been reported very rarely in patients treated by ibandronic acid.

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.

Although the pathophysiology is uncertain, consistent evidence from epidemiological studies suggests an increased risk of atypical subtrochanteric and diaphyseal femoral fractures with long-term bisphosphonate therapy, including ibandronate (see sections 4.2 Dose and method of administration and 4.4 Special warnings and precautions). The absolute risk of atypical subtrochanteric and diaphyseal long bone fractures (bisphosphonate class adverse reaction) remains very low.

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 (see PRECAUTIONS).

Allergic reactions including asthma exacerbation have been reported.

Severe cutaneous adverse reactions including Stevens-Johnson Syndrome, Erythema Multiforme and Bullous Dermatitis have been reported.

Reporting suspected adverse reactions

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at https://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

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

Standard haemodialysis procedures result in significant clearance of ibandronic acid.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Ibandronic acid is a nitrogen-containing bisphosphonate with affinity for bone that inhibits osteoclast-mediated bone resorption. In animals, ibandronic acid inhibits experimentally induced bone resorption caused by ovariectomy, retinoids, tumours or parathyroid hormone-related protein but does not interfere with osteoclast recruitment. The inhibition of endogenous bone resorption has been documented by ^{45}Ca kinetic studies and by the release of radioactive tetracycline previously incorporated into the skeleton.

There was no evidence of impaired mineralisation after short-term subcutaneous treatment of growing rats with 5 mg/kg/day of ibandronic acid. This dose is greater than 300 times the dose shown to inhibit tumour related osteolysis in rats, and 5000 times the optimal antiresorptive dose in aged ovariectomised rats. In animal models of metastatic bone disease, ibandronic acid not only prevented the development of osteolytic bone lesions but also suppressed the progression of already established lesions, which were induced by human breast cancer cells. Several mechanisms may be involved in the inhibition of tumour osteolytic lesion development by ibandronic acid, including direct effects on bone, osteoclasts and tumour cells.

Clinical studies in patients with tumour-induced hypercalcaemia demonstrated that the inhibitory effect of ibandronic acid on tumour-induced osteolysis, and specifically on tumour-induced hypercalcaemia, is characterised by a decrease in serum calcium and urinary calcium excretion.

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

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

Clinical trials

Treatment of Metastatic Bone Disease

Three similarly designed phase III multi-centre, randomised, double-blind, placebo-controlled trials were conducted to investigate the efficacy and safety of BONDRONAT in the treatment of metastatic bone disease (MBD) due to breast cancer. The primary efficacy endpoint was the Skeletal Morbidity Period Rate (SMPR), defined as the number of 12 week Periods with New Bone Complications (PNBC) of Metastatic Bone Disease over Total Observation Time. A new bone complication was defined as a composite endpoint comprising the following skeletal related events (SREs) as sub-components:

- vertebral fractures
- non-vertebral pathological fractures
- bone complications requiring radiotherapy
- bone complications requiring surgery.

The analysis of the SMPR was time-adjusted and considered that one or more events occurring in a single 12 week period could be potentially related. Multiple events were therefore counted only once in any given 12 week period for the purposes of the analysis. Supportive analyses for the primary efficacy endpoint included mean number of bone events, proportion of patients with new events and time to first new bone event. Secondary efficacy endpoints included quality of life (sum of scores of five functional parameters), bone pain score, analgesic requirement, WHO performance status, patient survival and markers of bone turnover.

Intravenous

In the IV study 466 patients were randomised to receive 4 weekly treatment for up to 60 weeks. 154 patients received BONDRONAT 2 mg IV injection, 154 received 6 mg BONDRONAT by infusion (over 1 - 2 hours) and 158 patients received placebo approximately half by bolus injection and half by infusion.

A statistically significant reduction (20%) in the SMPR was shown for the 6 mg treatment group compared to placebo. The beneficial effects of the 6 mg dose were most apparent in the reduced need for radiotherapy and the number of vertebral fractures. A statistically significant reduction was also observed in the mean number of new bone events for the 6 mg treatment group compared placebo and time to first event (Table 3).

For secondary efficacy endpoints, a statistically significant improvement in bone pain score was shown for BONDRONAT 6 mg treatment group compared to placebo. The pain reduction was consistently below baseline throughout the entire study and accompanied by a significantly reduced use of analgesic. The bone pain and analgesic consumption assessments were performed using a scoring system, with a score of 0 – 4 for bone pain and a score of 0 – 6 for analgesic consumption. The quality of life was assessed as the sum of scores of five functional parameters (physical, role, cognitive, emotional and social function) and demonstrated that the overall quality of life scores decreased significantly less for patients treated with BONDRONAT compared with placebo (Table 3). There was a marked depression of urinary markers of bone resorption (pyridinoline and deoxypyridinoline) in patients treated with BONDRONAT that was statistically significant compared to placebo.

Table 3 Summary of Efficacy Results for IV Study[1]

	Placebo ***n* = 158**	**BONDRONAT 6 mg** ***n* = 154**
Mean SMPR (per patient year) - All New Bone Events	1.48	1.19 $p = 0.004$[2]
Mean SMPR (per patient year) – Bone Events requiring Radiotherapy	1.09	0.91 $p = 0.011$[2]
Mean Number of New Events per patient	3.64	2.65 $p = 0.025$[2]
Mean Number of New Events – Bone Events requiring Radiotherapy	2.73	1.76 $p = 0.032$[2]
Time to First Event (weeks)	33.1	50.5 $p = 0.018$[3]
Percentage of Patients with Events (%)	62.0	50.6 $p = 0.052$[4]
Bone pain score[5]	0.21	-0.28 $p < 0.001$[2]
Analgesic use[5]	0.90	0.51 $p = 0.083$[2]
Quality of life[5]	-45.4	-10.3 $p = 0.004$[2]

[1] intent to treat population
[2] pairwise comparison between treatments using Wilcoxon rank sum test, unadjusted for multiplicity
[3] log rank test
[4] pairwise comparison between treatments using exact Pearson chi-square test for 2 x 2 table
[5] absolute change from baseline

Oral

The treatment of metastatic bone disease of breast cancer with BONDRONAT 50 mg tablets was assessed in two randomised placebo controlled phase III trials with duration of 96 weeks. Female patients with breast cancer and radiologically confirmed bone metastases were randomised to receive placebo (*n* = 277) or BONDRONAT 50 mg (*n* = 287) once daily.

In order to minimise the effect of early selective dropout and pre-scheduled radiotherapy in some patients which was completed during the first treatment period, all data from the first 12 weeks has been excluded from the efficacy analysis.

Pooled data demonstrated a significant reduction in SMPR for the treatment group compared to placebo, with a reduced need for radiotherapy being the most apparent difference. There was also a significant reduction in the mean number of events per patient for the treatment group compared to placebo (Table 4).

Table 4 Summary of Efficacy Results for Oral Studies (excluding first efficacy period)

	Placebo ***n* = 268**	**BONDRONAT 50 mg** ***n* = 276**
Mean SMPR (per patient year) – All New Bone Events	1.18	0.95 $p = 0.004$[1]
Mean SMPR (per patient year) – Bone Events Requiring Radiotherapy	0.98	0.73 $p < 0.001$[1]
Mean Number of New Events per patient	1.85	1.15 $p = 0.008$[1]
Time to First Event (weeks)	64.9	90.3 $p = 0.089$[1]
Percentage of Patients with Events (%)	52.2	45.3 $p = 0.122$[2]

[1] pairwise comparison between treatments using Wilcoxon Rank sum test, unadjusted for multiplicity
[2] pairwise comparison between treatments using exact Pearson chi-square test for 2x2 table

For the secondary endpoints, a statistically significant improvement in bone pain score was shown for BONDRONAT 50 mg compared to placebo. The pain reduction was consistently below baseline throughout the entire study and accompanied by a significantly reduced use of analgesics compared to placebo. The deterioration in Quality of Life and WHO performance status was significantly less in BONDRONAT treated patients compared with placebo. There was a marked depression of urinary CTx, a marker of bone resorption, which was statistically significant compared to placebo (Table 5).

Table 5 Summary of Secondary Efficacy Results for Oral Studies[1]

	Placebo ***n* = 277**	**BONDRONAT 50 mg** ***n* = 287**
Bone pain score	0.20	-0.10 *p* = 0.001
Analgesic use[2]	0.85	0.60 *p* = 0.019
Quality of Life[2]	-26.8	-8.3 *p* = 0.032
WHO performance status	0.54	0.33 *p* = 0.008
Urinary CTx (%) (96 weeks)	11.0	-77.3 *p* < 0.001

p value = pairwise comparisons between treatments using Wilcoxon Rank sum test, unadjusted for multiplicity
[1] pooled data
[2] absolute change from baseline

A Poisson regression multivariate analysis was conducted to determine the number of new bone events while adjusting for the differences in the baseline characteristics of the patients treated. The 6 mg IV dose demonstrated a significant treatment effect over placebo with a mean risk reduction of approximately 40% (*p* = 0.0033), while the 50 mg oral dose demonstrated a mean risk reduction of 38% (*p* = 0.0001) (Table 6).

Table 6 Number of New Bone Events[1]

	Relative Risk Estimate (95% CI)	***p*-value**
6 mg IV	0.60 (0.43, 0.85)	0.0033
50 mg oral	0.62 (0.48, 0.79)	0.0001

[1] Intent to treat population

Treatment for Tumour-Induced Hypercalcaemia

Clinical studies in hypercalcaemia of malignancy demonstrated that the inhibitory effect of ibandronic acid on tumour-induced osteolysis, and specifically on tumour-induced hypercalcaemia, is characterised by a decrease in serum calcium and urinary calcium excretion.

A single infusion of 2 - 6 mg BONDRONAT was effective in reducing elevated serum calcium levels in patients with hypercalcaemia of malignancy with and without metastases. Lower initial calcium levels were associated with a greater likelihood of treatment response, as were higher doses (up to 4 mg). The drug was also more likely to be effective in patients with hypercalcaemia due to local osteolytic lesions than in those with humoral hypercalcaemia. The time to response was 2 - 4 days in 75% of responding patients with the remaining 25% of responses occurring on days 5 - 7. The median time to relapse (re-increase of albumin-corrected serum calcium to above 3 mmol/L) was 18 - 19 days.

Study P3

Study P3 was an open, randomised, multicentre, phase II dose-finding study in which the efficacy and safety of BONDRONAT was evaluated in 174 patients with hypercalcaemia of malignancy. One patient died prior to

treatment with the study drug. Of the 173 patients eligible for evaluation, 56, 56 and 60 patients were treated with a single IV infusion of 0.6, 1.1 and 2 mg BONDRONAT, respectively.

Response to this single infusion was defined as attainment of the normal range of albumin-corrected serum calcium (≤ 2.7 mmol/L) for at least one visit and a reduction of the albumin-corrected serum calcium ≥ 0.3 mmol/L, compared with baseline.

The response was dose related. 44%, 52.2% and 67.3% of the patients achieved a normal range of serum calcium with a single dose of 0.6 mg, 1.1 mg and 2 mg BONDRONAT, respectively.

Forty nine patients (28.3%) then received a second infusion of BONDRONAT between days 2 and 49 after the first infusion because of insufficient efficacy or hypercalcaemia relapse. 46, 2 and 1 patient(s) received 2, 1.6 and 1.1 mg BONDRONAT, respectively. Response was measured using the same criteria as above. Twenty one patients were withdrawn prior to response and were censored from the study and 9 patients reached the normal range.

Study P6

Study P6 was a double blind, randomised, multicentre, dose-finding study in which the efficacy and safety were assessed in 147 patients with malignant hypercalcaemia (baseline albumin-corrected serum calcium ≥ 3.0 mmol/L after adequate hydration). Of the 131 randomised patients eligible for final evaluation, 45, 44 and 42 patients were treated with 2, 4 and 6 mg, respectively.

Response was defined as achieving the normal range of serum calcium (≤ 2.7 mmol/L) on at least one visit and a reduction of the albumin-corrected serum calcium of ≥ 0.3mmol/L, compared with baseline. Pooled response rates for the studies are presented in Table 7.

Table 7 Pooled Patient Response Rates for 2, 4 & 6 mg Doses

Dose	**% of Patients Responding** (90% Confidence Interval)
2 mg	**54** (44-63)
4 mg	**76** (62-86)
6 mg	**78** (64-88)

5.2 PHARMACOKINETIC PROPERTIES

The pharmacological effects of ibandronic acid are not directly related to actual plasma concentrations. This was demonstrated by various studies in animals and humans, in which equivalent efficacy of ibandronic acid was demonstrated following either daily or intermittent regimens, consisting of a drug-free interval of several weeks (at least 6 weeks in rats, at least 11 weeks in dogs, at least 30 days in monkeys, and at least 9.5 weeks in humans) provided the same total dose was administered over this period.

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 - 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 drink (other than plain water).

Bioavailability

Bioavailability is reduced by about 90% when oral ibandronic acid is administered with food in comparison with bioavailability seen in fasted subjects. When taken 30 minutes before a meal, the reduction in bioavailability is approximately 50%. There is no meaningful reduction in bioavailability provided ibandronic acid is taken 60 minutes before a meal.

Plasma concentrations of ibandronic acid increase in a dose-proportional manner after oral administration up to 100 mg and after IV administration up to 6 mg.

Bioavailability was reduced by approximately 75% when BONDRONAT tablets were administered 2 hours after a standard meal. Therefore, it is recommended that the tablets be taken after an overnight fast, and fasting should continue for at least 30 minutes after the dose.

Distribution

After initial systemic exposure, ibandronic acid rapidly binds to bone or is excreted into urine. In humans, the volume of distribution is at least 90 L and the amount reaching the bone is estimated to be 40 - 50% of the dose. Protein binding in human plasma is low (approximately 87% bound at therapeutic concentrations).

Metabolism

There is no evidence that ibandronic acid is metabolised in humans.

Elimination

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 faeces.

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 - 8 hours after IV or oral administration, respectively. No systemic accumulation was observed when ibandronic acid was administered intravenously once every 4 weeks for 48 weeks to patients with metastatic bone disease.

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.

Pharmacokinetics in Special Populations

Gender

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

Race

Studies involving Asian and Caucasian healthy volunteers showed no clinically relevant differences in the pharmacokinetics of ibandronic acid.

Patients with renal impairment

Intravenous:

Exposure to ibandronic acid in patients with various degree of renal impairment is related to creatinine clearance (CLcr). In clinical pharmacology trial WP18551, after a single dose IV administration of 6 mg (infusion time of 15 minutes), mean AUC0-24 increased by 14% and 86% respectively, in subjects with mild (mean estimated CLcr = 68.1 mL/min) and moderate (mean estimated CLcr = 41.2 mL/min) renal impairment compared to healthy volunteers (mean estimated CLcr = 120 mL/min). In subjects with severe renal impairment (mean estimated CLcr = 21.2 mL/min), who received a single dose of 2 mg (infusion time of 15 minutes), mean AUC0-24h was increased by 110% compared to healthy volunteers. Mean Cmax was not increased in patients with mild renal impairment and increased by 12% in patients with moderate renal impairment. There is no evidence of a reduction in tolerability associated with an increase in exposure. However, an adjustment in the dose is recommended in patients with moderate renal impairment (CLcr ≥ 30 and ≤ 50 mL/min) or severe renal impairment (CLcr ≤ 30 mL/min) being treated for the prevention of skeletal events in patients with breast cancer and metastatic bone disease (see Dosage and Administration – Special Patient Groups).

Oral:

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 > 90 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. There was no reduction in tolerability associated with the increase in exposure. However, reduction of the oral dose to one 50 mg tablet once weekly is recommended in patients with severe renal impairment (CLcr ≤ 30 mL/min). No dosage adjustment is necessary for patients with mild renal impairment (CLcr ≥ 50 and < 80 mL/min). A reduction in the oral dose to one 50 mg tablet every second day is recommended in patients with moderate renal impairment (CLcr ≥ 30 and < 50 mL/min) (see Dosage and Administration – Special Patient Groups).

Approximately 37% of ibandronic acid was cleared from the body during a standard 4 hour haemodialysis 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 cleared by renal excretion and by uptake into bone. No dosage adjustment is necessary in patients with hepatic impairment. Further, as protein binding of ibandronic acid is low at therapeutic concentrations (85%), hypoproteinaemia in severe liver disease is unlikely to lead to clinically significant increases in free plasma concentration.

Elderly

There were no clinically significant differences in the pharmacokinetics of ibandronic acid in elderly patients. No dosage adjustment is necessary.

Children

The pharmacokinetics of ibandronic acid in patients less than 18 years of age has not been studied.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

The mutagenic and clastogenic potential of ibandronic acid was assessed in a standard range of tests. *In vitro* tests included the *Salmonella typhimurium*, *Escherichia coli* and Chinese hamster V79 mammalian cell line assays for gene mutation and a human peripheral lymphocyte assay for chromosomal aberrations, each with and without metabolic-activation. *In vivo* mouse micronucleus tests for chromosomal damage were conducted by both the oral and IV routes of administration. There was no evidence for any mutagenic or clastogenic activity with ibandronic acid.

Carcinogenicity

A two year carcinogenicity study was conducted with ibandronic acid administrated to rats at oral doses of 0 (control), 3, 7 or 15 mg/kg/day. There were no neoplastic findings considered to be related to treatment with ibandronic acid. In an 18 month carcinogenicity study ibandronic acid was administered to mice at oral doses of 0 (control), 5, 20, or 40 mg/kg/day. There were no neoplastic findings as a result of treatment with ibandronic acid. In a 90 week carcinogenicity study ibandronic acid was administered to mice at oral (drinking water) doses of 0 (control), 5, 20, and 80 mg/kg/day. There were no neoplastic findings as a result of treatment with ibandronic acid.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Concentrated Injection for IV Infusion:

The concentrated injection also contains sodium chloride, glacial acetic acid, sodium acetate and water for injections.

Film-coated Tablets:

The tablets also contain lactose monohydrate, microcrystalline cellulose, povidone, crospovidone, stearic acid and colloidal anhydrous silica. The tablet film-coating contains hypromellose, titanium dioxide, purified talc and macrogol 6000.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Concentrated Injection for IV Infusion:

Store below 30°C. After reconstitution, store at 2 – 8°C (Refrigerate. Do not freeze).

BONDRONAT is for single use in one patient only. Discard any residue.

From a microbiological point of view, BONDRONAT infusion solution should be used immediately. If necessary, storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours, stored at 2 – 8°C (Refrigerate. Do not freeze). The product is not intended to be stored after dilution unless the dilution has taken place under controlled and validated aseptic conditions.

Film-coated Tablets:

Store below 30°C.

6.5 NATURE AND CONTENTS OF CONTAINER

Concentrated Injection for IV Infusion:

BONDRONAT 6 mg/6 mL vial is available in packs of one.

Film-coated Tablets:

The tablets are available in blister packs of 28.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

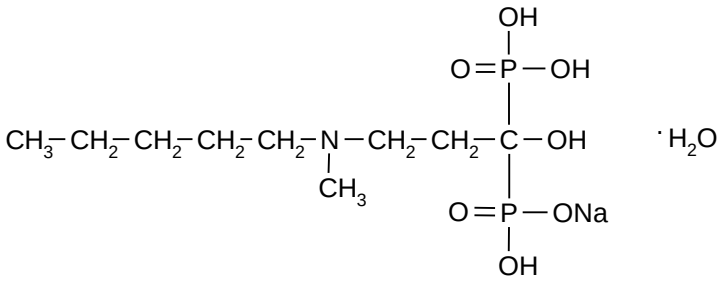
The release of medicines into the environment should be minimised. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Unused or expired medicine should be returned to a pharmacy for disposal.

6.7 PHYSICOCHEMICAL PROPERTIES

Ibandronate sodium has the full chemical name of [1-hydroxy-3-(methylpentylamino)propylidene]bis-phosphonic acid, monosodium salt, monohydrate.

Chemical Structure

Its molecular weight is 359.



CAS Number

CAS registry number: 138926-19-9

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 - Prescription only medicine

8. SPONSOR

Atnahs Pharma Australia Pty Ltd

Level 10 / 10 Shelley Street,

Sydney, NSW, 2000, Australia

Ph: 1800 899 005

9. DATE OF FIRST APPROVAL

13 April 2004

10. DATE OF REVISION

24 February 2023

Summary table of changes

Section changed	Summary of new information
4.2	Addition of temporary drug discontinuation advice
4.4	Addition of gastrointestinal information, atypical fractures of the femur and atypical fractures of other long bones
4.8	Addition of post-marketing table, revision of risk of atypical subtrochanteric and diaphyseal femoral fractures