Bondronat®

Ibandronic acid

1. Pharmaceutical Form

Concentrate for solution for infusion.

2. Qualitative and Quantitative Composition

Active ingredient: ibandronic acid.
Ampoules with 1 ml of concentrate for infusion. Vials with 2 ml or 6ml of concentrate for solution for infusion.

Ampoules of 1 ml contain 1.125 mg ibandronic acid, monosodium salt, monohydrate corresponding to 1 mg ibandronic acid; vials of 2 ml contain 2.25 mg ibandronic acid, monosodium salt, monohydrate corresponding to 2 mg ibandronic acid; vials of 6 ml contain 6.75 mg ibandronic acid, monosodium salt, monohydrate, corresponding to 6 mg ibandronic acid.

3. Clinical Particulars

3.1 Therapeutic Indications

- Prevention of skeletal events associated with metastatic bone disease due to breast cancer.
- Treatment of pathologically (abnormally) elevated serum calcium levels (hypercalcemia) as a result of tumours.

3.2 Dosage and Method of Administration

Treatment of Metastatic Bone Disease
The recommended dose for metastatic bone disease is 6 mg IV given every 3-4 weeks. The dose should be infused over at least 15 minutes. For infusion, the contents of the ampoule(s)/vials(s) should be added to 100 ml isotonic sodium chloride solution (or 100 ml 5% dextrose solution).

A shorter (i.e 15 min) infusion time should only be used for patients with normal renal function or mild renal impairment. There are no data available characterizing the use of a shorter infusion time in patients with creatinine clearance below 50ml/min. Prescribers should consult the section *Patients with renal impairment* for recommendations on dosing and administration in this patient group.

Treatment of hypercalcemia
Bondronat concentrate for infusion is usually administered in a hospital setting. The dose is determined by the doctor considering the following factors.

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 hypercalcemia as well as the tumour type. In general patients with osteolytic bone metastases require lower doses than patients with the humoral type of hypercalcemia. In most patients with severe hypercalcemia (albumin-corrected serum calcium* ≥ 3 mmol/l or ≥ 12 mg/dl) 4 mg will be an adequate single dosage. In patients with moderate hypercalcemia (albumin-corrected serum calcium < 3 mmol/l or < 12 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 (reincrease of serum 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 hypercalcemia.

Repeated treatment may be considered in case of recurrent hypercalcemia or insufficient efficacy.

Bondronat concentrate for infusion should be administered as an intravenous infusion. For this purpose the contents of the ampoules are to be added to 500 ml isotonic sodium chloride solution or 500 ml 5% dextrose solution and infused over two hours.

Note
In order to avoid potential incompatibilities, Bondronat concentrate for infusion should only be mixed with isotonic sodium chloride solution or with 5% dextrose solution. Calcium containing solutions should not be mixed with Bondronat concentrate for infusion.

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.

Patients with renal impairment
Concentrate for solution for infusion in patients with ***Metastatic Bone Disease:***
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) being treated for the prevention of skeletal events in patients with breast cancer and metastatic bone disease the following dosing recommendations should be followed.

Creatinine Clearance (mL/min)	Dosage / Infusion time [1]	Infusion Volume [2]
≥50 CLcr <80	6 mg / 15 minutes	100 mL
≥30 CLcr <50	4 mg / 1 hour	500 mL
<30	2 mg / 1 hour	500 mL

[1] Administration every 3 to 4 weeks
[2] 0.9% sodium chloride solution or 5% glucose solution

A 15 minute infusion time has not been studied in cancer patients with CLcr <50 mL/min

3.3 Contraindications

Bondronat is contraindicated in patients with:

- Hypocalcemia (see 3.4 Warnings and Precautions for Use)
- known hypersensitivity to ibandronic acid or to any of its excipients.

Caution is to be taken in patients with known hypersensitivity to other bisphosphonates.

3.4 Warnings and Precautions for Use

Bondronat concentrate for infusion should not be used in children because of lack of clinical experience.

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 concentrate for infusion.

As no clinical data are available, dosage recommendations cannot be given for patients with severe liver disease (hepatic insufficiency).

Overhydration should be avoided in patients at risk of heart failure.

Hypocalcaemia and other disturbances of bone and mineral metabolism should be effectively treated before starting Bondronat therapy for metastatic bone disease. 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.

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 solution for infusion is administered intravenously.

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.

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. 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

Bondronat should not be mixed with calcium containing solutions.

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 (oestrogen).

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, antibiotics and analgesics without clinically apparent interactions occurring.
Interaction studies have only been performed in adults.

3.6 Pregnancy and Lactation

Bondronat should not be used during pregnancy and lactation.

Pregnancy
In fertility studies, ibandronic acid impaired fertility in female rats at 1.2 mg/kg/day i.v. and decreased the number of implantation sites at 1.0 to 16.0 mg/kg/day p.o. and 1.2 mg/kg/day i.v. At 5.0 to 20 mg/kg/day p.o. and 0.05 to 0.5 mg/kg/day i.v. ibandronic acid interfered with natural delivery (dystocia). There was no evidence for any fetal toxic or teratogenic effects in ibandronic acid treated rats. There was an increase in visceral variations (renal pelvis ureter syndrome) in ibandronic acid-treated rats at 10 to 100 mg/kg/day p.o. or 1 mg/kg/day i.v. In ibandronic acid-treated rabbits, there was no evidence for any embryo-fetal-toxic or teratogenic effects at doses up to 20 mg/kg/day p.o. or 0.07 mg/kg/day i.v.

There is no clinical experience with Bondronat in pregnant women.

Lactation
It is not known whether Bondronat 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.

Bondronat should not be used during lactation.

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

In patients treated for hypercalcemia, intravenous administration of Bondronat concentrate for infusion was most commonly associated with a rise in body temperature. Occasionally, a flu-like syndrome consisting of fever, chills, bone and/or muscle ache-like pain was reported. In most cases no specific treatment is required and the symptoms subside after a couple of hours/days.

Frequently, the decreased renal calcium excretion is accompanied by a fall in serum phosphate levels not requiring therapeutic measures. The serum calcium level may fall to hypocalcemic values.

Gastrointestinal intolerability (side effects involving the stomach and intestine) has been reported in isolated cases.

Administration of other bisphosphonates has been associated with bronchoconstriction (wheezing, breathlessness) in acetylsalicylic acid-sensitive asthmatic patients.

In patients with metastatic bone disease, the most common adverse events were headache, diarrhea, myalgia, asthenia and influenza-like illness.

Patients are requested to inform their physician or pharmacist if undesirable effects occur, in particular if they are not listed in this package insert.

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 very rarely in patients treated with 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.

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 section 3.4 Warnings and 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.

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

Up to now there is no experience of acute poisoning with Bondronat concentrate for infusion.

Since both the kidney and the liver were found to be target organs for toxicity in preclinical studies with high doses, kidney and liver function should be monitored.

Clinically relevant hypocalcemia (very low serum calcium levels) should be corrected by i.v. administration of calcium gluconate.

Standard haemodialysis procedures result in significant clearance of ibandronic acid.

4. Pharmacological Properties & Effects

4.1 Pharmacodynamic Properties

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 been documented by Ca 45 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 mineralization.

Clinical studies in hypercalcemia demonstrated that the inhibitory effect of ibandronic acid on tumour-induced osteolysis, and specifically on tumour-induced hypercalcemia, 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 on bone osteolysis, expressed by markers of bone resorption, and a dose dependent effect on skeletal events.

4.1.1 Mechanism of Action

Ibandronic acid is a highly potent bisphosphonate belonging to the nitrogen-containing group of bisphosphonates, which act on bone tissue and specifically inhibit osteoclast activity. It does not interfere with osteoclast recruitment. The selective action of ibandronic acid on bone tissue is based on the high affinity of this compound for hydroxyapatite, which represents the mineral matrix of the bone.

Ibandronic acid reduces bone resorption, with no direct effect on bone formation.

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

4.1.2 Clinical / Efficacy Studies

Treatment of Metastatic Bone Disease
Bondronat 6 mg administered intravenously was assessed in one randomized placebo controlled phase III trial with duration of 96 weeks with the same endpoints. Female patients with breast cancer and radiologically confirmed bone metastases were randomised to receive placebo (158 patients) or 6 mg Bondronat (154 patients).The results are summarized in the following table:

Treatment	SMPR per patient		SREs	
	Reduction in Rate compared to placebo Treatment	p-value	Risk Reduction compared to placebo (%)	p-value
Intravenous Infusion (6mg every 3 to 4 weeks	0.29	0.004	40	0.003

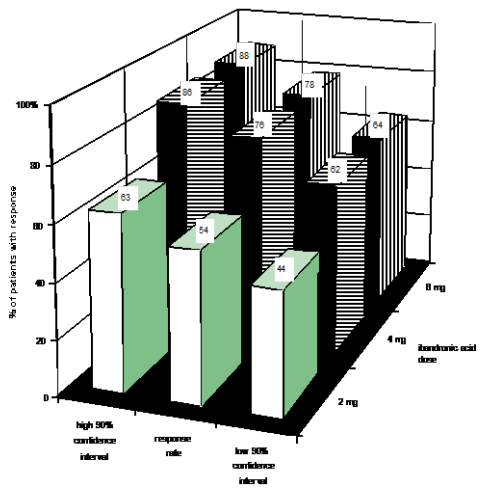
Secondary end points included the measurement of Bone Pain, Quality of Life and the measurement of markers of bone resorption in urine. Bondronat showed improvements in these measurements when compared with placebo.

In a study in 130 patients with metastatic breast cancer the safety of Bondronat infused over 1 hour or 15 minutes was compared. No difference was observed in the indicators of renal function. The overall adverse event profile of ibandronic acid following the 15 minute infusion was consistent with the known safety profile over longer infusion times and no new safety concerns were identified relating to the use of a 15 minute infusion time.

A 15 minute infusion time has not been studied in cancer patients with a creatinine clearance of <50ml/min.

Treatment of tumor-induced hypercalcemia
Bondronat concentrate for solution for infusion:
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.

In the dose range recommended for treatment, the following response rates with the respective confidence intervals have been shown in clinical trials for patients with baseline albumin-corrected serum calcium ≥ 3.0 mmol/l after adequate rehydration:



For these patients and dosages, the median time to achieve normocalcemia was 4 to 7 days. The median time to relapse (re-increase of albumin-corrected serum calcium above 3.0 mmol/l) was 18 to 26 days.

4.2 Pharmacokinetic Properties
After a 2 hour infusion of 2, 4 and 6 mg, ibandronic acid pharmacokinetic parameters are dose proportional.

4.2.1 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 87% bound at therapeutic concentrations), and thus there is a low potential for drug-drug interaction due to displacement.

4.2.2 Metabolism
There is no evidence that ibandronic acid is metabolised in animals or humans.

4.2.3 Elimination
The systemically available 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. Accumulation in plasma was less than 2-fold after 12 months daily oral dosing in patients with osteoporosis. 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.

4.2.4 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
Exposure to ibandronic acid in patients with various degrees of renal impairment is related to creatinine clearance (CLcr).

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 AUC_{0-24h} was increased by 110% compared to healthy volunteers. After a single dose intravenous administration of 6 mg (infusion time of 15 minutes), mean $AUC0-_{24h}$ 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). Mean Cmax was not increased in patients with mild renal impairment and increased by 12% in patients with moderate 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) 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 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 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 (see section Patients with renal impairment, mentioned above).

Children
Bondronat should not be used in children because of lack of clinical experience.

4.3 Preclinical Safety
As with other bisphosphonates, the kidney was identified to be the primary target organ of systemic toxicity. Clinically relevant kidney changes in animals were observed at higher than 3 times the maximal human exposure (based on peak plasma concentration after intravenous administration), indicating sufficient safety margin for clinical use.

4.3.1 Carcinogenicity
No indication of carcinogenic potential has been observed.

4.3.2 Mutagenicity
No indication of genotoxic potential has been observed.

4.3.3 Impairment of Fertility
In fertility studies, ibandronic acid impaired fertility in female rats at 1.2 mg/kg/day i.v.] and decreased the number of implantation sites at 1.0 to 16 mg/kg/day p.o. and 1.2 mg/kg/day i.v..

4.3.4 Teratogenicity
No evidence of direct foetal toxicity or teratogenic effects was observed for ibandronic acid in intravenously or orally treated rats and rabbits.

4.3.5 Other
Adverse effects of ibandronic acid in reproductive toxicity studies in the rat were those expected for this class of drug (bisphosphonates). They include a decreased number of implantation sites, interference with natural delivery (dystocia), an increase in visceral variations (renal pelvis ureter syndrome) and teeth abnormalities in F1 offspring in rats.

5. Pharmaceutical Particulars
5.1 List of Excipients
Sodium chloride, acetic acid, sodium acetate, water for injections.

5.2 Stability
The infusion solution containing the product is chemically and physically stable for 24 hours (do not store above 25°C).

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8 °C, unless dilution has taken place in controlled and validated aseptic conditions.

The expiry date of the ampoules and vials is printed on the outer carton and labels. Do not use the ampoules and vials after this date!

See also outer pack for storage remark.

5.3 Special Instructions for Use, Handling and Disposal
The concentrate for solution for infusion is for single use only. Only clear solution without particles should be used.

Strict adherence to the intravenous route is recommended on parenteral administration of Bondronat concentrate for solution for infusion.

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

Bondronat concentrate for solution for infusion should not be mixed with calcium containing solutions.

Unused solution should be discarded.

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
Vials 2 ml	1, 5
Vials 6ml	1, 5

Medicine: keep out of reach of children

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