SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

BONDRONAT® 2 mg/2 mℓ, injection
BONDRONAT® 6 mg/6 mℓ, injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

BONDRONAT 2 mg/2 mℓ contains 2 mg ibandronic acid per 2 mℓ, as 2,25 mg ibandronic acid, monosodium salt, monohydrate.

BONDRONAT 6 mg/6 mℓ contains 6 mg ibandronic acid per 6 mℓ, as 6,75 mg ibandronic acid, monosodium salt, monohydrate.

Sugar free

For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Injection (concentrate for solution for infusion).

Clear, colourless solution, free from visible particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

BONDRONAT is indicated in:

- the treatment of tumour-induced hypercalcaemia with, or without, metastases.
- patients with breast cancer and bone metastases for the prevention of skeletal complications requiring radiotherapy.

4.2 Posology and method of administration

Posology

Treatment of Metastatic Bone Disease

The recommended dose for metastatic bone disease is 6 mg *i.v*. given every 3 - 4 weeks. The dose should be infused over at least 15 minutes. For infusion, the contents of the ampoule/vial should be added to 100 mℓ isotonic sodium chloride solution (or 100 mℓ of 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 characterising the use of a shorter infusion time in patients with creatinine clearance below 50 mℓ/min. Refer to the section further below, ‘Patients with renal impairment’, for recommendations on dosing and administration in this patient group.

Treatment of Tumour-Induced Hypercalcaemia

Adults and elderly: Consideration should be given to the severity of 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.

***Recommended single dose*:** Prior to treatment with **BONDRONAT** injection solution, the patient should be adequately rehydrated with 0,9 % sodium chloride.

Warning: Overhydration should be avoided in patients at risk of cardiac failure/pulmonary oedema.

Repeated treatment is possible in case of recurrent hypercalcaemia or insufficient efficacy. However, until adequate clinical experience has been gained, a cumulative dose of 6 mg should not be exceeded. **BONDRONAT** injection solution should be administered as an intravenous infusion. The contents of the ampoule/vials are to be added to 500 mℓ isotonic sodium chloride solution (or 500 mℓ of 5 % dextrose solution) and infused over 2 hours.

	Albumin-corrected serum calcium* after adequate rehydration	**Dose**
Severe hypercalcaemia	> 3,5 mmol/ℓ (≥ 12 mg/dℓ)	2 - 4 mg
Moderate hypercalcaemia	< 3,5 mmol/ℓ (< 12 mg/dℓ)	1 - 2 mg

The highest dose used in clinical trials (for hypercalcaemia) was 6 mg, but this dose does not add any further benefit in terms of efficacy.

***** Note: Albumin-corrected serum calcium concentrations are calculated as follows:

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. Median time to relapse (re-increase of serum albumin corrected serum calcium above 3 mmol/ℓ) was 18 - 19 days for the 2 mg and 4 mg doses, and 26 days for the 6 mg dose.

Special populations

Special Dosage instructions

Patients with hepatic impairment

No dosage adjustment is expected to be necessary. See section 5.2, **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) or severe renal impairment (CLcr < 30 mℓ/min), being treated for the treatment of skeletal events in breast cancer and metastatic bone disease, the following dosing recommendations should be followed.

See section 5.2, **Pharmacokinetics in special populations**.

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.

Elderly
No dose adjustment is necessary.

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

Method of administration
- For intravenous administration.
- The concentrate for solution for infusion is for single use only.
- Only clear solution without particles should be used.
- Unused solution should be discarded.

4.3 Contraindications
- Hypersensitivity to ibandronic acid, or other bisphosphonate or to any of the excipients listed in section 6.1.
- Hypocalcaemia, see section 4.4.
- **BONDRONAT** injection should not be used during pregnancy and lactation due to a lack of clinical experience (see section 4.6).

4.4 Special warnings and precautions for use
Administration failures
The inadvertent intra-arterial administration, as well as perivenous administration, is not recommended. This can lead to tissue damage. Ensure that **BONDRONAT** is only administered intravenously.

Patients with disturbances of bone and mineral metabolism
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. Patients should receive supplemental calcium and/or vitamin D if dietary intake is inadequate.

Anaphylactic reaction/shock

Cases of anaphylactic reaction/shock, including fatal events, have been reported in patients treated with i.v. **BONDRONAT**.

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

Osteonecrosis of the jaw

Osteonecrosis of the jaw (ONJ) has been reported very rarely in the post-marketing setting in patients receiving **BONDRONAT** for oncology indications (see section 4.8).

The start of treatment, or of a new course of treatment, should be delayed in patients with unhealed open soft tissue lesions in the mouth.

A dental examination with preventive dentistry and an individual benefit-risk assessment is recommended prior to treatment with **BONDRONAT** in patients with concomitant risk factors.

The following risk factors should be considered when evaluating a patient's risk of developing ONJ:

- Potency of the medicinal product that inhibit bone resorption (higher risk for highly potent compounds), route of administration (higher risk for parenteral administration) and cumulative dose of bone resorption therapy.
- Cancer, co-morbid conditions (e.g. anaemia, coagulopathies, infection), smoking.
- Concomitant therapies: corticosteroids, chemotherapy, angiogenesis inhibitors, radiotherapy to head and neck.
- Poor oral hygiene, periodontal disease, poorly fitting dentures, history of dental disease, invasive dental procedures e.g. tooth extractions.

All patients should be encouraged to maintain good oral hygiene, undergo routine dental check-ups, and immediately report any oral symptoms such as dental mobility, pain or swelling, or non-healing of sores or discharge during treatment with **BONDRONAT**. While on treatment, invasive dental procedures should be performed only after careful consideration and be avoided in close proximity to **BONDRONAT** administration.

The management plan of the patients who develop ONJ should be set up in close collaboration between the treating physician and a dentist or oral surgeon with expertise in ONJ. Temporary interruption of **BONDRONAT** treatment should be considered until the condition resolves and contributing risk factors are mitigated where possible.

Osteonecrosis of the external auditory canal

Osteonecrosis of the external auditory canal has been reported with bisphosphonates, mainly in association with long-term therapy. Possible risk factors for osteonecrosis of the external auditory canal include steroid use and chemotherapy and/or local risk factors such as infection or trauma.

The possibility of osteonecrosis of the external auditory canal should be considered in patients receiving bisphosphonates who present with ear symptoms including chronic ear infections.

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 (see section 4.8).

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).

Patients with renal impairment
Clinical studies 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 the renal function, serum calcium, phosphate, and magnesium should be monitored in patients treated with **BONDRONAT** (see section 4.2).

Patients with hepatic impairment
As no clinical data are available, dosage recommendations cannot be given for patients with severe hepatic insufficiency (see section 4.2).

Patients with cardiac impairment
Overhydration should be avoided in patients at risk of cardiac failure.

Paediatric population
BONDRONAT injection should not be used in children due to a lack of clinical experience (see section 4.2 and section 5.2).

Excipients with known effect
BONDRONAT is essentially sodium free.

4.5 Interaction with other medicines and other forms of interaction
BONDRONAT should not be mixed with calcium containing solutions.

Medicine 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 (oestrogen).
In relation to disposition, no medicine interactions of clinical significance are likely. **BONDRONAT** is eliminated by renal secretion only and does not undergo any biotransformation. The secretory pathway appears not to include known acidic or basic transport systems involved in the excretion of other medicines. In addition, **BONDRONAT** does not inhibit the major human hepatic P450 isoenzymes and has been shown not to induce the hepatic cytochrome P450 system in rats. Plasma protein binding is low at therapeutic concentrations and **BONDRONAT** is therefore unlikely to displace other active substances.

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.
Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation
BONDRONAT injection should not be used during pregnancy and lactation due to a lack of clinical experience. See section 4.3.

Pregnancy
There are no adequate data from the use of ibandronic acid in pregnant women. Studies in rats have shown reproductive toxicity. The potential risk for humans is unknown. Therefore, **BONDRONAT** should not be used during pregnancy.

Breastfeeding
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. **BONDRONAT** should not be used during breastfeeding.

Fertility
There are no data on the effects of ibandronic acid in humans. In reproductive studies in rats by the oral route, ibandronic acid decreased fertility. In studies in rats using the intravenous route, ibandronic acid decreased fertility at high daily doses.

4.7 Effects on ability to drive and use machines
Since undesirable effects such as dizziness and amnesia have been reported in patients receiving **BONDRONAT**, patients should not drive, use machinery, or perform any tasks that require concentration, until they are certain that **BONDRONAT** does not adversely affect their ability to do so (see section 4.8).

4.8 Undesirable effects
a) Summary of the safety profile
The most serious reported adverse reactions are anaphylactic reaction/shock, atypical fractures of the femur, osteonecrosis for the jaw, and ocular inflammation (see paragraph “description of selected adverse reactions” and section 4.4).
Treatment of tumour induced hypercalcaemia is most frequently associated with a rise in body temperature. Less frequently, a decrease in serum calcium below normal range (hypocalcaemia) is reported. In most cases no specific treatment is required, and the symptoms subside after a couple of hours/days.
In the prevention of skeletal events in patients with breast cancer and bone metastases, treatment is most frequently associated with asthenia followed by rise in body temperature and headache.

b) Tabulated list of adverse reactions
Table 1 lists adverse drug reactions from the pivotal phase III studies (Treatment of tumour induced hypercalcaemia: 311 patients treated with **BONDRONAT** 2 mg or 4 mg; Prevention of skeletal events in patients with breast cancer and bone metastases: 152 patients treated with **BONDRONAT** 6 mg), and from post-marketing experience.

Adverse reactions are listed according to MedDRA system organ class and frequency category. Frequency categories are defined using the following convention: very common (>1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1: Adverse Reactions Reported for Intravenous Administration of **BONDRONAT**

System Organ Class	**Frequency**	**Adverse reaction**
Infections and infestations	Common	Infection
	Uncommon	Cystitis, vaginitis,

		oral candidiasis
Neoplasms benign, malignant and unspecified	Uncommon	Benign skin neoplasm
Blood and lymphatic system disorders	Uncommon	Anaemia, blood dyscrasia
Immune system disorders	Very rare	Hypersensitivity†, bronchospasm, angioedema†, Anaphylactic reaction/shock†**
	Not Known	Asthma exacerbation
Endocrine disorders	Common	Parathyroid disorder
Metabolism and nutrition disorders	Common	Hypocalcaemia**
	Uncommon	Hypophosphataemia
Psychiatric disorders	Uncommon	Sleep disorder, anxiety, affection lability
Nervous system disorders	Common	Headache, dizziness, dysgeusia (taste perversion)
	Uncommon	Cerebrovascular disorder, nerve root lesion, amnesia, migraine, neuralgia, hypertonia, hyperaesthesia, paraesthesia circumoral, parosmia
Eye disorders	Common	Cataract
	Uncommon	Ocular inflammation†**
Ear and labyrinth disorders	Uncommon	Deafness
Cardiac disorders	Common	Bundle branch block
	Uncommon	Myocardial

		ischaemia, cardiovascular disorder, palpitations
Respiratory, thoracic, and mediastinal disorders	Common	Pharyngitis
	Uncommon	Lung oedema, stridor
Gastrointestinal disorders	Common	Diarrhoea, vomiting, dyspepsia, gastrointestinal pain, tooth disorder
	Uncommon	Gastroenteritis, gastritis, mouth ulceration, dysphagia, cheilitis
Hepatobiliary disorders	Uncommon	Cholelithiasis
Skin and subcutaneous tissues disorders	Common	Skin disorder, ecchymosis
	Uncommon	Rash, alopecia
	Very rare	Stevens-Johnson Syndrome†, Erythema multiforme†, Dermatitis bullous†
Musculoskeletal and, connective tissue disorders	Common	Osteoarthritis, myalgia, arthralgia, joint disorder, bone pain
	Rare	Atypical subtrochanteric and diaphyseal femoral fractures†
	Very rare	Osteonecrosis of jaw†**, Osteonecrosis of the external auditory canal (bisphosphonate class adverse reaction) †
	Not known	Atypical fractures of long bones other

		than the femur
Renal and urinary disorders	Uncommon	Urinary retention, renal cyst
Reproductive system and breast disorders	Uncommon	Pelvic pain
General disorders and administration site conditions	Common	Pyrexia, influenza-like illness**, oedema peripheral, asthenia, thirst
	Uncommon	Hypothermia
Investigations	Common	Gamma-GT increased, creatinine increased
	Uncommon	Blood alkaline phosphatase increase, weight decrease
Injury, poisoning and procedural complications	Uncommon	Injury, injection site pain

**See further information below
†Identified in post-marketing experience.

c) Description of selected adverse reactions

Hypocalcaemia

Decreased renal calcium excretion may be accompanied by a fall in serum phosphate levels not requiring therapeutic measures. The serum calcium level may fall to hypocalcaemic values.

Influenza-like illness

A flu-like syndrome consisting of fever, chills, bone and/or muscle ache-like pain has occurred. In most cases, no specific treatment was required, and the symptoms subsided after a couple of hours/days.

Osteonecrosis of jaw (ONJ)

Cases of osteonecrosis of the jaw have been reported, predominantly in cancer patients treated with medicinal products that inhibit bone resorption, such as ibandronic acid (see section 4.4.) Cases of ONJ have been reported in the post-marketing setting for ibandronic acid.

Atypical subtrochanteric and diaphyseal femoral fractures

Although the pathophysiology is uncertain, evidence from epidemiological studies suggests an increased risk of atypical subtrochanteric and diaphyseal femoral fractures with long-term bisphosphonate therapy for postmenopausal osteoporosis, particularly beyond three to five years of use. The absolute risk of atypical subtrochanteric and diaphyseal long bone fractures (bisphosphonate class adverse reaction) remains very low.

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

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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

Reporting can also be done directly to Adcock Ingram Limited at Adcock.aereports@adcock.com.

4.9 Overdose
Up to now there is no experience of acute poisoning with **BONDRONAT** injection solution. Since both the kidney and the liver were found to be target organs for toxicity, kidney and liver function should be monitored. Clinically relevant hypocalcaemia should be corrected by i.v. administration of calcium gluconate.
Standard haemodialysis procedures result in significant clearance of ibandronic acid.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Category and class: A3.2 Connective tissue medicines. Non-hormonal preparations.
Pharmacotherapeutic group: Medicinal products for treatment of bone diseases, bisphosphonates, ATC code: M05BA06

Mechanism of action
Ibandronic acid is a bisphosphonate belonging to the nitrogen-containing group of bisphosphonates, which act on bone tissue and inhibit osteoclast activity. It does not interfere with osteoclast recruitment. The 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.

Pharmacodynamic effects
The pharmacodynamic action of ibandronic acid is inhibition of bone resorption. *In vivo*, ibandronic acid prevents experimentally induced bone destruction caused by cessation of gonadal function, retinoids, tumours or tumour extracts. In young (fast growing) rats, the endogenous bone resorption is also inhibited, leading to increased bone mass compared with untreated animals.

In vitro, ibandronic acid pretreatment of bone slices inhibited tumour cell attachment and spreading as well as tumour cell invasion. When added with tumour cells to untreated bone slices, ibandronic acid showed additive effects with cytotoxic agents such as taxoids.

5.2 Pharmacokinetic properties

Absorption

After infusion of 2, 4 and 6 mg ibandronic acid over 2 hours, pharmacokinetic parameters are dose proportional.

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 there is a low potential for medicine interaction due to displacement.

Metabolism

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

Elimination

The systemically available fraction of ibandronic acid is removed from the circulation via bone adsorption (40 - 50 %) and the remainder is eliminated unchanged by the kidney. The unabsorbed fraction of ibandronic acid (oral dose) 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 plasma half-life is generally in the range of 10 - 60 hours. However, early plasma levels fall quickly, reaching 10 % of peak values within 3 hours after intravenous administration. 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 are similar in both men and women.

Race

There is no evidence for clinically relevant inter-ethnic differences between Asians and Caucasians in ibandronic acid disposition. There are only very limited data available on patients of 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 AUC0-24h was increased by 110 % compared with healthy volunteers.

After a single dose, intravenous administration of 6 mg (15 minutes infusion), 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). 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. See section 4.2, *Special Dosage Instructions.*

Approximately 37 % of ibandronate 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. Therefore, dosage adjustment is not 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

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

There are no data on the use of ibandronic acid in patients less than 18 years old

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glacial acetic acid
Sodium acetate trihydrate
Sodium chloride
Water for injections

6.2 Incompatibilities
BONDRONAT concentrate for solution for infusion should not be mixed with calcium containing solutions.

6.3 Shelf life
5 years
After reconstitution: 24 hours.

6.4 Special precautions for storage
Store at or below 25 °C. Keep in original pack until required for use.

After reconstitution: Store at 2 °C – 8 °C (in a refrigerator).

From a microbiological point of view, the intravenous infusion solution 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 reconstitution has taken place in controlled and validated aseptic conditions. The concentrate for solution for infusion is for single use only. Only clear solution without particles should be used. Unused solution should be discarded.

6.5 Nature and contents of container
BONDRONAT 2 mg/2 mℓ injection: is supplied as packs containing 1 or 5 ampoules/vials (2 mℓ type I glass vial with a bromobutyl rubber stopper).

BONDRONAT 6 mg/6 mℓ injection: is supplied as packs containing 1 or 5 ampoules/vials (6 mℓ type I glass vial with a bromobutyl rubber stopper).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling
No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION
Adcock Ingram Limited
1 New Road
Erand Gardens
Midrand, 1685
Customer Care: 0860 ADCOCK / 232625

8. REGISTRATION NUMBER(S)
BONDRONAT 2 mg/2 mℓ injection: 32/3.2/0114
BONDRONAT 6 mg/6 mℓ injection: A38/3.2/0381

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Registration: 2 mg/2 ml: 13 October 1998
6 mg/6 ml: 18 April 2008

10. DATE OF REVISION OF THE TEXT

24 October 2025