

**ANNEX I**  
**SUMMARY OF PRODUCT CHARACTERISTICS**

## 1. NAME OF THE MEDICINAL PRODUCT

Bondronat 2 mg/2 ml  
Concentrate for solution for infusion

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

### Qualitative composition

Ibandronic acid, monosodium salt, monohydrate

### Quantitative composition

One vial with 2 ml concentrate for solution for infusion (colourless, clear solution) contains 2.25 mg ibandronic acid, monosodium salt, monohydrate corresponding to 2 mg ibandronic acid.  
1 ml of solution contains 1.125 mg ibandronic acid, monosodium salt, monohydrate, corresponding to 1 mg ibandronic acid.

For excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Bondronat is indicated for

- Prevention of skeletal events (pathological fractures, bone complications requiring radiotherapy or surgery) in patients with breast cancer and bone metastases.
- Treatment of tumour-induced hypercalcaemia with or without metastases.

### 4.2 Posology and method of administration

Bondronat therapy should only be initiated by physicians experienced in the treatment of cancer.

For intravenous administration.

#### Prevention of Skeletal Events in Patients with Breast Cancer and Bone Metastases

The recommended dose for prevention of skeletal events in patients with breast cancer and bone metastases is 6 mg IV given every 3-4 weeks. The dose should be infused over 1 hour. For infusion, the contents of the vial(s) should be added to 500 ml isotonic sodium chloride solution (or 500 ml 5% dextrose solution).

#### Treatment of Tumour-Induced Hypercalcaemia

##### *Adults and elderly:*

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\*  $\geq 3$  mmol/l or  $\geq 12$  mg/dl) 4 mg is an adequate single dosage. In patients with moderate hypercalcaemia (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 concentrations are calculated as follows:

$$\text{Albumin-corrected serum calcium (mmol/l)} = \text{serum calcium (mmol/l)} - [0.02 \times \text{albumin (g/l)}] + 0.8$$

**Or**

$$\text{Albumin-corrected serum calcium (mg/dl)} = \text{serum calcium (mg/dl)} + 0.8 \times [4 - \text{albumin (g/dl)}]$$

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 (return of albumin-corrected serum calcium to levels 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 (50 patients) have received a second infusion for hypercalcaemia. Repeated treatment may be considered in case of recurrent hypercalcaemia or insufficient efficacy.

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

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.

#### *Special Dosage Instructions:*

##### *Patients with hepatic impairment*

No dosage adjustment is expected to be necessary (see Section 5.2).

##### *Patients with renal impairment*

No dosage adjustment is necessary for patients with mild or moderate renal impairment where creatinine clearance is equal to or greater than 30 ml/min.

Below 30 ml/min creatinine clearance, the dose for prevention of skeletal events in patients with breast cancer and bone metastases should be reduced to 2 mg every 3-4 weeks, infused over 1 hour.

##### *Elderly*

No dose adjustment is necessary.

##### *Children and adolescents*

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

### **4.3 Contraindications**

Bondronat concentrate for solution for infusion must not be used in known hypersensitivity to the drug substance or to any of the excipients.

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

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

#### **4.4 Special warnings and special precautions for use**

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 renal function, serum calcium, phosphate and magnesium should be monitored in patients treated with Bondronat.

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

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

Hypocalcemia 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.

#### **4.5 Interaction with other medicinal products and other forms of interaction**

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 active substances. 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 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.

#### **4.6 Pregnancy and lactation**

There are no adequate data from the use of ibandronic acid in pregnant women. Studies in rats have shown reproductive toxicity (see Section 5.3). The potential risk for humans is unknown. Therefore, Bondronat should not be used during pregnancy.

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. Consequently, caution should be exercised when prescribing Bondronat to breast-feeding women.

#### **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 Undesirable effects

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

### *Treatment of Tumour Induced Hypercalcaemia*

The safety profile for Bondronat in tumour-induced hypercalcaemia is derived from controlled clinical trials in this indication and after the intravenous administration of Bondronat at the recommended doses. Treatment 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 was required and the symptoms subsided after a couple of hours/days.

**Table 1 Number (percentage) of Patients Reporting Adverse Events in Controlled Clinical Trials in Tumour-Induced Hypercalcaemia after Treatment with Bondronat**

Adverse Event	Frequency Number (%) (n=352)
<b>Metabolism and nutrition disorders</b> Common: Hypocalcaemia	10 (2.8)
<b>Musculoskeletal and connective tissue disorders:</b> Common: Bone Pain Uncommon: Myalgia	6 (1.7) 1 (0.3)
<b>General disorders and administration site conditions:</b> Very common: Pyrexia Uncommon: Influenza-like illness Rigors	39 (11.1) 2 (0.6) 1 (0.3)

Note: Data for both the 2 mg and 4 mg doses of ibandronic acid are pooled. Events were recorded irrespective of a determination of causality.

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

Other adverse events reported at lower frequency are as follows:

#### **Immune system disorders:**

Very rare: Hypersensitivity NOS.

#### **Skin and subcutaneous tissue disorders:**

Very rare: Angioneurotic oedema

#### **Respiratory, thoracic and mediastinal disorders:**

Very rare: Bronchospasm NOS.

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

### *Prevention of Skeletal Events in Patients with Breast Cancer and Bone Metastases*

The safety profile of intravenous Bondronat in patients with breast cancer and bone metastases is derived from a controlled clinical trial in this indication and after the intravenous administration of Bondronat at the recommended dose.

Table 2 lists adverse events from the pivotal phase III study (152 patients treated with Bondronat 6 mg), reported as remotely, possibly, or probably related to study medication, occurring commonly and more frequently in the active treatment group than in placebo.

**Table 2 Related Adverse Events Occurring Commonly and Greater than Placebo in Patients with Metastatic Bone Disease due to Breast Cancer Treated with Bondronat 6 mg i.v.**

<b>Adverse Drug Reaction</b>	<b>Placebo (n = 157) No. (%)</b>	<b>Bondronat 6mg (n = 152) No. (%)</b>
<b>Infections and Infestations:</b>		
Infection NOS	1 (0.6)	2 (1.3)
<b>Endocrine disorders:</b>		
Parathyroid disorder NOS	1 (0.6)	2 (1.3)
<b>Nervous System disorders:</b>		
Headache	4 (2.5)	9 (5.9)
Dizziness	2 (1.3)	4 (2.6)
Dysgeusia (taste perversion)	0 (0.0)	2 (1.3)
<b>Eye disorders:</b>		
Cataract	1 (0.6)	2 (1.3)
<b>Cardiac disorders:</b>		
Bundle branch block NOS	1 (0.6)	2 (1.3)
<b>Respiratory, thoracic and mediastinal disorders:</b>		
Pharyngitis	0 (0.0)	3 (2.0)
<b>Gastrointestinal disorders:</b>		
Diarrhoea NOS	1 (0.6)	8 (5.3)
Dyspepsia	5 (3.2)	6 (3.9)
Vomiting NOS	2 (1.3)	5 (3.3)
Gastrointestinal pain NOS	2 (1.3)	4 (2.6)
Tooth disorder NOS	0 (0.0)	3 (2.0)
<b>Skin and subcutaneous tissue disorders:</b>		
Skin disorder NOS	0 (0.0)	2 (1.3)
Ecchymosis	0 (0.0)	2 (1.3)
<b>Musculoskeletal and connective tissue disorders:</b>		
Myalgia	6 (3.8)	8 (5.3)
Arthralgia	1 (0.6)	2 (1.3)
Joint disorder NOS	0 (0.0)	2 (1.3)
Osteoarthritis NOS	0 (0.0)	2 (1.3)
<b>General disorders:</b>		
Asthenia	8 (5.1)	10 (6.6)
Influenza-like illness	2 (1.3)	8 (5.3)
Oedema peripheral	2 (1.3)	3 (2.0)
Thirst	0 (0.0)	2 (1.3)
<b>Investigations:</b>		
Gamma-GT increased	1 (0.6)	4 (2.6)
Creatinine increased	1 (0.6)	3 (2.0)

The following events occurred rarely (one patient in the Bondronat group): gastroenteritis NOS, oral candidiasis, vaginitis, benign skin neoplasm, anaemia NOS, blood dyscrasia NOS, hypophosphataemia, sleep disorder, anxiety, affect lability, amnesia, paraesthesia circumoral, hyperaesthesia, hypertonia, nerve root lesion NOS, neuralgia NOS, migraine, cerebrovascular disorder NOS, parosmia, deafness, cardiovascular disorder NOS, palpitations, myocardial ischaemia, hypertension, varicose veins NOS, lymphoedema, lung oedema, stridor, gastritis NOS, cheilitis,

dysphagia, mouth ulceration, cholelithiasis, rash NOS, alopecia, cystitis NOS, renal cyst NOS, urinary retention, pelvic pain NOS, injection site pain, blood alkaline phosphatase increase, weight decreased, injury, hypothermia.

#### **4.9 Overdose**

Up to now there is no experience of acute poisoning with Bondronat concentrate for solution 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 hypocalcaemia should be corrected by i.v. administration of calcium gluconate.

### **5. PHARMACOLOGICAL PROPERTIES**

#### **5.1 Pharmacodynamic properties**

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

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

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

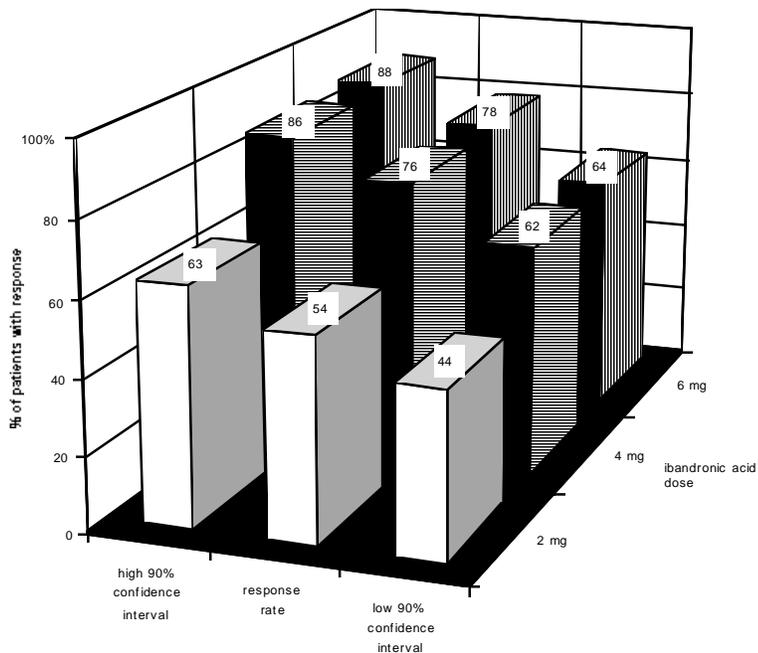
At doses that were considerably higher than the pharmacologically effective doses, ibandronic acid did not have any effect on bone mineralisation.

Bone resorption due to malignant disease is characterized by excessive bone resorption that is 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 Studies in the Treatment of 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.

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  $\geq 3.0$  mmol/l after adequate rehydration.



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

#### Clinical Studies in the Prevention of Skeletal Events in Patients with Breast Cancer and Bone Metastases

Clinical studies in patients with breast cancer and bone metastases 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.

Prevention of skeletal events in patients with breast cancer and bone metastases with Bondronat 6 mg IV was assessed in one randomized placebo controlled phase III trial with duration of 96 weeks. 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 from this trial are summarised below.

#### *Primary Efficacy Endpoints*

The primary endpoint of the trial was the skeletal morbidity period rate (SMPR). This was a composite endpoint which had the following skeletal related events (SREs) as sub-components:

- radiotherapy to bone for treatment of fractures/impending fractures
- surgery to bone for treatment of fractures
- vertebral fractures
- non-vertebral fractures.

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 for the purposes of the analysis. Data from this study demonstrated a significant advantage for Bondronat 6 mg IV over placebo in the reduction in SREs measured by the time-adjusted SMPR ( $p=0.004$ ). The number of SREs was also significantly reduced with Bondronat 6 mg and there was a 40% reduction in the risk of a SRE over placebo (relative risk 0.6,  $p = 0.003$ ). Efficacy results are summarised in Table 3.

**Table 3 Efficacy Results (Breast Cancer Patients with Metastatic Bone Disease)**

	All Skeletal Related Events (SREs)		
	Placebo n=158	Bondronat 6 mg n=154	p-value
SMPR (per patient year)	1.48	1.19	p=0.004
Number of events (per patient)	3.64	2.65	p=0.025
SRE relative risk	-	0.60	p=0.003

*Secondary Efficacy Endpoints*

A statistically significant improvement in bone pain score was shown for Bondronat 6 mg IV compared to placebo. The pain reduction was consistently below baseline throughout the entire study and accompanied by a significantly reduced use of analgesics. The deterioration in Quality of Life was significantly less in Bondronat treated patients compared with placebo. A tabular summary of these secondary efficacy results is presented in Table 4.

**Table 4 Secondary Efficacy Results (Breast cancer Patients with Metastatic Bone Disease)**

	Placebo n=158	Bondronat 6 mg n=154	p-value
Bone pain *	0.21	-0.28	p<0.001
Analgesic use *	0.90	0.51	p=0.083
Quality of Life *	-45.4	-10.3	p=0.004

\* Mean change from baseline to last assessment.

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.

**5.2 Pharmacokinetic properties**

After a 2 hour infusion of 2, 4 and 6 mg ibandronic acid 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 approximately 87% at therapeutic concentrations, and thus drug-drug interaction due to displacement is unlikely.

*Metabolism*

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

*Elimination*

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. 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 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*

Renal clearance of ibandronic acid in patients with various degrees of renal impairment is linearly related to creatinine clearance (CL<sub>Cr</sub>). No dosage adjustment is necessary for patients with mild or moderate renal impairment (CL<sub>Cr</sub> ≥30 ml/min). After IV administration of 0.5 mg, total, renal, and non-renal clearances decreased by 67%, 77% and 50%, respectively, in subjects with severe renal impairment. However, there was no reduction in tolerability associated with the increase in exposure. Reduction of the intravenous dose to 2 mg infused over 1 hour every 3-4 weeks is recommended in patients with severe renal impairment (CL<sub>Cr</sub> <30 ml/min) (see Section 4.2).

##### *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 metabolized but is cleared by renal excretion and by uptake into bone. Therefore dosage adjustment is not necessary in patients with hepatic impairment. Further, as protein binding of ibandronic acid is approximately 87% at therapeutic concentrations, 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 that should be considered (see renal impairment section).

##### *Children and adolescents*

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

### **5.3 Preclinical safety data**

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

##### *Mutagenicity/Carcinogenicity:*

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

##### *Reproductive toxicity:*

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

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Sodium chloride  
Acetic acid (99%)  
Sodium acetate  
Water for injections

### **6.2 Incompatibilities**

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

### **6.3 Shelf life**

5 years  
After reconstitution: 24 hours.

### **6.4 Special precautions for storage**

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

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 reconstitution has taken place in controlled and validated aseptic conditions.

### **6.5 Nature and contents of container**

Bondronat is supplied as packs containing 1 vial (2 ml glass vial glass type I).

### **6.6 Instructions for use and handling and disposal**

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.

Use only isotonic saline or 5% dextrose solution as infusion solution.

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

Unused solution should be discarded.

## **7. MARKETING AUTHORISATION HOLDER**

Roche Registration Limited  
40 Broadwater Road  
Welwyn Garden City  
Hertfordshire AL7 3AY

United Kingdom

**8.    MARKETING AUTHORISATION NUMBER(S)**

EU/1/96/012/004

**9.    DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

12 September 2001

**10.   DATE OF REVISION OF THE TEXT**

**ANNEX II**

- A. MANUFACTURING AUTHORISATION HOLDER  
RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OF THE MARKETING AUTHORISATION**

**A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE**

Name and address of the manufacturer responsible for batch release

Roche Diagnostics GmbH  
Sandhofer Strasse 116  
D-68305 Mannheim  
Germany

Manufacturing authorisation issued on 27 January 1999 by the Regierungspräsidium Karlsruhe (Postfach 5343, 76035 Karlsruhe), Germany.

**B. CONDITIONS OF THE MARKETING AUTHORISATION**

• **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, 4.2).

**ANNEX III**  
**LABELLING AND PACKAGE LEAFLET**

## **A. LABELLING**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING**

**Outer Carton**

**1. NAME OF THE MEDICINAL PRODUCT**

Bondronat 2 mg/2 ml concentrate for solution for infusion  
ibandronic acid

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each vial contains 2 mg of ibandronic acid (as monosodium salt, monohydrate).

**3. LIST OF EXCIPIENTS**

Each vial contains the following excipients: sodium acetate, sodium chloride, acetic acid and water for injections.

**4. PHARMACEUTICAL FORM AND CONTENTS**

1 vial

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Intravenous use, for infusion after dilution. Read package leaflet before use

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

Keep out of the reach and sight of children

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

After dilution the infusion solution is stable for 24 hours at 2 °C - 8 °C

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Roche Registration Limited, 40 Broadwater Road, Welwyn Garden City, Hertfordshire AL7 3AY  
United Kingdom

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/96/012/004

**13. MANUFACTURER'S BATCH NUMBER**

Batch

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription

**15. INSTRUCTIONS ON USE**

Must be diluted

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING**

**Vial**

**1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION**

Bondronat 2 mg/2 ml concentrate for solution for infusion  
Intravenous use

**2. METHOD OF ADMINISTRATION**

Read the package leaflet before use

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Batch

**5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT**

2 ml

**B. PACKAGE LEAFLET**

## PACKAGE LEAFLET

### **Read all of this leaflet carefully before you start using this medicine.**

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

### **In this leaflet:**

1. What Bondronat is and what it is used for
2. Before you use Bondronat
3. How to use Bondronat
4. Possible side effects
5. Storing Bondronat
6. Further information

### **Bondronat 2 mg/2 ml concentrate for solution for infusion**

Ibandronic acid

- The active substance is ibandronic acid. 1 vial with 2 ml of colourless, clear concentrate for solution for infusion contains 2.25 mg ibandronic acid, monosodium salt, monohydrate corresponding to 2 mg ibandronic acid.
- The other ingredients are sodium chloride, acetic acid, sodium acetate and water for injections.

### **Marketing Authorisation Holder**

Roche Registration Limited  
40 Broadwater Road  
Welwyn Garden City  
Hertfordshire AL7 3AY  
United Kingdom

### **Manufacturer**

Roche Diagnostics GmbH  
Sandhofer Strasse 116  
D-68305 Mannheim  
Germany

## **1. WHAT BONDRONAT IS AND WHAT IT IS USED FOR**

Bondronat 2 mg/2 ml vials contain 2 ml of a concentrate for solution for infusion and are available in packs of 1 vial.

The active substance of Bondronat, ibandronic acid, belongs to the group of medicines known as bisphosphonates. It inhibits increased loss of calcium from the bones (bone resorption), thus normalising elevated serum calcium levels. It also prevents bone complications and fractures related to the spread of cancer cells into bone.

Bondronat is indicated for:

- Pathologically (abnormally) elevated serum calcium levels (hypercalcaemia) as a result of tumours
- Prevention of skeletal events (pathological fractures, bone complications requiring radiotherapy or surgery) in patients with breast cancer and bone metastases.

## **2. BEFORE YOU ARE GIVEN BONDRONAT**

It is recommended that renal function, serum calcium, phosphate and magnesium should be monitored in patients treated with Bondronat concentrate for solution for infusion in line with clinical practice.

Dosage adjustment is not expected to be necessary in patients with hepatic impairment as the liver has no significant role in the elimination of ibandronic acid.

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

### **Do not use Bondronat:**

- if you are hypersensitive (allergic) to the drug substance or any of the other ingredients

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

### **Take special care with Bondronat:**

You should tell your doctor if you know or believe that you may have:

- hypersensitivity to other bisphosphonates
- low blood calcium
- other disturbances of mineral metabolism (such as vitamin D deficiency)
- severe kidney disease (renal insufficiency i.e. creatinine clearance <30 ml/min)

### **Pregnancy and breast-feeding**

Bondronat concentrate for solution for infusion should not be used during pregnancy and lactation.

There are no adequate data from the use of ibandronic acid in pregnant women. Reproductive studies in animals have shown adverse effects on the foetus and the presence of ibandronic acid in the breast milk of rats. The potential risk for humans is unknown.

### **Driving and using machines:**

The effects of Bondronat concentrate for solution for infusion on reactions, alertness or awareness have not been investigated.

### **Using other medicines:**

Please inform your doctor or pharmacist if you are taking or have recently taken any other medicines, even those not prescribed.

No interaction was observed when ibandronic acid was administered concomitantly with tamoxifen, or melphalan/prednisolone.

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

## **3. HOW BONDRONAT WILL BE GIVEN TO YOU:**

The amount of Bondronat that you are given may differ depending on your illness:

### **Dosage: Prevention of Skeletal Events in Patients with Breast Cancer and Bone Metastases**

The recommended dose for prevention of skeletal events in patients with breast cancer and bone metastases is 6 mg intravenously given every 3-4 weeks. The dose should be infused over 1 hour. In

patients with severe renal impairment (CLCr <30 ml/min), the recommended dose is 2 mg given every 3-4 weeks, infused over 1 hour.

### **Dosage: Tumour-induced Hypercalcemia**

Bondronat concentrate for solution 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 hypercalcaemia as well as the tumour type. In most patients with severe hypercalcaemia (albumin-corrected serum calcium\*  $\geq 3$  mmol/l or  $\geq 12$  mg/dl) 4 mg will be an adequate single dosage. In patients with moderate hypercalcaemia (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 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. 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.

### **Method and route of administration**

Bondronat concentrate for solution for infusion should be administered as an intravenous infusion.

For this purpose the contents of the vial are to be added to 500 ml isotonic sodium chloride solution or 500 ml 5% dextrose solution and infused over 1-2 hours depending on the indication.

Note:

In order to avoid potential incompatibilities, Bondronat concentrate for solution 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 solution for infusion.

Diluted solutions are for single use. Only clear solutions without particles should be used.

It is recommended that the product once diluted be used immediately (see point 5 of this leaflet "STORING BONDRONAT").

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.

### **Frequency of administration**

For treatment of tumour induced hypercalcemia, Bondronat concentrate for solution for infusion is generally given as a single infusion.

For the prevention of skeletal events in patients with breast cancer and bone metastases, the Bondronat infusion is repeated at 3-4 week intervals.

### **Duration of treatment**

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

For patients with breast cancer and bone metastases, Bondronat infusion should be administered every 3-4 weeks. In clinical trials, therapy has continued for up to 96 weeks.

**If you are given more Bondronat than is recommended:**

Up to now there is no experience of acute poisoning with Bondronat concentrate for solution 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 hypocalcaemia (very low serum calcium levels) should be corrected by i.v. administration of calcium gluconate.

#### **4. POSSIBLE SIDE EFFECTS**

Like all medicines, Bondronat can have side effects.

In patients with tumour-induced hypercalcemia, intravenous administration of Bondronat concentrate for solution 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 hypocalcaemic values.

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

In patients with breast cancer and bone metastases, intravenous administration of Bondronat was most commonly associated with tiredness, headache, flu-syndrome, diarrhoea and muscle pain (myalgia). Other common side effects include: indigestion (dyspepsia), vomiting, dizziness, gastrointestinal pain, raised liver enzyme levels, raised, serum creatinine levels, sore throat, swelling (oedema) of the lower limbs.

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

#### **5. STORING BONDRONAT**

Keep out of the reach and sight of children.

The shelf-life of Bondronat 2 mg/2 ml vials is 5 years.

Do not use Bondronat after the expiry date stated on the folding box and on the label.

After dilution the infusion solution is stable for 24 hours at 2-8°C (in a refrigerator).

Unused solution should be discarded.

#### **6. FURTHER INFORMATION**

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

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**This leaflet was last approved on {date}**