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

## 1. NAME OF THE MEDICINAL PRODUCT

Iasibon 1 mg concentrate for solution for infusion

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ampoule with 1 mL concentrate for solution for infusion contains 1 mg ibandronic acid (as sodium monohydrate).

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.
Clear, colourless solution.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Iasibon is indicated in adults 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

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

Posology
*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 intravenous injection given every 3 - 4 weeks. The dose should be infused over at least 15 minutes.

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. Prescribers should consult the section *Patients with Renal Impairment* (see section 4.2) for recommendations on dosing and administration in this patient group.

*Treatment of tumour-induced hypercalcaemia*

Prior to treatment with Iasibon the patient should be adequately rehydrated with 9 mg/mL (0.9 %) sodium chloride solution. 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 dose. 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 (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.

Iasibon concentrate for solution for infusion should be administered as an intravenous infusion over 2 hours.

*Special populations*
*Patients with hepatic impairment*
No dose adjustment is required (see section 5.2).

*Patients with renal impairment*
For patients with mild renal impairment (CLcr ≥ 50 and < 80 mL/min) no dose 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 (see section 5.2):

| Creatinine Clearance (mL/min) | Dosage | Infusion Volume [1] and Time [2] |
|---|---|---|
| ≥ 50 CLcr < 80 | 6 mg (6 mL of concentrate for solution for infusion) | 100 mL over 15 minutes |
| ≥ 30 CLcr < 50 | 4 mg (4 mL of concentrate for solution for infusion) | 500 mL over 1 hour |
| < 30 | 2 mg (2 mL of concentrate for solution for infusion) | 500 mL over 1 hour |

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

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

*Elderly population (> 65 years)*
No dose adjustment is required (see section 5.2).

*Paediatric population*
The safety and efficacy of Iasibon in children and adolescents below the age of 18 years have not been established. No data are available (see section 5.1 and section 5.2).

Method of administration
For intravenous administration.

The content of the ampoule is to be used as follows:

- Prevention of Skeletal Events - added to 100 mL isotonic sodium chloride solution or 100 mL 5 % dextrose solution and infused over at least 15 minutes. See also dose section above for patients with renal impairment

- Treatment of tumour-induced hypercalcaemia - added to 500 mL isotonic sodium chloride solution or 500 mL 5 % dextrose solution and infused over 2 hours

For single use only. Only clear solution without particles should be used.
Iasibon concentrate for solution for infusion should be administered as an intravenous infusion.
Care must be taken not to administer Iasibon concentrate for solution for infusion via intra-arterial or paravenous administration, as this could lead to tissue damage.

## 4.3 Contraindications

– Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
– Hypocalcaemia

## 4.4 Special warnings and precautions for use

Patients with disturbances of bone and mineral metabolism
Hypocalcaemia and other disturbances of bone and mineral metabolism should be effectively treated before starting Iasibon 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.

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

Appropriate medical support and monitoring measures should be readily available when Iasibon intravenous injection is administered. If anaphylactic or other severe hypersensitivity/allergic reactions occur, immediately discontinue the injection 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 ibandronate 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 ibandronate 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 Iasibon. While on treatment, invasive dental procedures should be performed only after careful consideration and be avoided in close proximity to Iasibon 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 Iasibon 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 Iasibon 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 Iasibon (see section 4.2).

Patients with hepatic impairment
As no clinical data are available, dose 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.

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

Excipients with known effect

Iasibon contains less than 1 mmol sodium (23 mg) per ampoule, that is to say essentially ‘sodium free’.

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

Metabolic interactions are not considered likely, since ibandronic acid does not inhibit the major human hepatic P450 isoenzymes and has been shown not to induce the hepatic cytochrome P450 system in rats (see section 5.2). Ibandronic acid is eliminated by renal excretion only and does not undergo any biotransformation.

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

## 4.6 Fertility, pregnancy and lactation

Pregnancy
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, Iasibon should not be used during pregnancy.

Breast –feeding
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. Iasibon should not be used during breast feeding.

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 (see section 5.3).

## 4.7 Effects on ability to drive and use machines

On the basis of the pharmacodynamic and pharmacokinetic profile and reported adverse reactions, it is expected that Iasibon has no or negligible influence on the ability to drive and use machines

## 4.8 Undesirable effects

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.

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 ibandronic acid 2 mg or 4 mg; Prevention of skeletal events in patients with breast cancer and bone metastases: 152 patients treated with ibandronic acid 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 Ibandronic Acid**

| System Organ Class | Very common | Common | Uncommon | Rare | Very rare | Not known |
|---|---|---|---|---|---|---|
| **Infections and infestations** | | Infection | Cystitis, vaginitis, oral candidiasis | | | |
| **Neoplasms benign, malignant, and unspecified** | | | Benign skin neoplasm | | | |
| **Blood and lymphatic system disorders** | | | Anaemia, blood dyscrasia | | | |
| **Immune system disorders** | | | | | Hypersensitivity †, bronchospasm†, angioedema† anaphylactic reaction/shock† ** | Asthma exacerbation |
| **Endocrine disorders** | | Parathyroid disorder | | | | |
| **Metabolism and nutrition disorders** | | Hypocalcaemia** | Hypophosphataemia | | | |
| **Psychiatric disorders** | | | Sleep disorder, anxiety, affection lability | | | |
| **Nervous system disorders** | | Headache, dizziness, dysgeusia (taste perversion) | Cerebrovascular disorder, nerve root lesion, amnesia, migraine, neuralgia, hypertonia, hyperaestesia, paraesthesia circumoral, parosmia | | | |
| **Eye disorders** | | Cataract | | Ocular inflammation†** | | |
| **Ear and labyrinth disorders** | | | Deafness | | | |
| **Cardiac** | | Bundle | Myocardial | | | |

| System Organ Class | Very common | Common | Uncommon | Rare | Very rare | Not known |
|---|---|---|---|---|---|---|
| **disorders** | | branch block | ischaemia, cardiovascular disorder, palpitations | | | |
| **Respiratory, thoracic, and mediastinal disorders** | | Pharyngitis | Lung oedema, stridor | | | |
| **Gastrointestinal disorders** | | Diarrhoea, vomiting, dyspepsia, gastrointestinal pain, tooth disorder | Gastroenteritis, gastritis, mouth ulceration, dysphagia, cheilitis | | | |
| **Hepatobiliary disorders** | | | Cholelithiasis | | | |
| **Skin and subcutaneous tissue disorders** | | Skin disorder, ecchymosis | Rash, alopecia | | Stevens-Johnson Syndrome†, Erythema Multiforme†, Dermatitis Bullous† | |
| **Musculoskeletal and connective tissue disorders** | | Osteoarthritis, myalgia, arthralgia, joint disorder, bone pain | | Atypical subtrochanteric and diaphyseal femoral fractures† | Osteonecrosis of jaw†**, osteonecrosis of the external auditory canal (bisphosphonate class adverse reaction)† | Atypical fractures of long bones other than the femur |
| **Renal and urinary disorders** | | | Urinary retention, renal cyst | | | |
| **Reproductive system and breast disorders** | | | Pelvic pain | | | |
| **General disorders and administration site conditions** | | Pyrexia, influenza-like illness**, oedema peripheral, asthenia, thirst | Hypothermia | | | |
| **Investigations** | | Gamma-GT increased, creatinine increased | Blood alkaline phosphatase increase, weight decrease | | | |
| **Injury, poisoning and** | | | Injury, injection site pain | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| **System Organ Class** | **Very common** | **Common** | **Uncommon** | **Rare** | **Very rare** | **Not known** |
| **procedural complications** | | | | | | |

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

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*
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 medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

### 4.9 Overdose

Up to now there is no experience of acute poisoning with Iasibon 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 intravenous administration of calcium gluconate.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmaco-therapeutic group: Medicinal products for treatment of bone diseases, bisphosphonate, ATC

Code: M05BA06

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

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

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

Bone resorption due to malignant disease is characterised by excessive bone resorption that is not balanced with appropriate bone formation. 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 ≥ 3.0 mmol/L after adequate rehydration.

| Ibandronic acid dose | % of Patients with Response | 90 % Confidence Interval |
|---|---|---|
| 2 mg | 54 | 44-63 |
| 4 mg | 76 | 62-86 |
| 6 mg | 78 | 64-88 |

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 Ibandronate 6 mg administered intravenously 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 Ibandronate (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 intravenous Ibandronate 6 mg 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 Ibandronate 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 2.

**Table 2 Efficacy Results (Breast Cancer Patients with Metastatic Bone Disease)**

| | All Skeletal Related Events (SREs) | | |
|---|---|---|---|
| | Placebo n = 158 | Ibandronate 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 intravenous Ibandronate 6 mg 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 Ibandronate treated patients compared with placebo. A tabular summary of these secondary efficacy results is presented in Table 3.

**Table 3 Secondary efficacy results (breast cancer patients with metastatic bone disease)**

| | Placebo n = 158 | Ibandronate 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 Ibandronate that was statistically significant compared to placebo.

In a study in 130 patients with metastatic breast cancer the safety of Ibandronate 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 < 50 mL/min.

*Paediatric population (see section 4.2 and section 5.2)*
The safety and efficacy of Iasibon in children and adolescents below the age of 18 years have not been established. No data is available.

## 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 interaction with other medicinal products, due to displacement is unlikely.

*Biotransformation*
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.

The secretory pathway of renal elimination 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.

*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), dose-adjusted mean $AUC_{0-24h}$ was increased by 110 % compared to healthy volunteers. In clinical pharmacology trial WP18551, after a single dose intravenous administration of 6 mg (15 minutes infusion), mean $AUC_{0-24}$ 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 $C_{max}$ 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).

*Patients with hepatic impairment* (see section 4.2)
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* (see section 4.2)
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).

*Paediatric population* (see section 4.2 and section 5.1)
There are no data on the use of Iasibon in patients less than 18 years old.

### 5.3 Preclinical safety data
Effects in non-clinical studies were observed only at exposures sufficiently in excess of the maximum human exposure indicating little relevance to clinical use. As with other bisphosphonates, the kidney was identified to be the primary target organ of systemic toxicity.

*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. In reproductive studies in rats by the oral route, effects on fertility consisted of increased preimplantation losses at dose levels of 1 mg/kg/day and higher. In reproductive studies in rats by the intravenous route, ibandronic acid decreased sperm counts at doses of 0.3 and 1 mg/kg/day and decreased fertility in males at 1 mg/kg/day and in females at 1.2 mg/kg/day. Adverse effects of ibandronic acid in reproductive toxicity studies in the rat were those expected for this class of medicinal products (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, glacial
Sodium acetate trihydrate
Water for injections

### 6.2 Incompatibilities

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

Iasibon should not be mixed with calcium containing solutions.

### 6.3 Shelf life

5 years.
After reconstitution: 24 hours.

### 6.4 Special precautions for storage

This medicinal product does not require any special storage conditions prior to reconstitution.

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

Iasibon 1 mg is supplied as pack containing 1 ampoule (2 mL type I glass ampoule).

### 6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.
The release of pharmaceuticals in the environment should be minimized.

## 7. MARKETING AUTHORISATION HOLDER

Pharmathen S.A.
Dervenakion 6
Pallini Attiki, 15351
Greece

## 8. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/659/003

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

Date of first authorisation: 21 January 2011
Date of latest renewal: 30 September 2015

## 10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu/.

## 1. NAME OF THE MEDICINAL PRODUCT

Iasibon 2 mg concentrate for solution for infusion

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ampoule with 2 mL concentrate for solution for infusion contains 2 mg ibandronic acid (as sodium monohydrate).

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.
Clear, colourless solution.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Iasibon is indicated in adults 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

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

Posology
*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 intravenous injection given every 3-4 weeks. The dose should be infused over at least 15 minutes.

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. Prescribers should consult the section *Patients with Renal Impairment* (see section 4.2) for recommendations on dosing and administration in this patient group.

*Treatment of tumour-induced hypercalcaemia*

Prior to treatment with Iasibon the patient should be adequately rehydrated with 9 mg/mL (0.9 %) sodium chloride solution. 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 dose. 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 (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.

Iasibon concentrate for solution for infusion should be administered as an intravenous infusion over 2 hours.

*Special populations*
*Patients with hepatic impairment*
No dose adjustment is required (see section 5.2).

*Patients with renal impairment*
For patients with mild renal impairment (CLcr ≥ 50 and < 80 mL/min) no dose 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 (see section 5.2):

| Creatinine Clearance (mL/min) | Dosage | Infusion Volume [1] and Time [2] |
|---|---|---|
| ≥ 50 CLcr < 80 | 6 mg (6 mL of concentrate for solution for infusion) | 100 mL over 15 minutes |
| ≥ 30 CLcr < 50 | 4 mg (4 mL of concentrate for solution for infusion) | 500 mL over 1 hour |
| < 30 | 2 mg (2 mL of concentrate for solution for infusion) | 500 mL over 1 hour |

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

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

*Elderly population (> 65 years)*
No dose adjustment is required (see section 5.2).

*Paediatric population*
The safety and efficacy of Iasibon in children and adolescents below the age of 18 years have not been established. No data are available. (see section 5.1 and section 5.2).

Method of administration
For intravenous administration.

The content of the ampoule is to be used as follows:

- Prevention of Skeletal Events - added to 100 mL isotonic sodium chloride solution or 100 mL 5 % dextrose solution and infused over at least 15 minutes. See also dose section above for patients with renal impairment

- Treatment of tumour-induced hypercalcaemia - added to 500 mL isotonic sodium chloride solution or 500 mL 5 % dextrose solution and infused over 2 hours

For single use only. Only clear solution without particles should be used.
Iasibon concentrate for solution for infusion should be administered as an intravenous infusion.
Care must be taken not to administer Iasibon concentrate for solution for infusion via intra-arterial or paravenous administration, as this could lead to tissue damage.

## 4.3 Contraindications

– Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
– Hypocalcaemia

## 4.4 Special warnings and precautions for use

Patients with disturbances of bone and mineral metabolism
Hypocalcaemia and other disturbances of bone and mineral metabolism should be effectively treated before starting Iasibon 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.

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

Appropriate medical support and monitoring measures should be readily available when Iasibon intravenous injection is administered. If anaphylactic or other severe hypersensitivity/allergic reactions occur, immediately discontinue the injection 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 ibandronate 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 ibandronate 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 Iasibon. While on treatment, invasive dental procedures should be performed only after careful consideration and be avoided in close proximity to Iasibon 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 Iasibon 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. 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 Iasibon 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 Iasibon. (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.

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

Excipients with known effect

Iasibon contains less than 1 mmol sodium (23 mg) per ampoule, that is to say essentially ‘sodium free’.

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

Metabolic interactions are not considered likely, since ibandronic acid does not inhibit the major human hepatic P450 isoenzymes and has been shown not to induce the hepatic cytochrome P450 system in rats (see section 5.2). Ibandronic acid is eliminated by renal excretion only and does not undergo any biotransformation.

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

## 4.6 Fertility, pregnancy and lactation

Pregnancy
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, Iasibon should not be used during pregnancy.

Breast –feeding
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. Iasibon should not be used during breast-feeding.

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 (see section 5.3).

## 4.7 Effects on ability to drive and use machines

On the basis of the pharmacodynamic and pharmacokinetic profile and reported adverse reactions, it is expected that Iasibon has no or negligible influence on the ability to drive and use machines.

## 4.8 Undesirable effects

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.

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 ibandronic acid 2 mg or 4 mg; Prevention of skeletal events in patients with breast cancer and bone metastases: 152 patients treated with ibandronic acid 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 Ibandronic Acid**

| System Organ Class | Very common | Common | Uncommon | Rare | Very rare | Not known |
|---|---|---|---|---|---|---|
| **Infections and infestations** | | Infection | Cystitis, vaginitis, oral candidiasis | | | |
| **Neoplasms benign, malignant, and unspecified** | | | Benign skin neoplasm | | | |
| **Blood and lymphatic system disorders** | | | Anaemia, blood dyscrasia | | | |
| **Immune system disorders** | | | | | Hypersensitivity†, bronchospasm†, angioedema† anaphylactic reaction/shock†** | Asthma exacerbation |
| **Endocrine disorders** | | Parathyroid disorder | | | | |
| **Metabolism and nutrition disorders** | | Hypocalcaemia** | Hypophosphataemia | | | |
| **Psychiatric disorders** | | | Sleep disorder, anxiety, affection lability | | | |
| **Nervous system disorders** | | Headache, dizziness, dysgeusia (taste perversion) | Cerebrovascular disorder, nerve root lesion, amnesia, migraine, neuralgia, hypertonia, hyperaestesia, paraesthesia circumoral, parosmia | | | |
| **Eye disorders** | | Cataract | | Ocular inflammation†** | | |
| **Ear and labyrinth disorders** | | | Deafness | | | |
| **Cardiac disorders** | | Bundle branch block | Myocardial ischaemia, cardiovascular disorder, palpitations | | | |

| System Organ Class | Very common | Common | Uncommon | Rare | Very rare | Not known |
|---|---|---|---|---|---|---|
| **Respiratory, thoracic, and mediastinal disorders** | | Pharyngitis | Lung oedema, stridor | | | |
| **Gastrointestinal disorders** | | Diarrhoea, vomiting, dyspepsia, gastrointestinal pain, tooth disorder | Gastroenteritis, gastritis, mouth ulceration, dysphagia, cheilitis | | | |
| **Hepatobiliary disorders** | | | Cholelithiasis | | | |
| **Skin and subcutaneous tissue disorders** | | Skin disorder, ecchymosis | Rash, alopecia | | Stevens-Johnson Syndrome†, Erythema Multiforme†, Dermatitis Bullous† | |
| **Musculoskeletal and connective tissue disorders** | | Osteoarthritis, myalgia, arthralgia, joint disorder, bone pain | | Atypical subtrochanteric and diaphyseal femoral fractures† | Osteonecrosis of jaw†**, osteonecrosis of the external auditory canal (bisphosphonate class adverse reaction)† | Atypical fractures of long bones other than the femur |
| **Renal and urinary disorders** | | | Urinary retention, renal cyst | | | |
| **Reproductive system and breast disorders** | | | Pelvic pain | | | |
| **General disorders and administration site conditions** | | Pyrexia, influenza-like illness**, oedema peripheral, asthenia, thirst | Hypothermia | | | |
| **Investigations** | | Gamma-GT increased, creatinine increased | Blood alkaline phosphatase increase, weight decrease | | | |
| **Injury, poisoning and procedural complications** | | | Injury, injection site pain | | | |

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

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*
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 medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

### 4.9 Overdose

Up to now there is no experience of acute poisoning with Iasibon 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 intravenous administration of calcium gluconate.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmaco-therapeutic group: Medicinal products for treatment of bone diseases, bisphosphonate, ATC Code: M05BA06

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

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

previously incorporated into the skeleton.

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

Bone resorption due to malignant disease is characterised by excessive bone resorption that is not balanced with appropriate bone formation. 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 ≥ 3.0 mmol/L after adequate rehydration.

| Ibandronic acid dose | % of Patients with Response | 90 % Confidence Interval |
|---|---|---|
| 2 mg | 54 | 44-63 |
| 4 mg | 76 | 62-86 |
| 6 mg | 78 | 64-88 |

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 Ibandronate 6 mg administered intravenously 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 Ibandronate (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 intravenous Ibandronate 6 mg 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 Ibandronate 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 2.

**Table 2 Efficacy Results (Breast Cancer Patients with Metastatic Bone Disease)**

| | All Skeletal Related Events (SREs) | | |
|---|---|---|---|
| | Placebo n = 158 | Ibandronate 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 intravenous Ibandronate 6 mg 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 Ibandronate treated patients compared with placebo. A tabular summary of these secondary efficacy results is presented in table 3.

**Table 3 Secondary efficacy results (breast cancer patients with metastatic bone disease)**

| | Placebo n = 158 | Ibandronate 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 Ibandronate that was statistically significant compared to placebo.

In a study in 130 patients with metastatic breast cancer the safety of Ibandronate 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 < 50 mL/min.

*Paediatric population (see section 4.2 and section 5.2)*
The safety and efficacy of Iasibon in children and adolescents below the age of 18 years have not been established. No data are available.

## 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 interaction with other medicinal products, due to displacement is unlikely.

*Biotransformation*
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.

The secretory pathway of renal elimination 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 P 450 isoenzymes and does not induce the hepatic cytochrome P 450 system in rats.

*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), dose-adjusted mean $AUC_{0-24h}$ was increased by 110 % compared to healthy volunteers. In clinical pharmacology trial WP18551, after a single dose intravenous administration of 6 mg (15 minutes infusion), mean $AUC_{0-24}$ 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 $C_{max}$ 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 $\geq$ 50 and < 80 mL/min) no dosage adjustment is necessary. For patients with moderate renal impairment (CLcr $\geq$ 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).

*Patients with hepatic impairment* (see section 4.2)
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* (see section 4.2)
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).

*Paediatric population* (see section 4.2 and section 5.1)
There are no data on the use of Iasibon in patients less than 18 years old.

### 5.3 Preclinical safety data

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

*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. In reproductive studies in rats by the oral route, effects on fertility consisted of increased preimplantation losses at dose levels of 1 mg/kg/day and higher. In reproductive studies in rats by the intravenous route, ibandronic acid decreased sperm counts at doses of 0.3 and 1 mg/kg/day and decreased fertility in males at 1 mg/kg/day and in females at 1.2 mg/kg/day. Adverse effects of ibandronic acid in reproductive toxicity studies in the rat were those expected for this class of medicinal products (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, glacial
Sodium acetate trihydrate
Water for injections

### 6.2 Incompatibilities

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

Iasibon should not be mixed with calcium containing solutions.

### 6.3 Shelf life

5 years.
After reconstitution: 24 hours.

### 6.4 Special precautions for storage

This medicinal product does not require any special storage conditions prior to reconstitution.
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

Iasibon 2 mg is supplied as pack containing 1 ampoule (4 mL type I glass ampoule).

### 6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.
The release of pharmaceuticals in the environment should be minimized.

## 7. MARKETING AUTHORISATION HOLDER

Pharmathen S.A.
Dervenakion 6
Pallini Attiki, 15351
Greece

## 8. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/659/004

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

Date of first authorisation: 21 January 2011
Date of latest renewal: 30 September 2015

## 10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu/.

## 1. NAME OF THE MEDICINAL PRODUCT

Iasibon 6 mg concentrate for solution for infusion

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial with 6 mL concentrate for solution for infusion contains 6 mg ibandronic acid (as sodium monohydrate).

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.
Clear, colourless solution.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Iasibon is indicated in adults 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

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

Posology
*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 intravenous injection given every 3-4 weeks. The dose should be infused over at least 15 minutes.

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. Prescribers should consult the section *Patients with Renal Impairment* (see section 4.2) for recommendations on dosing and administration in this patient group.

*Treatment of tumour-induced hypercalcaemia*

Prior to treatment with Iasibon the patient should be adequately rehydrated with 9 mg/mL (0.9 %) sodium chloride solution. 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 dose. 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 (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.

Iasibon concentrate for solution for infusion should be administered as an intravenous infusion over 2 hours.

*Special populations*
*Patients with hepatic impairment*
No dose adjustment is required (see section 5.2).

*Patients with renal impairment*
For patients with mild renal impairment (CLcr ≥ 50 and < 80 mL/min) no dose 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 (see section 5.2):

| Creatinine Clearance (mL/min) | Dosage | Infusion Volume [1] and Time [2] |
|---|---|---|
| ≥ 50 CLcr < 80 | 6 mg (6 mL of concentrate for solution for infusion) | 100 mL over 15 minutes |
| ≥ 30 CLcr < 50 | 4 mg (4 mL of concentrate for solution for infusion) | 500 mL over 1 hour |
| < 30 | 2 mg (2 mL of concentrate for solution for infusion) | 500 mL over 1 hour |

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

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

*Elderly population (> 65 years)*
No dose adjustment is required (see section 5.2).

*Paediatric population*
The safety and efficacy of Iasibon in children and adolescents below the age of 18 years have not been established. No data are available. (see section 5.1 and section 5.2).

Method of administration
For intravenous administration.

The content of the vial is to be used as follows:

- Prevention of Skeletal Events - added to 100 mL isotonic sodium chloride solution or 100 mL 5 % dextrose solution and infused over at least 15 minutes. See also dose section above for patients with renal impairment

- Treatment of tumour-induced hypercalcaemia - added to 500 mL isotonic sodium chloride solution or 500 mL 5 % dextrose solution and infused over 2 hours

For single use only. Only clear solution without particles should be used.
Iasibon concentrate for solution for infusion should be administered as an intravenous infusion.
Care must be taken not to administer Iasibon concentrate for solution for infusion via intra-arterial or paravenous administration, as this could lead to tissue damage.

## 4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Hypocalcaemia

## 4.4 Special warnings and precautions for use

Patients with disturbances of bone and mineral metabolism
Hypocalcaemia and other disturbances of bone and mineral metabolism should be effectively treated before starting Iasibon 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

Anaphylactic reaction/shock
Cases of anaphylactic reaction/shock, including fatal events, have been reported in patients treated with intravenous ibandronic acid.
Appropriate medical support and monitoring measures should be readily available when Iasibon intravenous injection is administered. If anaphylactic or other severe hypersensitivity/allergic reactions occur, immediately discontinue the injection 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 ibandronate 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 ibandronate 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 Iasibon. While on treatment, invasive dental procedures should be performed only after careful consideration and be avoided in close proximity to Iasibon 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 Iasibon 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 (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 Iasibon 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 Iasibon (see section 4.2).

Patients with hepatic impairment
As no clinical data are available, dose 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.

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

Excipients with known effect

Iasibon contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially ‘sodium free’.

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

Metabolic interactions are not considered likely, since ibandronic acid does not inhibit the major human hepatic P450 isoenzymes and has been shown not to induce the hepatic cytochrome P450 system in rats (see section 5.2). Ibandronic acid is eliminated by renal excretion only and does not undergo any biotransformation.

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

## 4.6 Fertility, pregnancy and lactation

Pregnancy
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, Iasibon should not be used during pregnancy.

Breast –feeding
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. Iasibon should not be used during breast-feeding.

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 (see section 5.3).

## 4.7 Effects on ability to drive and use machines

On the basis of the pharmacodynamic and pharmacokinetic profile and reported adverse reactions, it is expected that Iasibon has no or negligible influence on the ability to drive and use machines.

## 4.8 Undesirable effects

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 was required, and the symptoms subsided 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.

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 ibandronic acid 2 mg or 4 mg; Prevention of skeletal events in patients with breast cancer and bone metastases: 152 patients treated with ibandronic acid 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 Ibandronic Acid**

| System Organ Class | Very common | Common | Uncommon | Rare | Very rare | Not known |
|---|---|---|---|---|---|---|
| **Infections and infestations** | | Infection | Cystitis, vaginitis, oral candidiasis | | | |
| **Neoplasms benign, malignant, and unspecified** | | | Benign skin neoplasm | | | |
| **Blood and lymphatic system disorders** | | | Anaemia, blood dyscrasia | | | |
| **Immune system disorders** | | | | | Hypersensitivity†, bronchospasm†, angioedema† anaphylactic reaction/shock†** | Asthma exacerbation |
| **Endocrine disorders** | | Parathyroid disorder | | | | |
| **Metabolism and nutrition disorders** | | Hypocalcaemia** | Hypophosphataemia | | | |
| **Psychiatric disorders** | | | Sleep disorder, anxiety, affection lability | | | |
| **Nervous system disorders** | | Headache, dizziness, dysgeusia (taste perversion) | Cerebrovascular disorder, nerve root lesion, amnesia, migraine, neuralgia, hypertonia, hyperaestesia, paraesthesia circumoral, parosmia | | | |
| **Eye disorders** | | Cataract | | Ocular inflammation†** | | |
| **Ear and labyrinth disorders** | | | Deafness | | | |
| **Cardiac disorders** | | Bundle branch block | Myocardial ischaemia, cardiovascular disorder, palpitations | | | |
| **Respiratory, thoracic, and mediastinal** | | Pharyngitis | Lung oedema, stridor | | | |

| System Organ Class | Very common | Common | Uncommon | Rare | Very rare | Not known |
|---|---|---|---|---|---|---|
| **disorders** | | | | | | |
| **Gastrointestinal disorders** | | Diarrhoea, vomiting, dyspepsia, gastrointestinal pain, tooth disorder | Gastroenteritis, gastritis, mouth ulceration, dysphagia, cheilitis | | | |
| **Hepatobiliary disorders** | | | Cholelithiasis | | | |
| **Skin and subcutaneous tissue disorders** | | Skin disorder, ecchymosis | Rash, alopecia | | Stevens-Johnson Syndrome†, Erythema Multiforme†, Dermatitis Bullous† | |
| **Musculoskeletal and connective tissue disorders** | | Osteoarthritis, myalgia, arthralgia, joint disorder, bone pain | | Atypical subtrochanteric and diaphyseal femoral fractures† | Osteonecrosis of jaw†**, osteonecrosis of the external auditory canal (bisphosphonate class adverse reaction)† | Atypical fractures of long bones other than the femur |
| **Renal and urinary disorders** | | | Urinary retention, renal cyst | | | |
| **Reproductive system and breast disorders** | | | Pelvic pain | | | |
| **General disorders and administration site conditions** | | Pyrexia, influenza-like illness**, oedema peripheral, asthenia, thirst | Hypothermia | | | |
| **Investigations** | | Gamma-GT increased, creatinine increased | Blood alkaline phosphatase increase, weight decrease | | | |
| **Injury, poisoning and procedural complications** | | | Injury, injection site pain | | | |

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

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*
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 medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

### 4.9 Overdose

Up to now there is no experience of acute poisoning with Iasibon 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 intravenous administration of calcium gluconate.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmaco-therapeutic group: Medicinal products for treatment of bone diseases, bisphosphonate, ATC Code: M05BA06

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

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

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

Bone resorption due to malignant disease is characterised by excessive bone resorption that is not balanced with appropriate bone formation. 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 ≥ 3.0 mmol/L after adequate rehydration.

| Ibandronic acid dose | % of Patients with Response | 90 % Confidence Interval |
|---|---|---|
| 2 mg | 54 | 44-63 |
| 4 mg | 76 | 62-86 |
| 6 mg | 78 | 64-88 |

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 Ibandronate 6 mg administered intravenously was assessed in one randomized placebo controlled phase III trial with a duration of 96 weeks. Female patients with breast cancer and radiologically confirmed bone metastases were randomised to receive placebo (158 patients) or 6 mg Ibandronate (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 intravenous Ibandronate 6 mg 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 Ibandronate 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 2.

**Table 2 Efficacy Results (Breast Cancer Patients with Metastatic Bone Disease)**

| | All Skeletal Related Events (SREs) |
|---|---|

| | Placebo n = 158 | Ibandronate 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 intravenous Ibandronate 6 mg 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 Ibandronate treated patients compared with placebo. A tabular summary of these secondary efficacy results is presented in table 3.

**Table 3 Secondary efficacy results (breast cancer patients with metastatic bone disease)**

| | Placebo n = 158 | Ibandronate 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 Ibandronate that was statistically significant compared to placebo.

In a study in 130 patients with metastatic breast cancer the safety of Ibandronate 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 < 50 mL/min.

*Paediatric population (see section 4.2 and section 5.2)*
The safety and efficacy of Iasibon in children and adolescents below the age of 18 years have not been established. No data are available.

## 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 interaction with other medicinal products,

due to displacement is unlikely.

*Biotransformation*
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.

The secretory pathway of renal elimination 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.

*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), dose-adjusted mean $AUC_{0-24h}$ was increased by 110 % compared to healthy volunteers. In clinical pharmacology trial WP18551, after a single dose intravenous administration of 6 mg (15 minutes infusion), mean $AUC_{0-24}$ 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 $C_{max}$ 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 $\geq$ 50 and < 80 mL/min) no dosage adjustment is necessary. For patients with moderate renal impairment (CLcr $\geq$ 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).

*Patients with hepatic impairment* (see section 4.2)
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* (see section 4.2)
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).

*Paediatric population* (see section 4.2 and section 5.1)
There are no data on the use of Iasibon in patients less than 18 years old.

### 5.3 Preclinical safety data

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

*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. In reproductive studies in rats by the oral route, effects on fertility consisted of increased preimplantation losses at dose levels of 1 mg/kg/day and higher. In reproductive studies in rats by the intravenous route, ibandronic acid decreased sperm counts at doses of 0.3 and 1 mg/kg/day and decreased fertility in males at 1 mg/kg/day and in females at 1.2 mg/kg/day. Adverse effects of ibandronic acid in reproductive toxicity studies in the rat were those expected for this class of medicinal products (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, glacial
Sodium acetate trihydrate
Water for injections

### 6.2 Incompatibilities

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

Iasibon should not be mixed with calcium containing solutions.

### 6.3 Shelf life

5 years.
After reconstitution: 24 hours.

### 6.4 Special precautions for storage

This medicinal product does not require any special storage conditions prior to reconstitution.
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

Iasibon 6 mg is supplied as packs containing 1,5,10 vials (9 mL type I glass vial with a bromobutyl rubber stopper).

### 6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.
The release of pharmaceuticals in the environment should be minimized.

## 7. MARKETING AUTHORISATION HOLDER

Pharmathen S.A.
Dervenakion 6
Pallini Attiki, 15351
Greece

## 8. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/659/005
EU/1/10/659/006
EU/1/10/659/007

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

Date of first authorisation: 21 January 2011
Date of latest renewal: 30 September 2015

## 10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu/.

## 1. NAME OF THE MEDICINAL PRODUCT

Iasibon 50 mg film coated tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 50 mg of ibandronic acid (as sodium monohydrate).

Excipients with known effect:
Contains 0.86 mg lactose (as lactose monohydrate).

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Film-coated tablets.
White round biconvex tablets

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Iasibon is indicated in adults for the prevention of skeletal events (pathological fractures, bone complications requiring radiotherapy or surgery) in patients with breast cancer and bone metastases.

### 4.2 Posology and method of administration

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

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

*Special populations*
*Patients with hepatic impairment*
No dose adjustment is required (see section 5.2).

*Patients with renal impairment*
No dose adjustment is necessary for patients with mild renal impairment (CLcr ≥ 50 and < 80 mL/min).

For patients with moderate renal impairment (CLcr ≥ 30 and < 50 mL/min) a dosage adjustment to one 50 mg film-coated tablet every second day is recommended (see section 5.2).

For patients with severe renal impairment (CLcr < 30 mL/min) the recommended dose is one 50 mg film-coated tablet once weekly. See dosing instructions, above.

*Elderly population (> 65 years)*
No dose adjustment is necessary (see section 5.2).

*Paediatric population*
The safety and efficacy of Iasibon in children and adolescents below the age of 18 years have not been established. No data are available (see section 5.1 and 5.2).

Method of administration
For oral use.

Iasibon tablets should be taken after an overnight fast (at least 6 hours) and before the first food or drink of the day. Medicinal products and supplements (including calcium) should similarly be avoided prior to taking Iasibon tablets. Fasting should be continued for at least 30 minutes after taking the tablet. Water may be taken at any time during the course of Iasibon treatment (see section 4.5). Water with a high concentration of calcium should not be used. If there is concern regarding potentially high levels of calcium in the tap water (hard water), it is advised to use bottled water with a low mineral content.

- The tablets should be swallowed whole with a full glass of water (180 to 240 mL) while the patient is standing or sitting in an upright position.

- Patients should not lie down for 60 minutes after taking Iasibon.

- Patients should not chew, suck or crush the tablet because of a potential for oropharyngeal ulceration.

- Water is the only drink that should be taken with Iasibon.

## 4.3 Contraindications

- Hypersensitivity to ibandronic acid or to any of the excipients listed in section 6.1.
- Hypocalcaemia
- Abnormalities of the oesophagus which delay oesophageal emptying such as stricture or achalasia
- Inability to stand or sit upright for at least 60 minutes

## 4.4 Special warnings and precautions for use

Patients with disturbances of bone and mineral metabolism
Hypocalcaemia and other disturbances of bone and mineral metabolism should be effectively treated before starting Iasibon 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.

Gastrointestinal irritation
Orally administered bisphosphonates may cause local irritation of the upper gastrointestinal mucosa. Because of these possible irritant effects and a potential for worsening of the underlying disease, caution should be used when Iasibon is given to patients with active upper gastrointestinal problems (e.g. known Barrett's oesophagus, dysphagia, other oesophageal diseases, gastritis, duodenitis or ulcers).

Adverse experiences such as oesophagitis, oesophageal ulcers and oesophageal erosions, in some cases severe and requiring hospitalization, rarely with bleeding or followed by oesophageal stricture or perforation, have been reported in patients receiving treatment with oral bisphosphonates. The risk of severe oesophageal adverse experiences appears to be greater in patients who do not comply with the dosing instruction and/or who continue to take oral bisphosphonates after developing symptoms suggestive of oesophageal irritation. Patients should pay particular attention and be able to comply with the dosing instructions (see section 4.2).

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

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

Acetylsalicylic acid and NSAIDs
Since Acetylsalicylic acid, Nonsteroidal Anti-Inflammatory medicinal products (NSAIDs) and bisphosphonates are associated with gastrointestinal irritation, caution should be taken during concomitant administration.

Osteonecrosis of the jaw

Osteonecrosis of the jaw (ONJ) has been reported very rarely in the post-marketing setting in patients receiving ibandronate 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 ibandronate 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 Iasibon. While on treatment, invasive dental procedures should be performed only after careful consideration and be avoided in close proximity to Iasibon 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 Iasibon 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 (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).

Renal function
Clinical studies have not shown any evidence of deterioration in renal function with long term Iasibon 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 Iasibon.

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

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

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

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

Bioavailability was reduced by approximately 75 % when Iasibon tablets were administered 2 hours after a standard meal. Therefore, it is recommended that the tablets should be taken after an overnight fast (at least 6 hours) and fasting should continue for at least 30 minutes after the dose has been taken (see section 4.2).

*Interactions with other medicinal products*

Metabolic interactions are not considered likely, since ibandronic acid does not inhibit the major human hepatic P 450 isoenzymes and has been shown not to induce the hepatic cytochrome P 450 system in rats (see section 5.2). Ibandronic acid is eliminated by renal excretion only and does not undergo any biotransformation.

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

Acetylsalicylic acid and NSAIDs
Since Acetylsalicylic acid, Nonsteroidal Anti-Inflammatory medicinal products (NSAIDs) and bisphosphonates are associated with gastrointestinal irritation, caution should be taken during concomitant administration (see section 4.4).

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

## 4.6 Fertility, pregnancy and lactation

Pregnancy
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, Iasibon should not be used during pregnancy.

Breast-feeding
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. Iasibon should not be used during breast-feeding.

Fertility
There is 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 (see section 5.3).

## 4.7 Effects on ability to drive and use machines

On the basis of the pharmacodynamic and pharmacokinetic profile and reported adverse reactions, it is expected that Iasibon has no or negligible influence on the ability to drive and use machines.

## 4.8 Undesirable effects

Summary of the safety profile
The most serious reported adverse reactions are anaphylactic reaction/shock, atypical fractures of the femur, osteonecrosis of the jaw, gastrointestinal irritation, and ocular inflammation (see paragraph "Description of selected adverse reactions" and section 4.4).

Treatment was most frequently associated with a decrease in serum calcium to below normal range (hypocalcaemia), followed by dyspepsia.

Tabulated list of adverse reactions
Table 1 lists adverse reactions from 2 pivotal phase III studies (Prevention of skeletal events in patients with breast cancer and bone metastases: 286 patients treated with ibandronic acid 50 mg administered orally), 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 Drug Reactions Reported for Oral Administration of Ibandronate**

| | | | | | | |
|---|---|---|---|---|---|---|
| **System Organ Class** | **Very common** | **Common** | **Uncommon** | **Rare** | **Very rare** | **Not known** |
| **Blood and lymphatic system disorders** | | | Anaemia | | | |

| System Organ Class | Very common | Common | Uncommon | Rare | Very rare | Not known |
|---|---|---|---|---|---|---|
| **Immune system disorders** | | | | | Hypersensitivity † bronchospasm†, angioedema†, Anaphylactic reaction/shock† ** | Asthma exacerbation |
| **Metabolism and nutrition disorders** | | Hypocalcaemia ** | | | | |
| **Nervous system disorders** | | | Paraesthesia, dysgeusia (taste perversion) | | | |
| **Eye disorders** | | | | Ocular inflammation †** | | |
| **Gastrointestinal disorders** | | Oesophagitis, abdominal pain, dyspepsia, nausea | Haemorrage, duodenal ulcer, gastritis, dysphagia, dry mouth | | | |
| **Skin and subcutaneous tissue disorders** | | | Pruritus | | Stevens-Johnson Syndrome†, Erythema Multiforme†, Dermatitis Bullous† | |
| **Musculoskeletal and connective tissue disorders** | | | | Atypical subtrochanteric and diaphyseal femoral fractures† | Osteonecrosis of jaw†**, osteonecrosis of the external auditory canal (bisphosphonate class adverse reaction)† | Atypical fractures of long bones other than the femur |
| **Renal and urinary disorders** | | | Azotaemia (uraemia) | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| **System Organ Class** | **Very common** | **Common** | **Uncommon** | **Rare** | **Very rare** | **Not known** |
| **General disorders and administration site conditions** | | Asthenia | Chest pain, influenza-like illness, malaise, pain | | | |
| **Investigations** | | | Blood parathyroid hormone increased | | | |

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

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.

*Osteonecrosis of jaw*
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 medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

## 4.9 Overdose

No specific information is available on the treatment of overdosage with Iasibon. However, oral overdosage may result in upper gastrointestinal events, such as upset stomach, heartburn, oesophagitis, gastritis or ulcer. Milk or antacids should be given to bind Iasibon. Due to the risk of oesophageal

irritation, vomiting should not be induced, and the patient should remain fully upright.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmaco-therapeutic group: Medicinal products for treatment of bone diseases, bisphosphonate, ATC Code: M05BA06

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

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

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

Bone resorption due to malignant disease is 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 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 Ibandronate 50 mg tablets was assessed in two randomized placebo controlled phase III trials with a duration of 96 weeks. Female patients with breast cancer and radiologically confirmed bone metastases were randomised to receive placebo (277 patients) or 50 mg Ibandronate (287 patients). The results from these trials are summarised below.

*Primary efficacy endpoints*
The primary endpoint of the trials 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 in any given 12 week period for the purposes of the analysis. Pooled data from these studies demonstrated a significant advantage for Ibandronate 50 mg p.o. over placebo in the reduction in SREs measured by the SMPR ($p = 0.041$). There was also a 38 % reduction in the risk of developing an SRE for Ibandronate treated patients when compared with placebo (relative risk 0.62, $p = 0.003$). Efficacy results are summarised in Table 2.

**Table 2 Efficacy Results (Breast Cancer Patients with Metastatic Bone Disease)**

| | All Skeletal Related Events (SREs) |
|---|---|

| | Placebo n = 277 | Ibandronate 50 mg n = 287 | p-value |
|---|---|---|---|
| SMPR (per patient year) | 1.15 | 0.99 | p = 0.041 |
| SRE relative risk | - | 0.62 | p = 0.003 |

*Secondary efficacy endpoints*
A statistically significant improvement in bone pain score was shown for Ibandronate 50 mg compared to placebo. The pain reduction was consistently below baseline throughout the entire study and accompanied by a significantly reduced use of analgesics compared to placebo. The deterioration in Quality of Life and WHO performance status was significantly less in Ibandronate treated patients compared with placebo. Urinary concentrations of the bone resorption marker CTx (C-terminal telopeptide released from Type I collagen) were significantly reduced in the Ibandronate group compared to placebo. This reduction in urinary CTx levels was significantly correlated with the primary efficacy endpoint SMPR (Kendall-tau-b ($p < 0.001$)). A tabular summary of the secondary efficacy results is presented in Table 3.

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

| | Placebo n = 277 | Ibandronate 50 mg n = 287 | p-value |
|---|---|---|---|
| Bone pain * | 0.20 | -0.10 | p = 0.001 |
| Analgesic use * | 0.85 | 0.60 | p = 0.019 |
| Quality of Life * | -26.8 | -8.3 | p = 0.032 |
| WHO performance score * | 0.54 | 0.33 | p = 0.008 |
| Urinary CTx ** | 10.95 | -77.32 | p = 0.001 |

* Mean change from baseline to last assessment.
** Median change from baseline to last assessment

*Paediatric population (see section 4.2 and section 5.2)*
The safety and efficacy of Iasibon in children and adolescents below the age of 18 years have not been established. No data is available.

## 5.2 Pharmacokinetic properties

*Absorption*
The absorption of ibandronic acid in the upper gastrointestinal tract is rapid after oral administration. Maximum observed plasma concentrations were reached within 0.5 to 2 hours (median 1 hour) in the fasted state and absolute bioavailability was about 0.6 %. The extent of absorption is impaired when taken together with food or beverages (other than water). Bioavailability is reduced by about 90 % when ibandronic acid is administered with a standard breakfast in comparison with bioavailability seen in fasted subjects. When taken 30 minutes before a meal, the reduction in bioavailability is approximately 30 %. There is no meaningful reduction in bioavailability provided ibandronic acid is taken 60 minutes before a meal.

Bioavailability was reduced by approximately 75 % when Iasibon tablets were administered 2 hours after a standard meal. Therefore, it is recommended that the tablets should be taken after an overnight fast (minimum 6 hours) and fasting should continue for at least 30 minutes after the dose has been taken (see section 4.2).

*Distribution*
After initial systemic exposure, ibandronic acid rapidly binds to bone or is excreted into urine. In humans, the apparent terminal volume of distribution is at least 90 l and the amount of dose reaching the bone is estimated to be 40-50 % of the circulating dose. Protein binding in human plasma is approximately 87 % at therapeutic concentrations, and thus interaction with other medicinal products, due to displacement is unlikely.

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

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

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

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

The secretory pathway of renal elimination 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 P 450 isoenzymes and does not induce the hepatic cytochrome P 450 system in rats.

*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 degree of renal impairment is related to creatinine clearance (CLcr). Subjects with severe renal impairment (CLcr ≤ 30 mL/min) receiving oral administration of 10 mg ibandronic acid daily for 21 days, had 2-3 fold higher plasma concentrations than subjects with normal renal function (CLcr ≥ 80 mL/min). Total clearance of ibandronic acid was reduced to 44 ml/min in the subjects with severe renal impairment compared with 129 mL/min in subjects with normal renal function. No dosage adjustment is necessary for patients with mild renal impairment (CLcr ≥ 50 and < 80 mL/min). For patients with moderate renal impairment (CLcr ≥ 30 and < 50 mL/min) or severe renal impairment (CLcr < 30 mL/min) an adjustment in the dose is recommended (see section 4.2).

*Patients with hepatic impairment (see section 4.2)*
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 (see section 4.2)*
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 renal impairment section).

*Paediatric population (see section 4.2 and section 5.1)*
There are no data on the use of Iasibon in patients less than 18 years old.

### 5.3 Preclinical safety data

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

*Mutagenicity/Carcinogenicity:*
No indication of carcinogenic potential was observed. Tests for genotoxicity revealed no evidence of genetic activity for ibandronic acid.

*Reproductive toxicity:*
No evidence of direct foetal toxicity or teratogenic effects was observed for ibandronic acid in intravenously or orally treated rats and rabbits. In reproductive studies in rats by the oral route effects on fertility consisted of increased preimplantation losses at dose levels of 1 mg/kg/day and higher. In reproductive studies in rats by the intravenous route, ibandronic acid decreased sperm counts at doses of 0.3 and 1 mg/kg/day and decreased fertility in males at 1 mg/kg/day and in females at 1.2 mg/kg/day. Adverse effects of ibandronic acid in reproductive toxicity studies in the rat were those expected for this class of medicinal products (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

*Tablet core:*
Povidone
Cellulose, microcrystalline
Crospovidone
Maize starch pregelatinised
Glycerol dibehenate
Silica, anhydrous colloidal

*Tablet coat:*
Lactose monohydrate
Macrogol 4 000
Hypromellose (E 464)
Titanium dioxide E 171

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

5 years.

### 6.4 Special precautions for storage

Store in the original package in order to protect from moisture.

### 6.5 Nature and contents of container

Iasibon 50 mg film coated tablets are supplied in Polyamide/Al/PVC - Aluminum foil blister with 3, 6, 9, 28 or 84 tablets, packaged in a cardboard box.
Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements. The release of pharmaceuticals in the environment should be minimized.

## 7. MARKETING AUTHORISATION HOLDER

Pharmathen S.A.
Dervenakion 6
15351 Pallini, Attiki
Greece

## 8. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/659/001
EU/1/10/659/002
EU/1/10/659/008
EU/1/10/659/009
EU/1/10/659/0010

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

Date of first authorisation: 21 January 2011
Date of latest renewal: 30 September 2015

## 10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu/

# ANNEX II

**A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE**

**B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**

**C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**

**D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

## A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

***Concentrate for solution for infusion***

Pharmathen S.A.
Dervenakion 6
Pallini 15351
Attiki
Greece

***Film-coated tablet***

Pharmathen S.A.
Dervenakion 6
Pallini 15351
Attiki
Greece

And

Pharmathen International S.A.
Industrial Park Sapes, Street block 5
69300 Sapes, Prefecture of Rodopi
Greece

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

## B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

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

## C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

**Periodic safety update reports**

At the time of granting the marketing authorisation, the submission of periodic safety update reports is not required for this medicinal product. However, the marketing authorisation holder shall submit periodic safety update reports for this medicinal product if the product is included in the list of Union reference dates (EURD list) provided for under Article 107c (7) of Directive 2001/83/EC and published on the European medicines web-portal.

## D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

**Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

**ANNEX III**

**LABELLING AND PACKAGE LEAFLET**

# A. LABELLING

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON**

**1. NAME OF THE MEDICINAL PRODUCT**

Iasibon 1 mg concentrate for solution for infusion
ibandronic acid

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

One ampoule with 1 mL concentrate for solution for infusion contains 1 mg ibandronic acid (sodium monohydrate).

**3. LIST OF EXCIPIENTS**

Sodium chloride, glacial acetic acid, sodium acetate trihydrate and water for injections. See package leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Concentrate for solution for infusion.
1 ampoule

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

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

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

Keep out of the sight and reach of children.

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

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

This medicinal product does not require any special storage conditions prior to reconstitution. After dilution the infusion solution is stable for 24 hours at 2 °C - 8 °C (in a refrigerator)

**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**

Pharmathen S.A.
6, Dervenakion str.
Pallini 15351, Attiki
Greece

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

EU/1/10/659/003

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Iasibon 1 mg

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER – HUMAN READABLE DATA**

PC
SN
NN

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

**AMPOULE**

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

Iasibon 1 mg concentrate for solution for infusion
ibandronic acid
I.V. use

## 2. METHOD OF ADMINISTRATION

Read the package leaflet before use

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

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

1 mL

## 6. OTHER

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON**

## 1. NAME OF THE MEDICINAL PRODUCT

Iasibon 2 mg concentrate for solution for infusion
ibandronic acid

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

One ampoule with 2 mL concentrate for solution for infusion contains 2 mg ibandronic acid (as sodium monohydrate).

## 3. LIST OF EXCIPIENTS

Sodium acetate trihydrate sodium chloride, glacial acetic acid and water for injections.

See package leaflet for further information.

## 4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion

1 ampoule

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

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

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

Keep out of the sight and reach of children

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

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

This medicinal product does not require any special storage conditions prior to reconstitution.

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

## 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

Pharmathen S.A.
6, Dervenakion str.
15351 Pallini, Attiki
Greece

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/659/004

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Iasibon 2 mg

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

## 18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

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

**AMPOULE**

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

Iasibon 2 mg concentrate for solution for infusion
ibandronic acid
I.V. use

## 2. METHOD OF ADMINISTRATION

Read the package leaflet before use

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

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

2 mL

## 6. OTHER

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON**

## 1. NAME OF THE MEDICINAL PRODUCT

Iasibon 6 mg concentrate for solution for infusion
ibandronic acid

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial with 6 mL concentrate for solution for infusion contains 6 mg ibandronic acid (as sodium monohydrate).

## 3. LIST OF EXCIPIENTS

Sodium chloride, glacial acetic acid, sodium acetate trihydrate and water for injections.
See package leaflet for further information.

## 4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion
1 vial
5 vials
10vials

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

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

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

Keep out of the sight and reach of children

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

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

This medicinal product does not require any special storage conditions prior to reconstitution. After dilution the infusion solution is stable for 24 hours at 2 °C - 8 °C (in a refrigerator)

## 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

Pharmathen S.A.
6, Dervenakion str.
15351 Pallini, Attiki
Greece

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/659/005
EU/1/10/659/006
EU/1/10/659/007

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Iasibon 6 mg

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

## 18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN
NN

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

**VIAL**

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

Iasibon 6 mg concentrate for solution for infusion
ibandronic acid
I.V. use

## 2. METHOD OF ADMINISTRATION

Read the package leaflet before use

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

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

6 mL

## 6. OTHER

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON**

## 1. NAME OF THE MEDICINAL PRODUCT

Iasibon 50 mg film-coated tablets
ibandronic acid

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 50 mg of ibandronic acid (as sodium monohydrate).

## 3. LIST OF EXCIPIENTS

The tablets also contain lactose. See package leaflet for further information.

## 4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets
3 film-coated tablets
6 film-coated tablets
9 film-coated tablets
28 film-coated tablets
84 film-coated tablets

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

Do not suck, chew or crush tablets
Read the package leaflet before use
Oral use

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

Keep out of the sight and reach of children

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

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture

**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**

Pharmathen S.A.
6, Dervenakion str
15351 Pallini, Attiki
Greece
Tel.: +302106604300

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

EU/1/10/659/001
EU/1/10/659/002
EU/1/10/659/008
EU/1/10/659/009
EU/1/10/659/0010

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Iasibon 50 mg

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER – HUMAN READABLE DATA**

PC
SN
NN

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**BLISTER FOIL**

## 1. NAME OF THE MEDICINAL PRODUCT

Iasibon 50 mg film-coated tablets
ibandronic acid

## 2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pharmathen S.A

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. OTHER

Mon
Tue
Wed
Thu
Fri
Sat
Sun

# B. PACKAGE LEAFLET

**Package leaflet: Information for the patient**

**Iasibon 1 mg concentrate for solution for infusion**
ibandronic acid

**Read all of this leaflet carefully before you start using this medicine because it contains important information for you.**
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4

**What is in this leaflet**:


## 1. What Iasibon is and what it is used for

Iasibon contains the active substance ibandronic acid. This belongs to a group of medicines called bisphosphonates.

Iasibon is used in adults and prescribed to you if you have breast cancer that has spread to your bones (called 'bone metastases').

- It helps to prevent your bones from breaking (fractures)
- It helps to prevent other bone problems that may need surgery or radiotherapy

Iasibon can also be prescribed if you have a raised calcium level in your blood due to a tumour.

Iasibon works by reducing the amount of calcium that is lost from your bones. This helps to stop your bones from getting weaker.

## 2. What you need to know before you receive Iasibon

**Do not receive Iasibon**
- if you are allergic to ibandronic acid or any of the other ingredients of this medicine that are listed in section 6.
- if you have, or have ever had low levels of calcium in your blood.

Do not receive this medicine if any of the above apply to you. If you are not sure, talk to your doctor or pharmacist before having Iasibon.

**Warnings and precautions**
A side effect called osteonecrosis of the jaw (ONJ) (bone damage in the jaw) has been reported very rarely in the post marketing setting in patients receiving ibandronate for cancer-related conditions. ONJ can also occur after stopping treatment.

It is important to try and prevent ONJ developing as it is a painful condition that can be difficult to treat. In order to reduce the risk of developing osteonecrosis of the jaw, there are some precautions you should take.

Before receiving treatment, tell your doctor/nurse (health care professional) if:
- you have any problems with your mouth or teeth such as poor dental health, gum disease, or a planned tooth extraction
- you don't receive routine dental care or have not had a dental check up for a long time
- you are a smoker (as this may increase the risk of dental problems)
- you have previously been treated with a bisphosphonate (used to treat or prevent bone disorders)
- you are taking medicines called corticosteroids (such as prednisolone or dexamethasone)
- you have cancer.

Your doctor may ask you to undergo a dental examination before starting treatment with Iasibon.

While being treated, you should maintain good oral hygiene (including regular teeth brushing) and receive routine dental check-ups. If you wear dentures you should make sure these fit properly. If you are under dental treatment or will undergo dental surgery (e.g. tooth extractions), inform your doctor about your dental treatment and tell your dentist that you are being treated with Iasibon.

Contact your doctor and dentist immediately if you experience any problems with your mouth or teeth such as loose teeth, pain or swelling, non-healing of sores or discharge, as these could be signs of osteonecrosis of the jaw.

Atypical fractures of the long bones, such as in the forearm bone (ulna) and the shinbone (tibia), have also been reported in patients receiving long-term treatment with Ibandronate. These fractures occur after minimal, or no trauma and some patients experience pain in the area of the fracture prior to presenting with a completed fracture.

Talk to your doctor, pharmacist or nurse before receiving Iasibon:
- if you are allergic to any other bisphosphonates
- if you have high or low levels of vitamin D, calcium or any other minerals
- if you have kidney problems
- if you have heart problems and the doctor recommended to limit your daily fluid intake

Cases of serious, sometimes fatal allergic reaction have been reported in patients treated with intravenous ibandronic acid.
If you experience one of the following symptoms, such as shortness of breath/difficulty breathing, tight feeling in throat, swelling of tongue, dizziness, feeling of loss of consciousness, redness or swelling of face, body rash, nausea and vomiting, you should immediately alert your doctor or nurse (see section 4).

**Children and adolescents**
Iasibon should not be used in children and adolescents below the age of 18 years.

**Other medicines and Iasibon**
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This is because Iasibon can affect the way some other medicines work. Also, some other medicines can affect the way Iasibon works.

**In particular, tell your doctor or pharmacist** if you are receiving a type of antibiotic injection called 'aminoglycoside' such as gentamicin. This is because aminoglycosides and Iasibon can both lower the amount of calcium in your blood.

**Pregnancy and breast-feeding**
Do not receive Iasibon if you are pregnant, planning to get pregnant or if you are breast-feeding. Ask your doctor or pharmacist for advice before taking this medicine.

**Driving and using machines**

You can drive and use machines as it's expected that Iasibon has no or negligible effect on your ability to drive and use machines. Talk to your doctor first if you want to drive, use machines or tools.

**Iasibon contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially "sodium-free".**

## 3. How to receive Iasibon

**Receiving this medicine**
- Iasibon is normally given by a doctor or other medical staff who have experience with the treatment of cancer.
- it is given as an infusion into your vein

Your doctor may do regular blood tests while you are receiving Iasibon. This is to check that you are being given the right amount of this medicine.

**How much to receive**
Your doctor will work out how much Iasibon you will be given depending on your illness.

If you have breast cancer that has spread to your bones, then the recommended dose is 6 ampoules (6 mg) every 3-4 weeks, as an infusion in your vein over at least 15 minutes.

If you have a raised calcium level in your blood due to a tumour then the recommended dose is a single administration of 2 ampoules (2 mg) or 4 ampoules (4 mg), depending on the severity of your illness. The medicine should be administered as an infusion in your vein over two hours. A repeated dose may be considered in case of insufficient response or if your illness reappears.

Your doctor may adjust your dose and duration of intravenous infusion if you have kidney problems.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

## 4. Possible side effects

Like all medicines, this medicine can cause side effects although not everybody gets them.

**Talk to a nurse or a doctor straight away if you notice any of the following serious side effects - you may need urgent medical treatment:**

**Rare** (may affect up to 1 in 1 000 people)
- persistent eye pain and inflammation
- new pain, weakness or discomfort in your thigh, hip or groin. You may have early signs of a possible unusual fracture of the thigh bone.

**Very rare** (may affect up to 1 in 10 000 people)
- pain or sore in your mouth or jaw. You may have early signs of severe jaw problems (necrosis (dead bone tissue) in the jaw bone.
- itching, swelling of your face, lips, tongue and throat, with difficulty breathing. You may be having a serious, potentially life threatening allergic reaction (see section 2).
- severe adverse skin reactions
- ear pain, discharge from the ear, and/or an ear infection. These could be signs of bone damage in the ear.

Not known (frequency cannot be estimated from the available data)
- asthma attack

**Other possible side effects**

**Common** (may affect up to 1 in 10 people)
- rise in body temperature.
- flu-like symptoms, including fever, shaking and shivering, feeling of discomfort, fatigue, bone pain and aching muscles and joints. These symptoms usually disappear within a couple of hours or days. Talk to a nurse or doctor if any effects become troublesome or last more than a couple of days
- stomach and tummy pain, indigestion, being sick vomiting or having diarrhoea (loose bowels)
- low calcium or phosphate levels in your blood
- changes in blood test results such as Gamma GT or creatinine
- a heart rhythm problem called 'bundle branch block'
- pain in your bone or muscles
- headache, feeling dizzy or feeling weak
- feeling thirsty, sore throat, changes in taste
- swollen legs or feet
- aching joints, arthritis, or other joint problems
- problems with your parathyroid gland
- bruising
- infections
- a problem with your eyes called 'cataracts'
- skin problems
- tooth problems.

**Uncommon** (may affect less than 1 in 100 people)
- shaking or shivering
- your body temperature getting too low ('hypothermia')
- a condition affecting the blood vessels in your brain called 'cerebrovascular disorder' (stroke or brain bleeding)
- heart and circulatory problems (including palpitations, heart attack, hypertension (high blood pressure) and varicose veins)
- changes in your blood cells ('anaemia')
- a high level of alkaline phosphatase in your blood
- fluid build up and swelling ('lymphoedema')
- fluid in your lungs
- stomach problems such as 'gastroenteritis' or 'gastritis'
- gallstones
- being unable to pass water (urine), cystitis (bladder inflammation)
- migraine
- pain in your nerves, damaged nerve root
- deafness
- increased sensitivity of sound, taste or touch or changes in smell
- difficulty swallowing
- mouth ulcers, swollen lips ('cheilitis'), oral thrush
- itching or tingling skin around your mouth
- pelvic pain, discharge, itching or pain in the vagina
- a skin growth called a 'benign skin neoplasm'
- memory loss
- sleep problems, feeling anxious, emotional instability, or mood swings
- skin rash
- hair loss
- injury or pain at the injection site
- weight loss
- kidney cyst (fluid-filled sac in the kidney)

**Reporting of side effects**
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

## 5. How to store Iasibon

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the folding box and on the label after EXP. The expiry date refers to the last day of that month.
- After dilution the infusion solution is stable for 24 hours at 2-8 °C (in a refrigerator).
- Do not use this medicine if you notice that the solution is not clear or contains particles.

## 6. Content of the pack and other information

**What Iasibon contains**
- The active substance is ibandronic acid. One ampoule with 1 mL of a concentrate for solution for infusion contains 1 mg ibandronic acid (as sodium monohydrate)
- The other ingredients are sodium chloride, glacial acetic acid, sodium acetate trihydrate and water for injections

**What Iasibon looks like and contents of the pack**
Iasibon is a colourless, clear solution. Iasibon 1 mg is supplied as pack containing 1 ampoule (2 mL type I glass ampoule).

**Marketing Authorisation Holder and Manufacturer**

**Marketing Authorisation Holder**
Pharmathen S.A.
Dervenakion 6
Pallini 15351
Attiki
Greece

**Manufacturer**
Pharmathen S.A.
Dervenakion 6
Pallini 15351
Attiki
Greece

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

**België/Belgique/Belgien**
Pharmathen S.A.
Tél/Tel: +30 210 66 04 300

**България**
Alvogen Pharma Bulgaria Ltd
Тел.: + 359 2 441 7136

**Lietuva**
Pharmathen S.A.
Tel: +30 210 66 04 300

**Luxembourg/Luxemburg**
Pharmathen S.A.
Tél/Tel: +30 210 66 04 300

**Česká republika**
Pharmathen S.A.
Tel: +30 210 66 04 300

**Danmark**
Pharmathen S.A.
Tlf: +30 210 66 04 300

**Deutschland**
Pharmathen S.A.
Tel: +30 210 66 04 300

**Eesti (Estonia)**
Pharmathen S.A.
Tel: +30 210 66 04 300

**Ελλάδα**
INNOVIS PHARMA AEBE
Τηλ: +30 210 6664805-806

**España**
Pharmathen S.A.
Tel: +30 210 66 04 300

**France**
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**Hrvatska**
Pharmathen S.A.
Tel: +30 210 66 04 300

**Ireland**
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**Ísland**
Alvogen ehf.
Sími: +354 522 2900

**Italia**
Pharmathen S.A.
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**Κύπρος**
The Star Medicines Importers Co. Ltd
Τηλ: +357 25371056

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**Malta**
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**Nederland**
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**Norge**
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Tel: +30 210 66 04 300

**Polska**
Pharmathen S.A.
Tel.: +30 210 66 04 300

**Portugal**
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Tel : +30 210 66 04 300

**România**
Labormed Pharma Trading SRL
Tel: +(40) 21 304 7597

**Slovenija**
Pharmathen S.A.
Tel: +30 210 66 04 300

**Slovenská republika**
Pharmathen S.A.
Tel: +30 210 66 04 300

**Suomi/Finland**
Pharmathen S.A.
Puh/Tel: +30 210 66 04 300

**Sverige**
Pharmathen S.A.
Tel: +30 210 66 04 300

**United Kingdom (Northern Ireland)**
Pharmathen S.A.
Tel: +30 210 66 04 300

**This leaflet was last revised in**

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/.

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**The following information is intended for healthcare professionals only**

**Dose: 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 at least 15 minutes.

*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 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 Volume [1] and Time [2] |
|---|---|---|
| ≥ 50 CLcr < 80 | 6 mg (6 mL of concentrate for solution for infusion) | 100 mL over 15 minutes |
| ≥ 30 CLcr < 50 | 4 mg (4 mL of concentrate for solution for infusion) | 500 mL over 1 hour |
| < 30 | 2 mg (2 mL of concentrate for solution for infusion) | 500 mL over 1 hour |

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

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

**Dose: Treatment of tumour-induced hypercalcaemia**
Iasibon is usually administered in a hospital setting. The dose is determined by the doctor considering the following factors.

Prior to treatment with Iasibon the patient should be adequately rehydrated with 9 mg/mL (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* ≥ 3 mmol/L or ≥ 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:

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

**or**

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

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

In most cases a raised serum calcium level can be reduced to the normal range within 7 days. The median time to relapse (re-increase of 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**
Iasibon concentrate for solution for infusion should be administered as an intravenous infusion.

For this purpose, the contents of the vial are to be used as follows:

- Prevention of Skeletal Events in patients with breast cancer and bone metastases - added to 100 mL isotonic sodium chloride solution or 100 mL 5 % dextrose solution and infused over at least 15 minutes. See also dosage section above for patients with renal impairment
- Treatment of tumour-induced hypercalcaemia - added to 500 mL isotonic sodium chloride solution or 500 mL 5 % dextrose solution and infused over 2 hours

Note:
In order to avoid potential incompatibilities Iasibon concentrate for solution for infusion should only be diluted with isotonic sodium chloride solution or 5% dextrose solution. Calcium containing solutions should not be mixed with Iasibon 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 "How to store Iasibon").

Iasibon concentrate for solution for infusion should be administered as an intravenous infusion.
Care must be taken not to administer Iasibon concentrate for solution for infusion via intra-arterial or paravenous administration, as this could lead to tissue damage.

**Frequency of administration**
For treatment of tumour induced hypercalcaemia, Iasibon 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 Iasibon infusion is repeated at 3-4 weeks 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, Iasibon infusion should be administered every 3-4 weeks. In clinical trials, therapy has continued for up to 96 weeks.

**Overdose**
Up to now there is no experience of acute poisoning with Iasibon 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 intravenous administration of calcium gluconate.

**Package leaflet: Information for the patient**

**Iasibon 2 mg concentrate for solution for infusion**
ibandronic acid

**Read all of this leaflet carefully before you start using this medicine because it contains important information for you.**
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

**What is in this leaflet**:


## 1. What Iasibon is and what it is used for

Iasibon contains the active substance ibandronic acid. This belongs to a group of medicines called bisphosphonates.

Iasibon is used in adults and prescribed to you if you have breast cancer that has spread to your bones (called 'bone metastases').
- It helps to prevent your bones from breaking (fractures)
- It helps to prevent other bone problems that may need surgery or radiotherapy

Iasibon can also be prescribed if you have a raised calcium level in your blood due to a tumour.

Iasibon works by reducing the amount of calcium that is lost from your bones. This helps to stop your bones from getting weaker.

## 2. What you need to know before you receive Iasibon

**Do not receive Iasibon**
- if you are allergic to ibandronic acid or any of the other ingredients of this medicine that are listed in section 6
- if you have, or have ever had low levels of calcium in your blood

Do not receive this medicine if any of the above apply to you. If you are not sure, talk to your doctor or pharmacist before having Iasibon.

**Warnings and precautions**
A side effect called osteonecrosis of the jaw (ONJ) (bone damage in the jaw) has been reported very rarely in the post marketing setting in patients receiving ibandronate for cancer-related conditions. ONJ can also occur after stopping treatment.

It is important to try and prevent ONJ developing as it is a painful condition that can be difficult to treat. In order to reduce the risk of developing osteonecrosis of the jaw, there are some precautions you should take.

Before receiving treatment, tell your doctor/nurse (health care professional) if:

- you have any problems with your mouth or teeth such as poor dental health, gum disease, or a planned tooth extraction
- you don't receive routine dental care or have not had a dental check up for a long time
- you are a smoker (as this may increase the risk of dental problems)
- you have previously been treated with a bisphosphonate (used to treat or prevent bone disorders)
- you are taking medicines called corticosteroids (such as prednisolone or dexamethasone)
- you have cancer.

Your doctor may ask you to undergo a dental examination before starting treatment with Iasibon.

While being treated, you should maintain good oral hygiene (including regular teeth brushing) and receive routine dental check-ups. If you wear dentures you should make sure these fit properly. If you are under dental treatment or will undergo dental surgery (e.g. tooth extractions), inform your doctor about your dental treatment and tell your dentist that you are being treated with Iasibon.

Contact your doctor and dentist immediately if you experience any problems with your mouth or teeth such as loose teeth, pain or swelling, non-healing of sores or discharge, as these could be signs of osteonecrosis of the jaw.

Atypical fractures of the long bones, such as in the forearm bone (ulna) and the shinbone (tibia), have also been reported in patients receiving long-term treatment with Ibandronate. These fractures occur after minimal, or no trauma and some patients experience pain in the area of the fracture prior to presenting with a completed fracture.

Talk to your doctor, pharmacist or nurse before receiving Iasibon:
- if you are allergic to any other bisphosphonates
- if you have high or low levels of vitamin D, calcium or any other minerals
- if you have kidney problems.
- if you have heart problems and the doctor recommended to limit your daily fluid intake

Cases of serious, sometimes fatal allergic reaction have been reported in patients treated with intravenous ibandronic acid.
If you experience one of the following symptoms, such as shortness of breath/difficulty breathing, tight feeling in throat, swelling of tongue, dizziness, feeling of loss of consciousness, redness or swelling of face, body rash, nausea and vomiting, you should immediately alert your doctor or nurse (see section 4).

**Children and adolescents**
Iasibon should not be used in children and adolescents below the age of 18 years.

**Other medicines and Iasibon**
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This is because Iasibon can affect the way some other medicines work. Also, some other medicines can affect the way Iasibon works.

**In particular, tell your doctor or pharmacist** if you are receiving a type of antibiotic injection called 'aminoglycoside' such as gentamicin. This is because aminoglycosides and Iasibon can both lower the amount of calcium in your blood.

**Pregnancy and breast-feeding**
Do not receive Iasibon if you are pregnant, planning to get pregnant or if you are breast-feeding. Ask your doctor or pharmacist for advice before taking this medicine.

**Driving and using machines**
You can drive and use machines as it's expected that Iasibon has no or negligible effect on your ability to drive and use machines. Talk to your doctor first if you want to drive, use machines or tools.

**Iasibon contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially "sodium-free".**

## 3. How to receive Iasibon

**Receiving this medicine**
- Iasibon is normally given by a doctor or other medical staff who have experience with the treatment of cancer.
- it is given as an infusion into your vein

Your doctor may do regular blood tests while you are receiving Iasibon. This is to check that you are being given the right amount of this medicine.

**How much to receive**
Your doctor will work out how much Iasibon you will be given depending on your illness.

If you have breast cancer that has spread to your bones, then the recommended dose is 3 ampoules (6 mg) every 3-4 weeks, as an infusion in your vein over at least 15 minutes.

If you have a raised calcium level in your blood due to a tumour then the recommended dose is a single administration of 1 ampoule (2 mg) or 2 ampoules (4 mg), depending on the severity of your illness. The medicine should be administered as an infusion in your vein, over two hours. A repeated dose may be considered in case of insufficient response or if your illness reappears.

Your doctor may adjust your dose and duration of intravenous infusion if you have kidney problems.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

## 4. Possible side effects

Like all medicines, this medicine can cause side effects although not everybody gets them.

**Talk to a nurse or a doctor straight away if you notice any of the following serious side effects - you may need urgent medical treatment:**

**Rare** (may affect up to 1 in 1 000 people)
- persistent eye pain and inflammation
- new pain, weakness or discomfort in your thigh, hip or groin. You may have early signs of a possible unusual fracture of the thigh bone.

**Very rare** (may affect up to 1 in 10 000 people)
- pain or sore in your mouth or jaw. You may have early signs of severe jaw problems (necrosis (dead bone tissue) in the jaw bone).
- itching, swelling of your face, lips, tongue and throat, with difficulty breathing. You may be having a serious, potentially life threatening allergic reaction (see section 2)
- severe adverse skin reactions
- ear pain, discharge from the ear, and/or an ear infection. These could be signs of bone damage in the ear.

**Not known** (frequency cannot be estimated from the available data)
- asthma attack

**Other possible side effects**

**Common** (may affect up to 1 in 10 people)

- flu-like symptoms, including fever, shaking and shivering, feeling of discomfort, fatigue, bone pain and aching muscles and joints. These symptoms usually disappear within a couple of hours or days. Talk to a nurse or doctor if any effects become troublesome or last more than a couple of days
- rise in body temperature.
- stomach and tummy pain, indigestion, being sick vomiting or having diarrhoea (loose bowels)
- low calcium or phosphate levels in your blood
- changes in blood test results such as Gamma GT or creatinine
- a heart rhythm problem called 'bundle branch block'
- pain in your bone or muscles
- headache, feeling dizzy or feeling weak
- feeling thirsty, sore throat, changes in taste
- swollen legs or feet
- aching joints, arthritis, or other joint problems
- problems with your parathyroid gland
- bruising
- infections
- a problem with your eyes called 'cataracts'
- skin problems
- tooth problems.

**Uncommon** (may affect less than 1 in 100 people)

- shaking or shivering
- your body temperature getting too low ('hypothermia')
- a condition affecting the blood vessels in your brain called 'cerebrovascular disorder' (stroke or brain bleeding)
- heart and circulatory problems (including palpitations, heart attack, hypertension (high blood pressure) and varicose veins)
- changes in your blood cells ('anaemia')
- a high level of alkaline phosphatase in your blood
- fluid build up and swelling ('lymphoedema')
- fluid in your lungs
- stomach problems such as 'gastroenteritis' or 'gastritis'
- gallstones
- being unable to pass water (urine), cystitis (bladder inflammation)
- migraine
- pain in your nerves, damaged nerve root
- deafness
- increased sensitivity of sound, taste or touch or changes in smell
- difficulty swallowing
- mouth ulcers, swollen lips ('cheilitis'), oral thrush
- itching or tingling skin around your mouth
- pelvic pain, discharge, itching or pain in the vagina
- a skin growth called a 'benign skin neoplasm'
- memory loss
- sleep problems, feeling anxious, emotional instability, or mood swings
- skin rash
- hair loss
- injury or pain at the injection site
- weight loss
- kidney cyst (fluid-filled sac in the kidney)

**Reporting of side effects**
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

## 5. How to store Iasibon

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the folding box and on the label after EXP. The expiry date refers to the last day of that month.
- After dilution the infusion solution is stable for 24 hours at 2-8 °C (in a refrigerator).
- Do not use this medicine if you notice that the solution is not clear or contains particles.

## 6. Content of the pack and other information

**What Iasibon contains**
- The active substance is ibandronic acid. One ampoule with 2 mL of a concentrate for solution for infusion contains 2 mg ibandronic acid (as sodium monohydrate)
- The other ingredients are sodium chloride, glacial acetic acid, sodium acetate trihydrate and water for injections

**What Iasibon looks like and contents of the pack**
Iasibon is a colourless, clear solution. Iasibon 2mg is supplied as pack containing 1 ampoule (4 mL type I glass ampoule).

**Marketing Authorisation Holder and Manufacturer**

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**This leaflet was last revised in {MM/YYYY}**

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/

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**The following information is intended for healthcare professionals only**

**Dose: 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 at least 15 minutes.

*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 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 Volume [1] and Time [2] |
|---|---|---|
| ≥ 50 CLcr < 80 | 6 mg (6 mL of concentrate for solution for infusion) | 100 mL over 15 minutes |
| ≥ 30 CLcr < 50 | 4 mg (4 mL of concentrate for solution for infusion) | 500 mL over 1 hour |
| < 30 | 2 mg (2 mL of concentrate for solution for infusion) | 500 mL over 1 hour |

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

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

**Dose: Treatment of tumour-induced hypercalcaemia**
Iasibon is usually administered in a hospital setting. The dose is determined by the doctor considering the following factors.

Prior to treatment with Iasibon the patient should be adequately rehydrated with 9 mg/mL (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* ≥ 3 mmol/L or ≥ 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:

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

**or**

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

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

In most cases a raised serum calcium level can be reduced to the normal range within 7 days. The median time to relapse (re-increase of 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**
Iasibon concentrate for solution for infusion should be administered as an intravenous infusion.

For this purpose, the contents of the vial are to be used as follows:

- Prevention of Skeletal Events in patients with breast cancer and bone metastases - added to 100 mL isotonic sodium chloride solution or 100 mL 5 % dextrose solution and infused over at least 15 minutes. See also dosage section above for patients with renal impairment
- Treatment of tumour-induced hypercalcaemia - added to 500 mL isotonic sodium chloride solution or 500 mL 5 % dextrose solution and infused over 2 hours

Note:
In order to avoid potential incompatibilities Iasibon concentrate for solution for infusion should only be diluted with isotonic sodium chloride solution or 5% dextrose solution. Calcium containing solutions should not be mixed with Iasibon 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 "How to store Iasibon").

Iasibon concentrate for solution for infusion should be administered as an intravenous infusion.
Care must be taken not to administer Iasibon concentrate for solution for infusion via intra-arterial or paravenous administration, as this could lead to tissue damage.

**Frequency of administration**
For treatment of tumour induced hypercalcaemia, Iasibon 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 Iasibon infusion is repeated at 3-4 weeks 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, Iasibon infusion should be administered every 3-4 weeks. In clinical trials, therapy has continued for up to 96 weeks.

**Overdose**
Up to now there is no experience of acute poisoning with Iasibon 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 intravenous administration of calcium gluconate.

**Package leaflet: Information for the patient**

**Iasibon 6 mg concentrate for solution for infusion**
ibandronic acid

**Read all of this leaflet carefully before you start using this medicine because it contains important information for you.**
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

**What is in this leaflet**:


## 1. What Iasibon is and what it is used for

Iasibon contains the active substance ibandronic acid. This belongs to a group of medicines called bisphosphonates.

Iasibon is used in adults and prescribed to you if you have breast cancer that has spread to your bones (called 'bone metastases')

- It helps to prevent your bones from breaking (fractures)
- It helps to prevent other bone problems that may need surgery or radiotherapy

Iasibon can also be prescribed if you have a raised calcium level in your blood due to a tumour.

Iasibon works by reducing the amount of calcium that is lost from your bones. This helps to stop your bones from getting weaker.

## 2. What you need to know before you receive Iasibon

**Do not receive Iasibon**
- if you are allergic to ibandronic acid or any of the other ingredients of this medicine that are listed in section 6
- if you have, or have ever had low levels of calcium in your blood.

Do not receive this medicine if any of the above apply to you. If you are not sure, talk to your doctor or pharmacist before having Iasibon.

**Warnings and precautions**

A side effect called osteonecrosis of the jaw (ONJ) (bone damage in the jaw) has been reported very rarely in the post marketing setting in patients receiving ibandronate for cancer-related conditions. ONJ can also occur after stopping treatment.

It is important to try and prevent ONJ developing as it is a painful condition that can be difficult to treat. In order to reduce the risk of developing osteonecrosis of the jaw, there are some precautions you should take.

Before receiving treatment, tell your doctor/nurse (health care professional) if:
- you have any problems with your mouth or teeth such as poor dental health, gum disease, or a planned tooth extraction
- you don't receive routine dental care or have not had a dental check up for a long time
- you are a smoker (as this may increase the risk of dental problems)
- you have previously been treated with a bisphosphonate (used to treat or prevent bone disorders)
- you are taking medicines called corticosteroids (such as prednisolone or dexamethasone)
- you have cancer.

Your doctor may ask you to undergo a dental examination before starting treatment with Iasibon.

While being treated, you should maintain good oral hygiene (including regular teeth brushing) and receive routine dental check-ups. If you wear dentures you should make sure these fit properly. If you are under dental treatment or will undergo dental surgery (e.g. tooth extractions), inform your doctor about your dental treatment and tell your dentist that you are being treated with Iasibon.

Contact your doctor and dentist immediately if you experience any problems with your mouth or teeth such as loose teeth, pain or swelling, non-healing of sores or discharge, as these could be signs of osteonecrosis of the jaw.

Atypical fractures of the long bones, such as in the forearm bone (ulna) and the shinbone (tibia), have also been reported in patients receiving long-term treatment with Ibandronate. These fractures occur after minimal, or no trauma and some patients experience pain in the area of the fracture prior to presenting with a completed fracture.

Talk to your doctor, pharmacist or nurse before receiving Iasibon:
- if you are allergic to any other bisphosphonates
- if you have high or low levels of vitamin D, calcium or any other minerals
- if you have kidney problems.
- if you have heart problems and the doctor recommended to limit your daily fluid intake

Cases of serious, sometimes fatal allergic reaction have been reported in patients treated with intravenous ibandronic acid.

If you experience one of the following symptoms, such as shortness of breath/difficulty breathing, tight feeling in throat, swelling of tongue, dizziness, feeling of loss of consciousness, redness or swelling of face, body rash, nausea and vomiting, you should immediately alert your doctor or nurse (see section 4).

**Children and adolescents**
Iasibon should not be used in children and adolescents below the age of 18 years.

**Other medicines and Iasibon**
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This is because Iasibon can affect the way some other medicines work. Also, some other medicines can affect the way Iasibon works.

**In particular, tell your doctor or pharmacist** if you are receiving a type of antibiotic injection called 'aminoglycoside' such as gentamicin. This is because aminoglycosides and Iasibon can both lower the amount of calcium in your blood.

**Pregnancy and breast-feeding**
Do not receive Iasibon if you are pregnant, planning to get pregnant or if you are breast-feeding. Ask your doctor or pharmacist for advice before taking this medicine.

**Driving and using machines:**
You can drive and use machines as it's expected that Iasibon has no or negligible effect on your ability to drive and use machines. Talk to your doctor first if you want to drive, use machines or tools.

**Iasibon contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially "sodium-free".**

## 3. How to receive Iasibon

**Receiving this medicine**
- Iasibon is normally given by a doctor or other medical staff who have experience with the treatment of cancer.
- It is given as an infusion into your vein

Your doctor may do regular blood tests while you are receiving Iasibon. This is to check that you are being given the right amount of this medicine.

**How much to receive**
Your doctor will work out how much Iasibon you will be given depending on your illness.
If you have breast cancer that has spread to your bones, then the recommended dose is 1 vial (6 mg) every 3-4 weeks, as an infusion in your vein over at least 15 minutes.

If you have a raised calcium level in your blood due to a tumour, then the recommended dose is a single administration of 2 mg or 4 mg, depending on the severity of your illness. The medicine should be administered as an infusion in your vein over two hours. A repeated dose may be considered in case of insufficient response or if your illness reappears.
Your doctor may adjust your dose and duration of intravenous infusion if you have kidney problems.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

## 4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

**Talk to a nurse or a doctor straight away if you notice any of the following serious side effects - you may need urgent medical treatment:**

**Rare** (may affect up to 1 in 1 000 people)
- persistent eye pain and inflammation
- new pain, weakness or discomfort in your thigh, hip or groin. You may have early signs of a possible unusual fracture of the thigh bone

**Very rare** (may affect up to 1 in 10 000 people)
- pain or sore in your mouth or jaw. You may have early signs of severe jaw problems (necrosis (dead bone tissue) in the jaw bone).
- itching, swelling of your face, lips, tongue and throat, with difficulty breathing. You may be having a serious, potentially life threatening allergic reaction (see section 2)

- severe adverse skin reactions
- ear pain, discharge from the ear, and/or an ear infection. These could be signs of bone damage in the ear.

**Not known** (frequency cannot be estimated from the available data)
- asthma attack

**Other possible side effects**

**Common** (may affect up to 1 in 10 people)
- flu-like symptoms, including fever, shaking and shivering, feeling of discomfort, fatigue, bone pain and aching muscles and joints. These symptoms usually disappear within a couple of hours or days. Talk to a nurse or doctor if any effects become troublesome or last more than a couple of days
- rise in body temperature.
- stomach and tummy pain, indigestion, being sick vomiting or having diarrhoea (loose bowels)
- low calcium or phosphate levels in your blood
- changes in blood test results such as Gamma GT or creatinine
- a heart rhythm problem called 'bundle branch block'
- pain in your bone or muscles
- headache, feeling dizzy or feeling weak
- feeling thirsty, sore throat, changes in taste
- swollen legs or feet
- aching joints, arthritis, or other joint problems
- problems with your parathyroid gland
- bruising
- infections
- a problem with your eyes called 'cataracts'
- skin problems
- tooth problems.

**Uncommon** (may affect less than 1 in 100 people)
- shaking or shivering
- your body temperature getting too low ('hypothermia')
- a condition affecting the blood vessels in your brain called 'cerebrovascular disorder' (stroke or brain bleeding)
- heart and circulatory problems (including palpitations, heart attack, hypertension , high blood pressure and varicose veins)
- changes in your blood cells ('anaemia')
- a high level of alkaline phosphatase in your blood
- fluid build up and swelling ('lymphoedema')
- fluid in your lungs
- stomach problems such as 'gastroenteritis' or 'gastritis'
- gallstones
- being unable to pass water (urine), cystitis (bladder inflammation)
- migraine
- pain in your nerves, damaged nerve root
- deafness
- increased sensitivity of sound, taste or touch or changes in smell
- difficulty swallowing
- mouth ulcers, swollen lips ('cheilitis'), oral thrush
- itching or tingling skin around your mouth
- pelvic pain, discharge, itching or pain in the vagina
- a skin growth called a 'benign skin neoplasm'

- memory loss
- sleep problems, feeling anxious, emotional instability, or mood swings
- skin rash
- hair loss
- injury or pain at the injection site
- weight loss
- kidney cyst (fluid-filled sac in the kidney).

**Reporting of side effects**
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

## 5. How to store Iasibon

- Keep this medicine out of the sight and reach of children
- Do not use this medicine after the expiry date which is stated on the folding box and on the label after EXP. The expiry date refers to the last day of that month.
- After dilution the infusion solution is stable for 24 hours at 2-8 °C (in a refrigerator)
- Do not use this medicine if you notice that the solution is not clear or contains particles

## 6. Content of the pack and other information

**What Iasibon contains**
- The active substance is ibandronic acid. One vial with 6 mL of a concentrate for solution for infusion contains 6 mg ibandronic acid (as sodium monohydrate).
- The other ingredients are sodium chloride, glacial acetic acid, sodium acetate trihydrate and water for injections.

**What Iasibon looks like and contents of the pack**
Iasibon is a colourless, clear solution. Iasibon 6mg is supplied as packs containing 1, 5 and 10 vials (9 mL type I glass vial with a bromobutyl rubber stopper).
Not all pack sizes may be marketed.

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**This leaflet was last revised in {**MM/YYYY**}**

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/

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**The following information is intended for healthcare professionals only**

**Dose: 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 at least 15 minutes.

*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 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 Volume [1] and Time [2] |
|---|---|---|
| ≥ 50 CLcr < 80 | 6 mg (6 mL of concentrate for solution for infusion) | 100 mL over 15 minutes |
| ≥ 30 CLcr < 50 | 4 mg (4 mL of concentrate for solution for infusion) | 500 mL over 1 hour |
| < 30 | 2 mg (2 mL of concentrate for solution for infusion) | 500 mL over 1 hour |

[1] 0.9 % sodium chloride solution or 5 % glucose solution
[2] Administration every 3 to 4 weeks
A 15 minutes infusion time has not been studied in cancer patients with CLCr < 50 mL/min.

**Dose: Treatment of tumour-induced hypercalcaemia**
Iasibon is usually administered in a hospital setting. The dose is determined by the doctor considering the following factors.

Prior to treatment with Iasibon the patient should be adequately rehydrated with 9 mg/mL (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* ≥ 3 mmol/L or ≥ 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:

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

**or**

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

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

In most cases a raised serum calcium level can be reduced to the normal range within 7 days. The median time to relapse (re-increase of 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**
Iasibon concentrate for solution for infusion should be administered as an intravenous infusion.

For this purpose, the contents of the vial are to be used as follows:

- Prevention of Skeletal Events in patients with breast cancer and bone metastases - added to 100 mL isotonic sodium chloride solution or 100 mL 5 % dextrose solution and infused over at least 15 minutes. See also dosage section above for patients with renal impairment
- Treatment of tumour-induced hypercalcaemia - added to 500 mL isotonic sodium chloride solution or 500 mL 5% dextrose solution and infused over 2 hours

Note:
In order to avoid potential incompatibilities Iasibon concentrate for solution for infusion should only be diluted with isotonic sodium chloride solution or 5 % dextrose solution. Calcium containing solutions should not be mixed with Iasibon 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 'How to store Iasibon').

Iasibon concentrate for solution for infusion should be administered as an intravenous infusion.
Care must be taken not to administer Iasibon concentrate for solution for infusion via intra-arterial or paravenous administration, as this could lead to tissue damage.

**Frequency of administration**
For treatment of tumour induced hypercalcaemia, Iasibon 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 Iasibon infusion is repeated at 3 - 4 weeks 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, Iasibon infusion should be administered every 3-4 weeks. In clinical trials, therapy has continued for up to 96 weeks.

**Overdose**
Up to now there is no experience of acute poisoning with Iasibon 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 intravenous administration of calcium gluconate.

**Package leaflet: Information for the patient**

**Iasibon 50 mg film-coated tablets**
ibandronic acid

**Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.**
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4

**What is in this leaflet**:


## 1. What Iasibon is and what it is used for

Iasibon contains the active substance ibandronic acid. This belongs to a group of medicines called bisphosphonates.

Iasibon is used in adults and prescribed to you if you have breast cancer that has spread to your bones (called 'bone metastases').

- It helps to prevent your bones from breaking (fractures).
- It also helps to prevent other bone problems that may need surgery or radiotherapy.

Ibandronate works by reducing the amount of calcium that is lost from your bones. This helps to stop your bones from getting weaker.

## 2. What you need to know before you take Iasibon

**Do not take Iasibon**
- if you are allergic to ibandronic acid or any of the other ingredients of this medicine that are listed in section 6
- if you have problems with your food pipe /gullet (oesophagus) such as narrowing or difficulty swallowing
- if you cannot stand or sit upright for at least one hour (60 minutes) at a time
- if you have or ever had low calcium in your blood.

Do not take this medicine if any of the above apply to you. If you are not sure, talk to your doctor or pharmacist before taking Iasibon.

**Warnings and precautions**
A side effect called osteonecrosis of the jaw (ONJ) (bone damage in the jaw) has been reported very rarely in the post marketing setting in patients receiving ibandronate for cancer-related conditions. ONJ can also occur after stopping treatment.

It is important to try and prevent ONJ developing as it is a painful condition that can be difficult to treat. In order to reduce the risk of developing osteonecrosis of the jaw, there are some precautions you should take.

Before receiving treatment, tell your doctor/nurse (health care professional) if:
- you have any problems with your mouth or teeth such as poor dental health, gum disease, or a planned tooth extraction
- you don't receive routine dental care or have not had a dental check up for a long time
- you are a smoker (as this may increase the risk of dental problems)
- you have previously been treated with a bisphosphonate (used to treat or prevent bone disorders)
- you are taking medicines called corticosteroids (such as prednisolone or dexamethasone)
- you have cancer.

Your doctor may ask you to undergo a dental examination before starting treatment with Iasibon.

While being treated, you should maintain good oral hygiene (including regular teeth brushing) and receive routine dental check-ups. If you wear dentures you should make sure these fit properly. If you are under dental treatment or will undergo dental surgery (e.g. tooth extractions), inform your doctor about your dental treatment and tell your dentist that you are being treated with Iasibon.

Contact your doctor and dentist immediately if you experience any problems with your mouth or teeth such as loose teeth, pain or swelling, non-healing of sores or discharge, as these could be signs of osteonecrosis of the jaw.

Atypical fractures of the long bones, such as in the forearm bone (ulna) and the shinbone (tibia), have also been reported in patients receiving long-term treatment with Ibandronate. These fractures occur after minimal, or no trauma and some patients experience pain in the area of the fracture prior to presenting with a completed fracture.

Talk to your doctor or pharmacist before taking Iasibon:
- if you are allergic to any other bisphosphonates
- if you have any swallowing or digestion problems
- if you have high or low blood levels of vitamin D or any other minerals
- if you have kidney problems

Irritation, inflammation or ulceration of the gullet/food pipe (oesophagus) often with symptoms of severe pain in the chest, severe pain after swallowing food and/or drink, severe nausea, or vomiting may occur, especially if you do not drink a full glass of water and/or if you lie down within an hour of taking Iasibon. If you develop these symptoms, stop taking Iasibon and tell your doctor straight away (see sections 3 and 4).

**Children and adolescents**
Iasibon should not be used in children and adolescents below the age of 18 years.

**Other medicines and Iasibon**
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This is because Iasibon can affect the way some other medicines work. Also, some other medicines can affect the way Iasibon works.

**In particular, tell your doctor or pharmacist** if you are taking any of the following medicines:
- supplements containing calcium, magnesium, iron or aluminium
- acetylsalicylic acid and non-steroidal anti-inflammatory medicines called "NSAIDs", such as, ibuprofen or naproxen. This is because NSAIDs and Iasibon can both irritate your stomach and gut

- a type of antibiotic injection called “aminoglycoside” such as gentamicin. This is because aminoglycosides and Iasibon can both lower the amount of calcium in your blood

Taking medicines that reduce stomach acid such as cimetidine and ranitidine, may slightly increase the effects of Iasibon.

**Iasibon with food and drink**
Do not take Iasibon with food or any other drinks except plain water as Iasibon is less effective if it is taken with food or drink (see section 3).

Take Iasibon at least 6 hours after you had last had anything to eat, drink or any other medicines or supplements (e.g. products containing calcium (milk), aluminium, magnesium and iron) except water. After taking your tablet, wait at least 30 minutes. Then you can have your first food and drink, and take any medicines or supplements (see section 3).

**Pregnancy and breast feeding**
Do not take Iasibon if you are pregnant, planning to get pregnant or if you are breast-feeding.
Ask your doctor or pharmacist for advice before taking this medicine.

**Driving and using machines**
You can drive and use machines as it’s expected that Iasibon has no or negligible effect on your ability to drive and use machines. Talk to your doctor first if you want to drive, use machines or tools.

**Iasibon contains lactose**.
If you have been told by your doctor that you cannot tolerate or digest some sugars, talk to your doctor before taking this medicine.

## 3. How to take Iasibon

Always take this medicine exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Take your tablet at least 6 hours after you had last had anything to eat, drink or any other medicines or supplements except water. Water with a high concentration of calcium should not be used. If there is concern regarding potentially high levels of calcium in the tap water (hard water), it is advised to use bottled water with a low mineral content.

Your doctor may do regular blood tests while you are taking Iasibon. This is to check that you are being given the right amount of medicine.

**Taking this medicine**
It is important that you take Iasibon at the right time and in the right way. This is because it can cause irritation, inflammation or ulcers in your food pipe/gullet (oesophagus).

You can help stop this happening by doing the following:
- Take your tablet as soon as you get up for the day before having your first food, drink, any medicine or supplements

- Take your tablet with a full glass of water only (about 200 mL). Do not take your tablet with any drink other than water

- Swallow the tablet whole. Do not chew, suck or crush the tablet. Do not let the tablet dissolve in your mouth

- After taking your tablet, wait at least 30 minutes. Then you can have your first food and drink and take any medicines or supplements

- Stay upright (sitting or standing) while taking your tablet and for the next hour (60 minutes). Otherwise, some of the medicine could leak back into your food pipe/gullet (oesophagus)

**How much to take**
The usual dose of Iasibon is one tablet each day. If you have moderate kidney problems, your doctor may reduce your dose to one tablet every other day. If you have severe kidney problems, your doctor may reduce your dose to one tablet each week.

**If you take more Iasibon than you should**
If you take too many tablets talk to a doctor or go to hospital straight away. Drink a full glass of milk before you go. Do not make yourself sick. Do not lie down.

**If you forget to take Iasibon**
Do not take a double dose to make up for a forgotten dose. If you are taking a tablet each day, skip the missed dose completely. Then carry on as usual the next day. If you are taking a tablet every other day or once a week, ask your doctor or pharmacist for advice.

**If you stop taking Iasibon**
Keep taking Iasibon for as long as your doctor tells you. This is because the medicine will only work if it is taken all the time.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

## 4. Possible side effects

Like all medicines, this medicine can cause side effects although not everybody gets them.

**Talk to a nurse or a doctor straight away if you notice any of the following serious side effects, you may need urgent medical treatment:**

**Common** (may affect up to 1 in 10 people):
- feeling sick, heartburn and discomfort in swallowing (inflammation of your gullet/ food pipe)

**Uncommon** (may affect less than 1 in 100 people):
- severe stomach pain. This could be a sign of an ulcer of the first section of the bowel (duodenum) that is bleeding, or that your stomach is inflamed (gastritis)

**Rare** (may affect up to 1 in 1 000 people)
- persistent eye pain and inflammation
- new pain, weakness or discomfort in your thigh, hip or groin. You may have early signs of a possible unusual fracture of the thigh bone

**Very rare** (may affect up to 1 in 10 000 people)
- pain or sore in your mouth or jaw. You may have early signs of severe jaw problems (necrosis (dead bone tissue) in the jaw bone)
- itching, swelling of your face, lips, tongue and throat, with difficulty breathing. You may be having a serious, potentially life threatening allergic reaction
- severe adverse skin reactions
- ear pain, discharge from the ear, and/or an ear infection. These could be signs of bone damage in the ear.

**Not known** (frequency cannot be estimated from the available data)
- asthma attack

**Other possible side effects**

**Common (**may affect up to 1 in 10 people):
- tummy pain, indigestion
- low calcium levels in your blood
- weakness

**Uncommon** (may affect less than 1 in 100 people):
- chest pain
- itching or tingling skin (paraesthesia)
- flu-like symptoms, feeling generally unwell or in pain
- dry mouth, strange taste in your mouth or difficulty swallowing
- anaemia (bloodlessness)
- high levels of urea or high levels of parathyroid hormone in your blood.

**Reporting of side effects**
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

## 5. How to store Iasibon

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the blister and carton after EXP. The expiry date refers to the last day of that month.
- Store in the original package in order to protect from moisture.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

## 6. Contents of the pack and other information

**What Iasibon contains**
- The active substance is ibandronic acid. Each film-coated tablet contains 50 mg of ibandronic acid (as sodium monohydrate)

The other ingredients are:
- tablet core: povidone, microcrystalline cellulose, crospovidone, maize starch pregelatinised, glycerol dibehenate, colloidal anhydrous silica.
- tablet coat: titanium dioxide (E 171), lactose monohydrate, hypromellose (E 464), macrogol 4 000

**What Iasibon looks like and contents of the pack**
The film-coated tablets are white, round biconvex tablets supplied in Polyamide/Al/PVC - Aluminum foil blister. They are available in packs of 3, 6, 9, 28 and 84 tablets.
Not all pack sizes may be marketed

**Marketing Authorisation Holder and Manufacturer**

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