Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ibandronic Acid 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 6.75 mg ibandronic acid, monosodium salt, monohydrate).

Excipients with known effect: Sodium (less than 1 mmol per dose).

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

Ibandronic Acid 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

Patients treated with Ibandronic Acid should be given the package leaflet and the patient reminder card.

Ibandronic Acid 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 Ibandronic Acid 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* ≥3 mmol/l or ≥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.

Ibandronic Acid 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 Ibandronic Acid 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% glucose 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% glucose solution and infused over 2 hours

For single use only. Only clear solution without particles should be used.
Ibandronic Acid concentrate for solution for infusion should be administered as an intravenous infusion.
Care must be taken not to administer Ibandronic Acid 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 Ibandronic Acid 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 IV ibandronic acid.
Appropriate medical support and monitoring measures should be readily available when Ibandronic Acid 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 ibandronic acid 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 Ibandronic Acid 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 Ibandronic Acid. While on treatment, invasive dental procedures should be performed only after careful consideration and be avoided in close proximity to Ibandronic Acid 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 Ibandronic Acid 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.

Patients with renal impairment
Clinical studies have not shown any evidence of deterioration in renal function with long term ibandronic acid 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 Ibandronic Acid (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
Ibandronic Acid is 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, Ibandronic Acid 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. Ibandronic Acid 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 Ibandronic Acid 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	Common	Uncommon	Rare	Very rare	Not known
Infections and infestations	Infection	Cystitis, vaginitis, oral candidiasis			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		Benign neoplasm of skin			
Blood and lymphatic system disorders		Anaemia, blood dyscrasia			

Immune system disorders				Hypersensitivity†, bronchospasm†, angioedema†, anaphylactic reaction/shock†**	Exacerbation of asthma
Endocrine disorders	Parathyroid disorder				
Metabolism and nutrition disorders	Hypocalcaemia**	Hypophosphataemia			
Psychiatric disorders		Sleep disorder, anxiety, affect lability			
Nervous system disorders	Headache, dizziness, dysgeusia (taste perversion)	Cerebrovascular disorder, nerve root lesion, amnesia, migraine, neuralgia, hypertonia, hyperaesthesia, 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 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 subcutatneous 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	Osteonecrosis of jaw†** Osteonecrosis of external auditory canal	

			fractures†	(bisphosphonate class adverse reaction)†	
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 increased, 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.

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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2, Tel: +353 1 6764971, Fax: +353 1 6762517, Website: www.hpra.ie, E-mail: medsafety@hpra.ie.

4.9 Overdose

Up to now there is no experience of acute poisoning with Ibandronic Acid 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 ibandronic acid 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 ibandronic acid (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 ibandronic acid 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 ibandronic acid 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	Ibandronic acid 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 ibandronic acid 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 ibandronic acid 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	Ibandronic acid 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 ibandronic acid that was statistically significant compared to placebo.

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

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

Paediatric population *(see section 4.2 and section 5.2)*
The safety and efficacy of Ibandronic Acid 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 ≥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 ibandronic acid 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 (E260)
Sodium acetate (E262)
Water for injections

6.2 Incompatibilities

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

Ibandronic Acid should not be mixed with calcium containing solutions.

6.3 Shelf life

2 years
Chemical and physical in-use stability has been shown for 24 hours under refrigeration and 25°C when the product is diluted with either 0.9% sodium chloride or 5% glucose to a concentration of 0.012mg/mL.

After dilution: From a microbiological point of view, the solution for infusion 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°C – 8°C.

6.4 Special precautions for storage

No special precautions for storage prior to reconstitution.

6.5 Nature and contents of container

Ibandronic Acid is supplied as packs containing 1, 5 and 10 vials (6 mL type 1 glass vials). The vials are closed with rubber stoppers complying with Ph.Eur.

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.

For single use only.

7 MARKETING AUTHORISATION HOLDER

Noridem Enterprises Ltd
Evagorou & Makariou
Mitsi Building 3
Office 115, 1065 Nicosia
Cyprus

8 MARKETING AUTHORISATION NUMBER

PA1122/018/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 3rd May 2013

Date of last renewal: 14th March 2018

10 DATE OF REVISION OF THE TEXT

July 2018