ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ibandronic acid Accord 2 mg concentrate for solution for infusion
Ibandronic acid Accord 6 mg concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial with 2 ml concentrate for solution for infusion contains 2 mg ibandronic acid (as sodium monohydrate).
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 (sterile concentrate).
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 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 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% 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.
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 intravenous 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 treatmentor 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 (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 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
This medicinal product 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, 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 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	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 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 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.

Mechanism of action
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 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 <50 ml/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
Sodium acetate trihydrate
Glacial acetic acid
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 concentrate for solution for infusion should not be mixed with calcium containing solutions.

6.3 Shelf life

3 years.

After dilution:

Chemical and physical in-use stability after dilution in 9 mg/ml (0.9 %) sodium chloride solution or 5% glucose solution has been demonstrated for 36 hours at 25°C and 2°C to 8°C.
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 to 8°C unless dilution has taken place in controlled and validated aseptic condition.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

For storage conditions of the diluted medicinal product, see section 6.3.

6.5 Nature and contents of container

6 ml, glass vial (type I) with ethylene tetrafluoroethylene rubber stopper and aluminium seals with lavender flip-off cap. It is supplied as packs containing 1 vial with 2 ml of concentrate.
6 ml, glass vial (type I) with ethylene tetrafluoroethylene rubber stopper and aluminium seals with pink flip-off cap. It is supplied as packs containing 1, 5 or 10 vials with 6 ml of concentrate.

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.

7. MARKETING AUTHORISATION HOLDER

Accord Healthcare S.L.U.
World Trade Center, Moll de Barcelona, s/n,
Edifici Est 6ª planta,
08039 Barcelona,
Spain

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/798/001
EU/1/12/798/002
EU/1/12/798/003
EU/1/12/798/004

9. DATE OF FIRST AUTHORISATION

Date of first authorisation: 19 November 2012
Date of latest renewal: 18 September 2017

10. DATE OF REVISION OF THE TEXT

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

1. NAME OF THE MEDICINAL PRODUCT

Ibandronic acid Accord 3 mg solution for injection in pre-filled syringe

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One pre-filled syringe of 3 ml solution contains 3 mg ibandronic acid (as sodium monohydrate).
Each ml of solution contains 1 mg ibandronic acid.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Solution for injection (injection)
Clear, colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of osteoporosis in postmenopausal women at increased risk of fracture (see section 5.1).
A reduction in the risk of vertebral fractures has been demonstrated, efficacy on femoral neck fractures has not been established.

4.2 Posology and method of administration

Patients treated with ibandronic acid should be given the package leaflet and the patient reminder card.

Posology

The recommended dose of ibandronic acid is 3 mg, administered as an intravenous injection over 15 - 30 seconds, every three months.

Patients must receive supplemental calcium and vitamin D (see section 4.4 and section 4.5).

If a dose is missed, the injection should be administered as soon as convenient. Thereafter, injections should be scheduled every 3 months from the date of the last injection.

The optimal duration of bisphosphonate treatment for osteoporosis has not been established. The need for continued treatment should be re-evaluated periodically based on the benefits and potential risks of ibandronic acid on an individual patient basis, particularly after 5 or more years of use.

Special populations
Patients with renal impairment
Ibandronic acid injection is not recommended for use in patients who have a serum creatinine above 200 µmol/l (2.3 mg/dl) or who have a creatinine clearance (measured or estimated) below 30 ml/min, because of limited clinical data available from studies including such patients (see section 4.4 and section 5.2)

No dose adjustment is necessary for patients with mild or moderate renal impairment where serum creatinine is equal or below 200 µmol/l (2.3 mg/dl) or where creatinine clearance (measured or estimated) is equal or greater than 30 ml/min.

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

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

Paediatric population
There is no relevant use of ibandronic acid in children below 18 years, and ibandronic acid was not studied in this population (see section 5.1 and 5.2).

Method of administration
For intravenous use over 15 - 30 seconds, every three months.

Strict adherence to the intravenous administration route is required (see section 4.4).

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

Administration failures

Care must be taken not to administer ibandronic acid injection via intra-arterial or paravenous administration as this could lead to tissue damage.

Hypocalcaemia

Ibandronic acid, like other bisphosphonates administered intravenously, may cause a transient decrease in serum calcium values.
Existing hypocalcaemia must be corrected before starting ibandronic acid injection therapy. Other disturbances of bone and mineral metabolism should also be effectively treated before starting ibandronic acid injection therapy.

All patients must receive adequate supplemental calcium and vitamin D.

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 ibandronic acid intravenous injection is administered. If anaphylactic or other severe hypersensitivity/allergic reactions occur, immediately discontinue the injection and initiate appropriate treatment.

Renal impairment

Patients with concomitant diseases, or who use medicinal products which have potential for undesirable effects on the kidney, should be reviewed regularly in line with good medical practice during treatment.

Due to limited clinical experience, ibandronic acid injection is not recommended for patients with a serum creatinine above 200 µmol/l (2.3 mg/dl) or with a creatinine clearance below 30 ml/min (see section 4.2 and section 5.2).

Patients with cardiac impairment

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

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 osteoporosis (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 (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).

Excipient with known effect
Ibandronic acid injection 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.

4.6 Fertility, pregnancy and lactation

Pregnancy

Ibandronic acid is only for use in postmenopausal women and must not be taken by women of child bearing potential.
There are no adequate data from the use of ibandronic acid in pregnant women. Studies in rats have shown some reproductive toxicity (see section 5.3). The potential risk for humans is unknown. 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 breastfeeding.

Fertility

There are no data on the effects of ibandronic acid from 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).
The most frequently reported adverse reactions are arthralgia and influenza-like symptoms. These symptoms are typically in association with the first dose, generally of short duration, mild or moderate

in intensity, and usually resolve during continuing treatment without requiring remedial measures (please see paragraph “Influenza like illness”).

Tabulated list of adverse reactions

In table 1 a complete list of known adverse reactions is presented.
The safety of oral treatment with ibandronic acid 2.5 mg daily was evaluated in 1251 patients treated in 4 placebo-controlled clinical studies, with the large majority of patients coming from the pivotal three-year fracture study (MF 4411).

In the pivotal two-year study in postmenopausal women with osteoporosis (BM16550), the overall safety of intravenous injection of ibandronic acid 3 mg every 3 months and oral ibandronic acid 2.5 mg daily were shown to be similar. The overall proportion of patients who experienced an adverse reaction was 26.0 % and 28.6 % for ibandronic acid 3 mg injection every 3 months after one year and two years, respectively. Most cases of adverse reactions did not lead to cessation of therapy.

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 occurring in postmenopausal women receiving ibandronic acid 3 mg injection every 3 months or ibandronic acid 2.5 mg daily in the phase III studies BM16550 and MF 4411, and in post-marketing experience.

System Organ Class	**Common**	**Uncommon**	**Rare**	**Very rare**	**Not Known**
Immune system disorders		Asthma exacerbation	Hypersensitivity reaction	Anaphylactic reaction/shock*†	
Metabolism and nutrition disorders		Hypocalcaemia†			
Nervous system disorders	Headache				
Eye disorders			Ocular inflammation*†		
Vascular disorders		Phlebitis/ thrombophlebitis			
Gastrointestinal disorders	Gastritis, Dyspepsia, Diarrhoea, Abdominal pain, Nausea, Constipation				
Skin and subcutaneous tissues disorders	Rash		Angioedema, Facial swelling/oedema, Urticaria	Stevens-Johnson Syndrome†, Erythema Multiforme†, Dermatitis Bullous†	
Musculoskeletal and , connective tissue disorders	Arthralgia, Myalgia, Musculoskeletal pain, Back pain	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
General disorders and administration site conditions	Influenza like illness*, Fatigue	Injection site reactions, Asthenia			

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

Description of selected adverse reactions

Influenza-like illness
Influenza-like illness includes events reported as acute phase reaction or symptoms, including myalgia, arthralgia, fever, chills, fatigue, nausea, loss of appetite, and bone pain.

Osteonecrosis of the 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, consistent 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 ibandronic acid injection.

Based on knowledge of this class of compounds, intravenous overdosage may result in hypocalcaemia, hypophosphataemia, and hypomagnesaemia. Clinically relevant reductions in serum levels of calcium, phosphorus, and magnesium should be corrected by intravenous administration of calcium gluconate, potassium or sodium phosphate, and magnesium sulfate, respectively.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Medicinal products for treatment of bone diseases, bisphosphonates, ATC code: M05BA06

Mechanism of action
Ibandronic acid is a highly potent bisphosphonate belonging to the nitrogen-containing group of bisphosphonates, which act selectively on bone tissue and specifically inhibit osteoclast activity without directly affecting bone formation. It does not interfere with osteoclast recruitment. Ibandronic acid leads to progressive net gains in bone mass and a decreased incidence of fractures through the reduction of elevated bone turnover towards premenopausal levels in postmenopausal women.

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

Animal models confirm that ibandronic acid is a highly potent inhibitor of osteoclastic activity. In growing rats, there was no evidence of impaired mineralisation even at doses greater than 5,000 times the dose required for osteoporosis treatment.

Both daily and intermittent (with prolonged dose-free intervals) long-term administration in rats, dogs and monkeys was associated with formation of new bone of normal quality and maintained or increased mechanical strength even at doses in the toxic range. In humans, the efficacy of both daily and intermittent administration with a dose-free interval of 9 - 10 weeks of ibandronic acid was confirmed in a clinical trial (MF 4411), in which ibandronic acid demonstrated anti-fracture efficacy.

In animal models ibandronic acid produced biochemical changes indicative of dose-dependent inhibition of bone resorption, including suppression of urinary biochemical markers of bone collagen degradation (such as deoxypyridinoline, and cross-linked N-telopeptides of type I collagen (NTX)).

Both daily, intermittent (with a dose-free interval of 9 - 10 weeks per quarter) oral doses as well as intravenous doses of ibandronic acid in postmenopausal women produced biochemical changes indicative of dose-dependent inhibition of bone resorption.

Ibandronic acid intravenous injection decreased levels of serum C-telopeptide of the alpha chain of Type I collagen (CTX) within 3 - 7 days of starting treatment and decreased levels of osteocalcin within 3 months.

Following treatment discontinuation, there is a reversion to the pathological pre-treatment rates of elevated bone resorption associated with postmenopausal osteoporosis.

The histological analysis of bone biopsies after two and three years of treatment of postmenopausal women with doses of oral ibandronic acid 2.5 mg daily and intermittent intravenous doses of up to 1 mg every 3 months showed bone of normal quality and no indication of a mineralisation defect. An expected decrease in bone turnover, normal quality of bone and absence of defects in mineralization were also seen after two years of treatment with ibandronic acid 3 mg injection.

Clinical efficacy

Independent risk factors, for example, low BMD, age, the existence of previous fractures, a family history of fractures, high bone turnover and low body mass index should be considered in order to identify women at increased risk of osteoporotic fractures.

Ibandronic acid 3 mg injection every 3 months

Bone mineral density (BMD)

Ibandronic acid 3 mg intravenous injection, administered every 3 months, was shown to be at least as effective as oral ibandronic acid 2.5 mg daily in a 2-year, randomised, double-blind, multicentre, non-inferiority study (BM16550) of postmenopausal women (1386 women aged 55 - 80) with osteoporosis (lumbar spine BMD T-score below -2.5 SD at baseline). This was demonstrated in both the primary analysis at one year and in the confirmatory analysis at two years endpoint (Table 2).

The primary analysis of data from study BM16550 at one year and the confirmatory analysis at 2 years demonstrated the non-inferiority of 3 mg every 3 months injection dosing regimen compared to 2.5 mg oral daily dosing regimen, in terms of mean increases in BMD at lumbar spine, total hip, femoral neck and trochanter (Table 2).

Table 2: Mean relative change from baseline of lumbar spine, total hip, femoral neck and trochanter BMD after one year (primary analysis) and two years of treatment (Per-Protocol Population) in study BM 16550.

	One year data in study BM 16550		Two year data in study BM 16550	
Mean relative changes from baseline % [95% CI]	ibandronic acid 2.5 mg daily (N=377)	ibandronic acid 3 mg injection every 3 months (N=365)	ibandronic acid 2.5 mg daily (N=334)	ibandronic acid 3 mg injection every 3 months (N=334)

Lumbar spine L2-L4 BMD	3.8 [3.4, 4.2]	4.8 [4.5, 5.2]	4.8 [4.3, 5.4]	6.3 [5.7, 6.8]
Total hip BMD	1.8 [1.5, 2.1]	2.4 [2.0, 2.7]	2.2 [1.8, 2.6]	3.1 [2.6, 3.6]
Femoral neck BMD	1.6 [1.2, 2.0]	2.3 [1.9, 2.7]	2.2 [1.8, 2.7]	2.8 [2.3, 3.3]
Trochanter BMD	3.0 [2.6, 3.4]	3.8 [3.2, 4.4]	3.5 [3.0, 4.0]	4.9 [4.1, 5.7]

Furthermore, ibandronic acid 3 mg injection every 3 months was proven superior to oral ibandronic acid 2.5 mg daily for increases in lumbar spine BMD in a prospectively planned analysis at one year, $p<0.001$, and at two years, $p<0.001$.

For lumbar spine BMD, 92.1 % of patients receiving 3 mg injection every 3 months increased or maintained their BMD after 1 year of treatment (i.e. were responders) compared with 84.9 % of patients receiving oral 2.5 mg daily ($p=0.002$). After 2 years of treatment, 92.8 % of patients receiving 3 mg injections and 84.7 % of patient receiving 2.5 mg oral therapy had increased or maintained lumbar spine BMD ($p=0.001$).

For total hip BMD, 82.3 % of patients receiving 3 mg injection every 3 months were responders at one year, compared with 75.1 % of patients receiving 2.5 mg daily orally ($p=0.02$). After 2 years of treatment, 85.6 % of patients receiving 3 mg injections and 77.0 % of patient receiving 2.5 mg oral therapy had increased or maintained total hip BMD ($p=0.004$).

The proportion of patients who increased or maintained their BMD at one year at both lumbar spine and total hip was 76.2 % in the 3 mg injection every 3 months arm and 67.2 % in the 2.5 mg daily orally arm ($p=0.007$). At two years, 80.1 % and 68.8 % of patients met this criterion in the 3 mg every 3 months injection arm and the 2.5 mg daily arm ($p=0.001$).

Biochemical markers of bone turn-over
Clinically meaningful reductions in serum CTX levels were observed at all time points measured. At 12 months median relative changes from baseline were –58.6 % for the intravenous injection of 3 mg every 3 months regimen and –62.6 % for oral 2.5 mg daily regimen. In addition, 64.8 % of patients receiving 3 mg every 3 months injection were identified as responders (defined as a decrease ≥ 50 % from baseline), compared with 64.9 % of patients receiving 2.5 mg daily orally. Serum CTX reduction was maintained over the 2 years, with more than half of the patients identified as responders in both treatment groups.

Based on the results of study BM 16550, ibandronic acid 3 mg intravenous injection, administered every 3 months is expected to be at least as effective in preventing fractures as the oral regimen of ibandronic acid 2.5 mg daily.

Ibandronic acid 2.5 mg daily tablets
In the initial three-year, randomised, double-blind, placebo-controlled, fracture study (MF 4411), a statistically significant and medically relevant decrease in the incidence of new radiographic morphometric and clinical vertebral fractures was demonstrated (table 3). In this study, ibandronic acid was evaluated at oral doses of 2.5 mg daily and 20 mg intermittently as an exploratory regimen. Ibandronic acid was taken 60 minutes before the first food or drink of the day (post-dose fasting period). The study enrolled women aged 55 to 80 years, who were at least 5 years postmenopausal, who had a BMD at the lumbar spine of -2 to -5 SD below the premenopausal mean (T-score) in at least one vertebra [L1-L4], and who had one to four prevalent vertebral fractures. All patients received 500 mg calcium and 400 IU vitamin D daily. Efficacy was evaluated in 2,928 patients. Ibandronic acid 2.5 mg administered daily, showed a statistically significant and medically relevant reduction in the incidence of new vertebral fractures. This regimen reduced the occurrence of new radiographic vertebral fractures by 62 % ($p=0.0001$) over the three year duration of the study. A relative risk reduction of 61 % was observed after 2 years ($p=0.0006$). No statistically significant difference was

attained after 1 year of treatment (p=0.056). The anti-fracture effect was consistent over the duration of the study. There was no indication of a waning of the effect over time.

The incidence of clinical vertebral fractures was also significantly reduced by 49 % after 3 years (p=0.011). The strong effect on vertebral fractures was furthermore reflected by a statistically significant reduction of height loss compared to placebo (p<0.0001).

Table 3: Results from 3 years fracture study MF 4411 (%, 95 % CI)

	Placebo (N=974)	ibandronic acid 2.5 mg daily (N=977)
Relative risk reduction New morphometric vertebral fractures		62% (40.9, 75.1)
Incidence of new morphometric vertebral fractures	9.56% (7.5, 11.7)	4.68% (3.2, 6.2)
Relative risk reduction of clinical vertebral fracture		49% (14.03, 69.49)
Incidence of clinical vertebral fracture	5.33% (3.73, 6.92)	2.75% (1.61, 3.89)
BMD – mean change relative to baseline lumbar spine at year 3	1.26% (0.8, 1.7)	6.54% (6.1, 7.0)
BMD – mean change relative to baseline total hip at year 3	-0.69% (-1.0, -0.4)	3.36% (3.0, 3.7)

The treatment effect of ibandronic acid was further assessed in an analysis of the subpopulation of patients who, at baseline, had a lumbar spine BMD T-score below –2.5 (table 4). The vertebral fracture risk reduction was very consistent with that seen in the overall population.

Table 4: Results from 3 years fracture study MF 4411 (%, 95 % CI) for patients with lumbar spine BMD T-score below –2.5 at baseline

	Placebo (N=587)	ibandronic acid 2.5 mg daily (N=575)
Relative Risk Reduction New morphometric vertebral fractures		59% (34.5, 74.3)
Incidence of new morphometric vertebral fractures	12.54% (9.53, 15.55)	5.36% (3.31, 7.41)
Relative risk reduction of clinical vertebral fracture		50% (9.49, 71.91)
Incidence of clinical vertebral fracture	6.97% (4.67, 9.27)	3.57% (1.89, 5.24)
BMD – mean change relative to baseline lumbar spine at year 3	1.13% (0.6, 1.7)	7.01% (6.5, 7.6)
BMD – mean change relative to baseline total hip at year 3	-0.70% (-1.1, -0.2)	3.59% (3.1, 4.1)

In the overall patient population of the study MF4411, no reduction was observed for non-vertebral fractures, however daily ibandronic acid appeared to be effective in a high-risk subpopulation (femoral neck BMD T-score < -3.0), where a non-vertebral fracture risk reduction of 69 % was observed.

Daily oral treatment with ibandronic acid 2.5 mg tablets resulted in progressive increases in BMD at vertebral and nonvertebral sites of the skeleton.

Three-year lumbar spine BMD increase compared to placebo was 5.3 % and 6.5 % compared to baseline. Increases at the hip compared to baseline were 2.8 % at the femoral neck, 3.4 % at the total hip, and 5.5 % at the trochanter.

Biochemical markers of bone turnover (such as urinary CTX and serum Osteocalcin) showed the expected pattern of suppression to premenopausal levels and reached maximum suppression within a period of 3 - 6 months of using 2.5 mg ibandronic acid daily.

A clinically meaningful reduction of 50 % of biochemical markers of bone resorption was observed as early as one month after starting treatment with ibandronic acid 2.5 mg.

Paediatric population (see section 4.2 and section 5.2).
Ibandronic acid was not studied in the paediatric population, therefore no efficacy or safety data are available for this patient population.

5.2 Pharmacokinetic properties

The primary pharmacological effects of ibandronic acid on bone are not directly related to actual plasma concentrations, as demonstrated by various studies in animals and humans.

Plasma concentrations of ibandronic acid increase in a dose-proportional manner after intravenous administration of 0.5 mg to 6 mg.

Absorption

Not applicable

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 85 % - 87 % (determined *in vitro* at therapeutic ibandronic acid concentrations), and thus there is a low potential for interaction with other medicinal products due to displacement.

Biotransformation

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

Elimination

Ibandronic acid is removed from the circulation via bone absorption (estimated to be 40 – 50 % in postmenopausal women) and the remainder is eliminated unchanged by the kidney.

The range of observed apparent half-lives is broad, the apparent terminal half-life is generally in the range of 10 - 72 hours. As the values calculated are largely a function of the duration of study, the dose used, and assay sensitivity, the true terminal half-life is likely to be substantially longer, in common with other bisphosphonates. Early plasma levels fall quickly, reaching 10 % of the 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 appears not to include known acidic or basic transport systems involved in the excretion of other active substances.(see section 4.5). 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 clinical situations

Gender
Pharmacokinetics of ibandronic acid are similar in men and women.

Race
There is no evidence for any clinically relevant inter-ethnic differences between Asians and Caucasians in ibandronic acid disposition. There is limited data available on patients of African origin.

Patients with renal impairment
Renal clearance of ibandronic acid in patients with various degrees of renal impairment is linearly related to creatinine clearance (CLcr).

No dose adjustment is necessary for patients with mild or moderate renal impairment (CLcr equal or above 30 ml/min).

Subjects with severe renal impairment (CLcr less than 30 ml/min) receiving daily oral administration of 10 mg ibandronic acid for 21 days, had 2 - 3 fold higher plasma concentrations than subjects with normal renal function and total clearance of ibandronic acid was 44 ml/min. After intravenous administration of 0.5 mg of ibandronic acid, total, renal, and non-renal clearances decreased by 67 %, 77 % and 50 %, respectively, in subjects with severe renal failure, but there was no reduction in tolerability associated with the increase in exposure. Due to the limited clinical experience, ibandronic acid is not recommended in patients with severe renal impairment (see section 4.2 and section 4.4). The pharmacokinetics of ibandronic acid in patients with end-stage renal disease was only assessed in a small number of patients managed by haemodialysis, therefore, the pharmacokinetics of ibandronic acid in the patients not undergoing haemodialysis is unknown. Due to the limited data available, ibandronic acid should not be used in all patients with end-stage renal disease.

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, which is not metabolised but is cleared by renal excretion and by uptake into bone. Therefore dose adjustment is not necessary in patients with hepatic impairment.

Elderly population (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, renal function 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 ibandronic acid in patients less than 18 years old.

5.3 Preclinical safety data

Toxic effects, e.g. signs of renal damage, were observed in dogs only at exposures considered sufficiently in excess of the maximum human exposure, indicating little relevance to clinical use.

Mutagenicity/Carcinogenicity:

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

Reproductive toxicity:

Specific studies for the 3-monthly dosing regimen have not been performed. In studies with daily i.v. dosing regimen, there was no evidence for a direct foetal toxic or teratogenic effect of ibandronic acid in rats and rabbits. Body weight gain was decreased in F_1 offspring in rats. 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. Other adverse reactions to ibandronic acid in reproductive toxicity studies in the rat were those observed with bisphosphonates as a class. They include a decreased number of implantation sites, interference with natural delivery (dystocia), and an increase in visceral variations (renal pelvis ureter syndrome).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Acetic acid, glacial
Sodium acetate trihydrate
Water for injections

6.2 Incompatibilities

Ibandronic acid solution for injection must not be mixed with calcium-containing solutions or other intravenously administered medicinal products.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Pre-filled syringes made of colourless glass, the grey plunger rubber stopper and tip cap, containing 3 ml of solution for injection.
Packs of 1 pre-filled syringe and 1 injection needle or 4 pre-filled syringes and 4 injection needles.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Where the medicinal product is administered into an existing intravenous infusion line, the infusate should be restricted to either isotonic saline or 50 mg/ml (5 %) glucose solution. This also applies to solutions used to flush butterfly and other devices.

Any unused solution for injection, syringe and injection needle should be disposed of in accordance with local requirements. The release of pharmaceuticals in the environment should be minimized.

The following points should be strictly adhered to regarding the use and disposal of syringes and other medicinal sharps:

- Needles and syringes should never be reused.
- Place all used needles and syringes into a sharps container (puncture-proof disposable container).
- Keep this container out of the reach of children.
- Placing used sharps containers in the household waste should be avoided.
- Dispose of the full container according to local requirements or as instructed by your healthcare professional.

7. MARKETING AUTHORISATION HOLDER

Accord Healthcare S.L.U.
World Trade Center, Moll de Barcelona, s/n,
Edifici Est 6ª planta,
08039 Barcelona,
Spain

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/798/005
EU/1/12/798/006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 November 2012
Date of latest renewal: 18 September 2017

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://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 manufacturer(s) responsible for batch release

Accord Healthcare Polska Sp.z o.o.,
ul. Lutomierska 50,95-200 Pabianice, Poland

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Ibandronic acid Accord 2 mg and 6 mg concentrate for solution for infusion (for oncology indications)
Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Ibandronic acid Accord 3 mg solutionfor injection (for osteoporosos indications)
Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates 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.

- **Additional risk minimisation measures**

The MAH shall ensure that a patient reminder card regarding osteonecrosis of the jaw is implemented.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Ibandronic acid Accord 2 mg concentrate for solution for infusion
ibandronic acid

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 2 mg of ibandronic acid (as sodium monohydrate).

3. LIST OF EXCIPIENTS

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

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion
1 vial (2 mg/2 ml)

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
Read the package leaflet for the shelf life after dilution.

9. SPECIAL STORAGE CONDITIONS

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

Accord Healthcare S.L.U.
World Trade Center, Moll de Barcelona, s/n,
Edifici Est 6ª planta,
08039 Barcelona,
Spain

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/798/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

[Justification for not including Braille accepted]

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

Ibandronic acid Accord 2 mg sterile concentrate
ibandronic acid
IV use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER<, DONATION AND PRODUCT CODES>

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2 mg/2 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Ibandronic acid Accord 6 mg concentrate for solution for infusion
ibandronic acid

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 6 mg of ibandronic acid (as sodium monohydrate).

3. LIST OF EXCIPIENTS

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

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion
1 vial (6 mg/6 ml)
5 vials (6 mg/6 ml)
10 vials (6 mg/6 ml)

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:
Read the package leaflet for the shelf life after dilution.

9. SPECIAL STORAGE CONDITIONS

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

Accord Healthcare S.L.U.
World Trade Center, Moll de Barcelona, s/n,
Edifici Est 6ª planta,
08039 Barcelona,
Spain

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/798/002
EU/1/12/798/003
EU/1/12/798/004

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

[Justification for not including Braille accepted]

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

Ibandronic acid Accord 6 mg sterile concentrate
ibandronic acid
IV use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER<, DONATION AND PRODUCT CODES>

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6 mg/6 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Ibandronic acid Accord 3 mg solution for injection in pre-filled syringe
Ibandronic acid

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One pre-filled syringe of 3 ml solution contains 3 mg of ibandronic acid (as sodium monohydrate).

3. LIST OF EXCIPIENTS

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

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
1 pre-filled syringe + 1 injection needle
4 pre-filled syringes + 4 injection needles

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For intravenous use only.

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

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

Accord Healthcare S.L.U.
World Trade Center, Moll de Barcelona, s/n,
Edifici Est 6ª planta,
08039 Barcelona,
Spain

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/798/005 1 pre-filled syringe
EU/1/12/798/006 4 pre-filled syringe

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

[Justification for not including Braille accepted]

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

PRE-FILLED SYRINGE

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

Ibandronic acid Accord 3 mg injection
Ibandronic acid
IV

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Ibandronic acid Accord 2 mg concentrate for solution for infusion
Ibandronic acid Accord 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 Ibandronic acid Accord is and what it is used for
2. What you need to know before you receive Ibandronic acid Accord
3. How to receive Ibandronic acid Accord
4. Possible side effects
5. How to store Ibandronic acid Accord
6. Contents of the pack and other information

1. What Ibandronic Acid Accord is and what it is used for

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

Ibandronic acid Accord 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.

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

Ibandronic acid Accord 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 Ibandronic acid Accord

Do not receive Ibandronic acid Accord
- if you are allergic to ibandronic acid or any of the other ingredients of this medicine (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 Ibandronic acid Accord.

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 ibandronic acid 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 ibandronic acid.

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 ibandronic acid.

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 Ibandronic acid Accord:
- 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
Ibandronic acid Accord should not be used in children and adolescents below the age of 18 years.

Other medicines and Ibandronic Acid Accord
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This is because Ibandronic acid Accord can affect the way some other medicines work. Also, some other medicines can affect the way Ibandronic acid Accord 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 Ibandronic acid Accord can both lower the amount of calcium in your blood.

Pregnancy and breast-feeding
Do not receive Ibandronic acid Accord 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 Ibandronic acid Accord 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.

This medicine contains less than 1 mmol sodium (23 mg) per vial, i.e. 'essentially sodium free'.

3. How to receive Ibandronic Acid Accord

Receiving this medicine
- Ibandronic acid Accord 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 Ibandronic acid Accord. 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 Ibandronic acid Accord 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 mg every 3-4 weeks, as an infusion in your vein over at least 15 minutes.
If you have 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).
- Talk to your doctor if you have ear pain, discharge from the ear, and/or an ear infection. These could be signs of bone damage in the ear.
- 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

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

Other possible side effects

Common (may affect upto 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 Ibandronic acid Accord

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 carton and on the label after EXP. The expiry date refers to the last day of that month.

This medicinal product does not require any special storage conditions.

After dilution
Chemical and physical in-use stability after dilution in 0.9 % sodium chloride or 5% glucose solution has been demonstrated for 36 hours at 25°C and 2°C to 8°C.
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 to 8°C unless dilution has taken place in controlled and validated aseptic condition.

Do not use this medicine if you notice that the solution is not clear or contains particles.

6. Contents of the pack and other information

What Ibandronic acid Accord contains

- The active substance is ibandronic acid.
  Ibandronic acid Accord 2 mg concentrate for solution for infusion
  One vial with 2 ml of a concentrate for solution for infusion contains 2 mg ibandronic acid (as 2.25 mg ibandronate sodium monohydrate).
  Ibandronic acid Accord 6 mg concentrate for solution for infusion
  One vial with 6 ml of a concentrate for solution for infusion contains 6 mg ibandronic acid (as 6.75 mg ibandronate sodium monohydrate).
- The other ingredients are sodium chloride, sodium acetate trihydrate, glacial acetic acid and water for injections.

What Ibandronic acid Accord looks like and contents of the pack
Ibandronic acid Accord is a concentrate for solution for infusion (sterile concentrate). Colourless, clear solution.

It is supplied in glass vials (type I) with rubber stopper and aluminium seals with flip-off cap.

Ibandronic acid Accord 2 mg concentrate for solution for infusion
Each vial contains 2 ml of concentrate. Each pack contains 1 vial.

Ibandronic acid Accord 6 mg concentrate for solution for infusion
Each vial contains 6 ml of concentrate. It is supplied as packs containing 1, 5 or 10 vials. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Marketing Authorisation Holder
Accord Healthcare S.L.U.
World Trade Center, Moll de Barcelona, s/n,
Edifici Est 6ª planta,

08039 Barcelona,
Spain

Manufacturer
Accord Healthcare Polska Sp.z o.o.,
ul. Lutomierska 50,95-200 Pabianice, Poland

This leaflet was last revised in {MM/YYYY}

Other sources of information

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

The following information is intended for healthcare professionals only:

Dosage: Prevention of Skeletal Events in Patients with Breast Cancer and Bone Metastases
The recommended dose for prevention of skeletal events in patients with breast cancer and bone metastases is 6 mg intravenously given every 3-4 weeks. The dose should be infused over 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 week

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

Dosage: Treatment of Tumour-induced hypercalcaemia
Ibandronic acid Accord is usually administered in a hospital setting. The dose is determined by the doctor considering the following factors.

Prior to treatment with Ibandronic acid Accord 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 will be an adequate single dosage. In patients with moderate hypercalcaemia (albumin-corrected serum calcium <3 mmol/l or <12 mg/dl) 2 mg is an effective dose. The highest dose used in clinical trials was 6 mg but this dose does not add any further benefit in terms of efficacy.

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

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

serum calcium (mmol/l)		
	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
Ibandronic acid Accord 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, Ibandronic acid Accord concentrate for solution for infusion should only be mixed with isotonic sodium chloride solution or with 5% dextrose solution. Calcium containing solutions should not be mixed with Ibandronic acid Accord 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 Ibandronic Acid Accord’).

Ibandronic acid Accord concentrate for solution for infusion should be administered as an intravenous infusion.Care must be taken not to administer Ibandronic acid Accord 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, Ibandronic acid Accord 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 Ibandronic acid Accord infusion is repeated at 3-4 week intervals.

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

For patients with breast cancer and bone metastases, Ibandronic acid Accord 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 Ibandronic acid Accord 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

Ibandronic acid Accord 3 mg solution for injection in pre-filled syringe
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 Ibandronic acid Accord is and what it is used for
2. What you need to know before you receive Ibandronic acid Accord
3. How to use Ibandronic acid Accord
4. Possible side effects
5. How to store Ibandronic acid Accord
6. Contents of the pack and other information

1. What Ibandronic acid Accord is and what it is used for

Ibandronic acid Accord belongs to a group of medicines called bisphosphonates. It contains the active substance ibandronic acid.
Ibandronic acid Accord may reverse bone loss by stopping more loss of bone and increasing bone mass in most women who take it, even though they won't be able to see or feel a difference.
Ibandronic acid Accord may help lower the chances of breaking bones (fractures). This reduction in fractures was shown for the spine but not for the hip.

Ibandronic acid Accord is prescribed to you to treat postmenopausal osteoporosis because you have an increased risk of fractures. Osteoporosis is a thinning and weakening of the bones, which is common in women after the menopause. At the menopause, a woman's ovaries stop producing the female hormone, oestrogen, which helps to keep her skeleton healthy. The earlier a woman reaches the menopause, the greater her risk of fractures in osteoporosis.

Other things that can increase the risk of fractures include:
- not enough calcium and vitamin D in the diet
- smoking cigarettes, or drinking too much alcohol
- not enough walking or other weight-bearing exercise
- a family history of osteoporosis

A healthy lifestyle will also help you to get the most benefit from your treatment. This includes:
- eating a balanced diet rich in calcium and vitamin D
- walking or other weight-bearing exercise
- not smoking and not drinking too much alcohol

2. What you need to know before you receive Ibandronic acid Accord

Do not use Ibandronic acid Accord
- **if you have, or had in the past, low blood calcium.** Please consult your doctor
- if you are allergic to ibandronic acid or any of the other ingredients of this medicine (listed in section 6).

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 ibandronic acid for osteoporosis. 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.

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.

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 ibandronic acid.

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 ibandronic acid.

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

Some patients need to be especially careful when using Ibandronic acid Accord. Talk to your doctor before receiving Ibandronic acid Accord:
- If you have or have ever had kidney problems, kidney failure or have needed dialysis, or if you have any other disease that may affect your kidneys
- If you have any disturbance of mineral metabolism (such as vitamin D deficiency)
- You should take calcium and vitamin-D supplements while receiving Ibandronic acid Accord. If you are unable to do so, you should inform your doctor

- 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
Ibandronic acid Accord must not be used in children or adolescents below 18 years.

Other medicines and Ibandronic acid Accord
Tell your doctor, nurse or pharmacist if you are taking, have recently taken or might take any other medicines.

Pregnancy and breast-feeding

Ibandronic acid Accord is for use only by postmenopausal women and must not be taken by women who could still have a baby.
Do not take Ibandronic acid Accord if you are pregnant or 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 Ibandronic acid Accord has no or negligible effect on your ability to drive and use machines.

Ibandronic acid Accord contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per dose (3 ml), i.e. 'essentially sodium-free'.

3. How to use Ibandronic acid Accord

The recommended dose of Ibandronic acid Accord for the intravenous injection is 3 mg (1 pre-filled syringe) once every 3 months.

The injection should be given into the vein by a physician or qualified/trained health care worker. Do not administer the injection to yourself.

The solution for injection must be administered into a vein only, and not anywhere else in the body.

Continuing to receive Ibandronic acid Accord
To get the most benefit from the treatment it is important to continue receiving the injections every 3 months for as long as your doctor prescribes it for you. Ibandronic acid Accord can treat osteoporosis only for as long as you keep receiving the treatment, even though you will not be able to see or feel a difference. After 5 years of receiving Ibandronic acid Accord, please consult with your doctor whether you should continue to receive Ibandronic acid Accord.

You should also take calcium and vitamin-D supplements, as recommended by your doctor.

If you use more Ibandronic acid Accord than you should
You may develop low levels of calcium, phosphorus or magnesium in the blood. Your doctor may take steps to correct such changes and may give you an injection containing these minerals.

If you forget to use Ibandronic acid Accord
You should arrange an appointment to get the next injection as soon as possible. After that, go back to getting the injections every 3 months from the date of the most recent injection.

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

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 1000 people):
- itching, swelling of your face, lips, tongue and throat, with difficulty breathing.
- persistent eye pain and inflammation (if prolonged)

- 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 10000 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).
- Talk to your doctor if you have ear pain, discharge from the ear, and/or an ear infection. These could be signs of bone damage in the ear.
- serious, potentially life-threatening allergic reaction (see section 2).
- severe adverse skin reactions

Other possible side effects

Common (may affect up to 1 in 10 people):
- headache
- stomach pain (such as gastritis) or tummy pain, , indigestion, nausea, having diarrhoea (loose bowels) or constipation
- pain in your muscles, joints, or back
- feeling tired and exhausted
- flu-like symptoms, including fever, shaking and shivering, feeling of discomfort, bone pain and aching muscles and joints. Talk to a nurse or doctor if any effects become troublesome or last more than a couple of days
- rash

Uncommon (may affect up to 1 in 100 people)
- inflammation of a vein
- pain or injury at the injection site
- symptoms of low blood calcium levels (hypocalcaemia) including muscle cramps or spasms and/or tingling sensation in the fingers or around the mouth
- bone pain
- feeling weak
- asthma attacks

Rare (may affect up to 1 in 1000 people):
- hives

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 Ibandronic acid Accord

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 carton and on the syringe after "EXP". The expiry date refers to the last day of that month.

This medicinal product does not require any special storage conditions.

The person giving the injection should throw away any unused solution and put the used syringe and injection needle into an appropriate disposal container.

6. Contents of the pack and other information

What Ibandronic acid Accord contains

- One pre-filled syringe of 3 ml solution contains 3 mg ibandronic acid (as sodium monohydrate). Each ml of solution contains 1 mg ibandronic acid..
- The other ingredients are sodium chloride, acetic acid, sodium acetate trihydrate and water for injections.

What Ibandronic acid Accord looks like and contents of the pack
Ibandronic acid Accord 3 mg solution for injection in pre-filled syringes is a clear colourless solution. Each pre-filled syringe contains 3 ml of solution. Ibandronic acid Accord is available in packs of 1 pre-filled syringe and 1 injection needle or 4 pre-filled syringes and 4 injection needles.
Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Marketing Authorisation Holder
Accord Healthcare S.L.U.
World Trade Center, Moll de Barcelona, s/n,
Edifici Est 6ª planta,
08039 Barcelona,
Spain

Manufacturer
Accord Healthcare Polska Sp.z o.o.,
ul. Lutomierska 50,95-200 Pabianice, Poland

This leaflet was last revised in {date}.

Other sources of information

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

This information is intended for healthcare professionals only:

Please see the summary of product characteristics for more information.

Administration of Ibandronic acid Accord 3 mg solution for injection in pre-filled syringe
Ibandronic acid Accord 3 mg solution for injection in pre-filled syringe should be injected intravenously over a period of 15 - 30 seconds.

The solution is irritant, therefore strict adherence to the intravenous route of administration is important. If you inadvertently inject into the tissues around the vein, patients may experience local irritation, pain and inflammation at the injection site.

Ibandronic acid Accord 3 mg solution for injection in pre-filled syringe **must not** be mixed with calcium-containing solutions (such as Ringer-Lactate solution, calcium heparin) or other intravenously administered medicinal products. Where Ibandronic acid Accord is administered via an existing intravenous infusion line, the intravenous infusate should be restricted to either isotonic saline or 50 mg/ml (5 %) glucose solution.

Missed dose
If a dose is missed, the injection should be administered as soon as convenient. Thereafter, injections should be scheduled every 3 months from the date of the last injection.

Overdose
No specific information is available on the treatment of overdosage with Ibandronic acid Accord.

Based on knowledge of this class of compounds, intravenous overdosage may result in hypocalcaemia, hypophosphataemia, and hypomagnesaemia, which can cause paraesthesia. In severe cases intravenous infusion of appropriate doses of calcium gluconate, potassium or sodium phosphate, and magnesium sulfate, may be needed.

General advice
Ibandronic acid Accord 3 mg solution for injection in pre-filled syringe like other bisphosphonates administered intravenously, may cause a transient decrease in serum calcium values.

Hypocalcaemia and other disturbances of bone and mineral metabolism should be assessed and effectively treated before starting Ibandronic acid Accord injection therapy. Adequate intake of calcium and vitamin D is important in all patients. All patients must receive supplemental calcium and vitamin D.

Patients with concomitant diseases, or who use medicinal products which have a potential for undesirable effects on the kidney, should be reviewed regularly in line with good medical practice during treatment.

Any unused solution for injection, syringe and injection needle should be disposed of in accordance with local requirements.