**ANNEX I**

**SUMMARY OF PRODUCT CHARACTERISTICS**

## 1. NAME OF THE MEDICINAL PRODUCT

Ibandronic acid Accord 2 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 2.25 mg ibandronate sodium monohydrate).

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.
Clear, colourless solution.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

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

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. For infusion, the contents of the vial(s) should only be added to 100 ml isotonic sodium chloride solution or 100 ml 5% glucose solution.

A shorter (i.e. 15 min) infusion time should only be used for patients with normal renal function or mild renal impairment. There are no data available characterizing 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. 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 dosage. In patients with moderate hypercalcaemia (albumin-corrected serum calcium <3 mmol/l or <12 mg/dl) 2 mg is an effective dose. The highest dose used in clinical trials was 6 mg but this dose does not add

any further benefit in terms of efficacy.

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

| | | |
|---|---|---|
| Albumin-corrected serum calcium (mmol/l) | = | serum calcium (mmol/l) - [0.02 x albumin (g/l)] + 0.8 |
| | **Or** | |
| Albumin-corrected serum calcium (mg/dl) | = | serum calcium (mg/dl) + 0.8 x [4 - albumin (g/dl)] |
| To convert the albumin-corrected serum calcium in mmol/l value to mg/dl, multiply by 4. | | |

In most cases a raised serum calcium level can be reduced to the normal range within 7 days. The median time to relapse (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.

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

*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 (see Section 5.2):

| Creatinine Clearance (ml/min) | Dosage / Infusion time [1] | Infusion Volume [2] |
|---|---|---|
| ≥50 CLcr <80 | 6 mg / 15 minutes | 100 ml |
| ≥30 CLcr <50 | 4 mg / 1 hour | 500 ml |
| <30 | 2 mg / 1 hour | 500 ml |

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

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

*Elderly*
No dose adjustment is required.

*Paediatric population*
The safety and efficacy of ibandronic acid in children and adolescents below age 18 years have not been established. No data are available.

Method of administration
For intravenous administration.

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. For this purpose, the contents of the vials are to be added to 500 ml isotonic sodium chloride solution (or 500 ml 5% dextrose solution) and infused over two hours.

As the inadvertent intra-arterial administration of preparations not expressly recommended for this purpose as well as paravenous administration can lead to tissue damage, care must be taken to ensure that ibandronic acid concentrate for solution for infusion is administered intravenously.

## 4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients.
- Caution is to be taken in patients with known hypersensitivity to other bisphosphonates.
- 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

*Osteonecrosis of the jaw (ONJ)*
Osteonecrosis of the jaw, generally associated with tooth extraction and/or local infection (including osteomyelitis) has been reported in patients with cancer receiving treatment regimens including primarily intravenously administered bisphosphonates. Many of these patients were also receiving chemotherapy and corticosteroids. Osteonecrosis of the jaw has also been reported in patients with osteoporosis receiving oral bisphosphonates.

A dental examination with appropriate preventive dentistry should be considered prior to treatment with bisphosphonates in patients with concomitant risk factors (e.g. cancer, chemotherapy, radiotherapy, corticosteroids, poor oral hygiene).

While on treatment, these patients should avoid invasive dental procedures if possible. For patients who develop osteonecrosis of the jaw while on bisphosphonate therapy, dental surgery may exacerbate the condition. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of osteonecrosis of the jaw. Clinical judgement of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

*Atypical fractures of the femur*
Atypical subtrochanteric and diaphyseal femoral fractures have been reported with bisphosphonate therapy, primarily in patients receiving long-term treatment for osteoporosis. These transverse or short oblique fractures can occur anywhere along the femur from just below the lesser trochanter to just above the supracondylar flare. These fractures occur after minimal or no trauma and some patients experience thigh or groin pain, often associated with imaging features of stress fractures, weeks to months before presenting with a completed femoral fracture. Fractures are often bilateral; therefore the contralateral femur should be examined in bisphosphonate-treated patients who have sustained a femoral shaft fracture. Poor healing of these fractures has also been reported. Discontinuation of bisphosphonate therapy in patients suspected to have an atypical femur fracture should be considered pending evaluation of the patient, based on an individual benefit risk assessment. During bisphosphonate treatment patients should be advised to report any thigh, hip or groin pain and any patient presenting with such symptoms should be evaluated for an incomplete femur fracture.

*Patients with renal impairment*
Clinical studies have not shown any evidence of deterioration in renal function with long term ibandronic acid therapy. Nevertheless, according to clinical assessment of the individual patient, it is recommended that renal function, serum calcium, phosphate and magnesium should be monitored in patients treated with ibandronic acid.

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

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

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

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

Interaction studies have only been performed in adults.

No interaction was observed when co-administered with melphalan/prednisolone in patients with multiple myeloma.

Other interaction studies in postmenopausal women have demonstrated the absence of any interaction potential with tamoxifen or hormone replacement therapy (oestrogen).

In relation to disposition, no drug interactions of clinical significance are likely. Ibandronic acid is eliminated by renal secretion only and does not undergo any biotransformation. The secretory pathway does not appear to include known acidic or basic transport systems involved in the excretion of other active substances. In addition, ibandronic acid does not inhibit the major human hepatic P450 isoenzymes and does not induce the hepatic cytochrome P450 system in rats. Plasma protein binding is low at therapeutic concentrations and ibandronic acid is therefore unlikely to displace other active substances.

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

In clinical studies, ibandronic acid has been administered concomitantly with commonly used antineoplastics, diuretics, antibiotics and analgesics without clinically apparent interactions occurring.

## 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 lactation.

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

No studies on the effects on the ability to drive and use machines have been performed.

## 4.8 Undesirable effects

Adverse reactions are ranked under heading of frequency, the most frequent first, using the following convention: very common ( ≥1/10), common ( ≥1/100 and <1/10), uncommon ( ≥1/1,000 and <1/100), rare ( ≥1/10,000 and <1/1,000), and very rare (<1/10,000).

*Treatment of tumour induced hypercalcaemia*
The safety profile for ibandronic acid in tumour-induced hypercalcaemia is derived from controlled clinical trials in this indication and after the intravenous administration of ibandronic acid at the recommended doses. Treatment was most commonly associated with a rise in body temperature. Occasionally, a flu-like syndrome consisting of fever, chills, bone and/or muscle ache-like pain was reported. In most cases no specific treatment was required and the symptoms subsided after a couple of hours/days.

**Table 1 Adverse Events in Controlled Clinical Trials in Tumour-Induced Hypercalcaemia after Treatment with Ibandronic acid**

| System Organ Class | Very common | Common | Uncommon | Rare | Very rare |
|---|---|---|---|---|---|
| **Immune system disorders** | | | | | Hypersensitivity |
| **Metabolism and nutritional disorders** | | Hypo-calcaemia** | | | |
| **Respiratory, thoracic, and mediastinal disorders** | | | | | Bronchospasm |
| **Skin and subcutaneous tissue disorders** | | | | | Angioneurotic oedema |
| **Musculo-skeletal and connective tissue disorders** | | Bone pain | Myalgia | | |
| **General disorders and administration site conditions** | Pyrexia | | Influenza-like illness**, rigors | | |

Note: Data for both the 2 mg and 4 mg doses of ibandronic acid are pooled.
**See further information below

*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.

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

Table 2 lists adverse drug reactions from the pivotal phase III study (152 patients treated with ibandronic acid 6 mg), i.e. adverse events with a remote, possible, or probable relationship to study medication, and from postmarketing experience.

**Table 2 Adverse Drug Reactions Occurring in Patients with Metastatic Bone Disease due to Breast Cancer Treated with Ibandronic acid 6 mg administered intravenously**

| System Organ Class | Very common | Common | Uncommon | Rare | Very rare |
|---|---|---|---|---|---|
| **Infections and infestations** | | Infection | Cystitis, vaginitis, oral candidiasis | | |
| **Neoplasms benign, malignant, and unspecified** | | | Benign skin neoplasm | | |
| **Blood and lymphatic system disorders** | | | Anaemia, blood dyscrasia | | |
| **Endocrine disorders** | | Parathyroid disorder | | | |
| **Metabolism and nutrition disorders** | | | Hypophosphataemia | | |
| **Psychiatric disorders** | | | Sleep disorder, anxiety, affection lability | | |
| **Nervous system disorders** | | Headache, dizziness, dysgeusia (taste perversion) | Cerbrovascular 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 | | |
| **Musculoskeletal and connective tissue disorders** | | Osteoarthritis, myalgia, arthralgia, joint disorder | | Atypical subtrochanteric and diaphyseal femoral fractures† (bisphosphonate class adverse reaction) | Osteonecrosis of jaw†** |
| **Renal and urinary** | | | Urinary retention, renal cyst | | |
| **Reproductive system and breast disorders** | | | Pelvic pain | | |
| **General disorders and administration site conditions** | | 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 postmarketing experience.

*Osteonecrosis of jaw*
Osteonecrosis of the jaw has been reported in patients treated by bisphosphonates. The majority of the reports refer to cancer patients, but such cases have also been reported in patients treated for osteoporosis. Osteonecrosis of the jaw is generally associated with tooth extraction and / or local infection (including osteomyelitis). Diagnosis of cancer, chemotherapy, radiotherapy, corticosteroids and poor oral hygiene are also deemed as risk factors (see section 4.4).

*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.

### 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: Drugs for treatment of bone diseases, bisphosphonate,
ATC Code: M05BA06

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

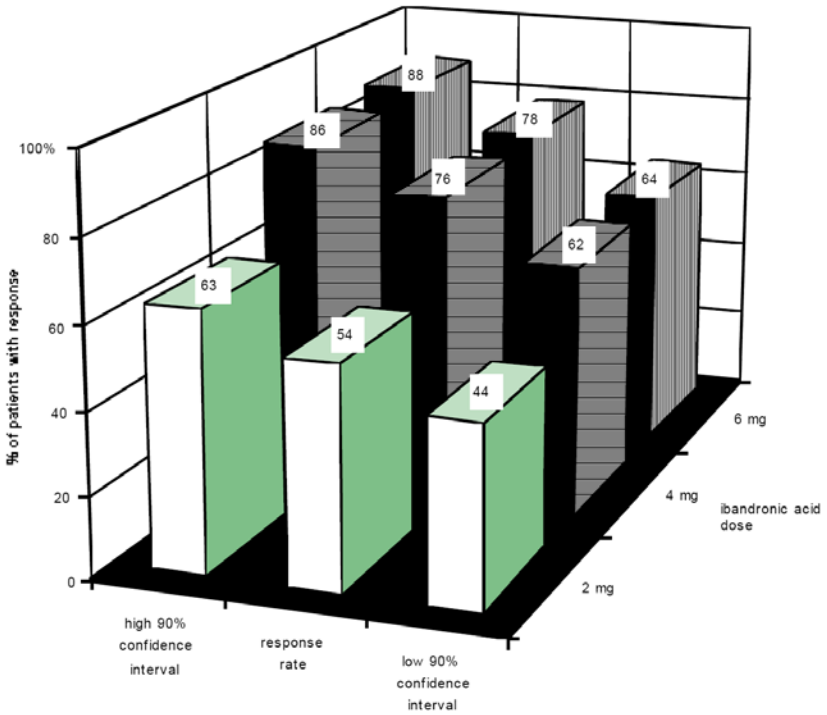
*In vivo*, ibandronic acid prevents experimentally-induced bone destruction caused by cessation of gonadal function, retinoids, tumours or tumour extracts. The inhibition of endogenous bone resorption has also been documented by $^{45}Ca$ kinetic studies and by the release of radioactive tetracycline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

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

Bone resorption due to malignant disease is characterized by excessive bone resorption that is not balanced with appropriate bone formation. Ibandronic acid selectively inhibits osteoclast activity, reducing bone resorption and thereby reducing skeletal complications of the malignant disease.

*Clinical studies in 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.




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 3.

**Table 3 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 4.

**Table 4 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*
The safety and efficacy of ibandronic acid in children and adolescents below age 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 drug-drug interaction 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.

*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*
There are no pharmacokinetic data for ibandronic acid in patients who have hepatic impairment. The liver has no significant role in the clearance of ibandronic acid since it is not metabolized but is cleared by renal excretion and by uptake into bone. Therefore dosage adjustment is not necessary in patients with hepatic impairment. Further, as protein binding of ibandronic acid is approximately 87% at therapeutic concentrations, hypoproteinaemia in severe liver disease is unlikely to lead to clinically significant increases in free plasma concentration.

*Elderly*
In a multivariate analysis, age was not found to be an independent factor of any of the pharmacokinetic parameters studied. As renal function decreases with age, this is the only factor that should be considered (see renal impairment section).

*Paediatric population*
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 drug (bisphosphonates). They include a decreased number of implantation sites, interference with natural delivery (dystocia), an increase in visceral variations (renal pelvis ureter syndrome) and teeth abnormalities in F1 offspring in rats.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Sodium chloride
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

2 years.

*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℃ and 2 ℃ to 8 ℃.
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℃ 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 fluorotec plus rubber stopper and aluminium seals with lavender flip-off cap. It is supplied as packs containing 1 vial.

### 6.6 Special precautions for disposal

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

## 7. MARKETING AUTHORISATION HOLDER

Accord Healthcare Limited
Sage House
319, Pinner Road
North Harrow
Middlesex HA1 4 HF
United Kingdom

## 8. MARKETING AUTHORISATION NUMBER(S)

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

## 10. DATE OF REVISION OF THE TEXT

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

## 1. NAME OF THE MEDICINAL PRODUCT

Ibandronic acid Accord 6 mg concentrate for solution for infusion

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial with 6 ml concentrate for solution for infusion contains 6 mg ibandronic acid (as 6.75 mg ibandronate sodium monohydrate).

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.
Clear, colourless solution.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

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

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. For infusion, the contents of the vial(s) should only be added to 100 ml isotonic sodium chloride solution or 100 ml 5% glucose solution.

A shorter (i.e. 15 min) infusion time should only be used for patients with normal renal function or mild renal impairment. There are no data available characterizing 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. 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 dosage. In patients with moderate hypercalcaemia (albumin-corrected serum calcium <3 mmol/l or <12 mg/dl) 2 mg is an effective dose. The highest dose used in clinical trials was 6 mg but this dose does not add

any further benefit in terms of efficacy.

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

| | | |
|---|---|---|
| Albumin-corrected serum calcium (mmol/l) | = | serum calcium (mmol/l) - [0.02 x albumin (g/l)] + 0.8 |
| | **Or** | |
| Albumin-corrected serum calcium (mg/dl) | = | serum calcium (mg/dl) + 0.8 x [4 - albumin (g/dl)] |
| To convert the albumin-corrected serum calcium in mmol/l value to mg/dl, multiply by 4. | | |

In most cases a raised serum calcium level can be reduced to the normal range within 7 days. The median time to relapse (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.

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

*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 (see Section 5.2):

| Creatinine Clearance (ml/min) | Dosage / Infusion time [1] | Infusion Volume [2] |
|---|---|---|
| ≥50 CLcr <80 | 6 mg / 15 minutes | 100 ml |
| ≥30 CLcr <50 | 4 mg / 1 hour | 500 ml |
| <30 | 2 mg / 1 hour | 500 ml |

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

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

*Elderly*
No dose adjustment is required.

*Paediatric population*
The safety and efficacy of ibandronic acid in children and adolescents below age 18 years have not been established. No data are available.

Method of administration
For intravenous administration.

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. For this purpose, the contents of the vials are to be added to 500 ml isotonic sodium chloride solution (or 500 ml 5% dextrose solution) and infused over two hours.

As the inadvertent intra-arterial administration of preparations not expressly recommended for this purpose as well as paravenous administration can lead to tissue damage, care must be taken to ensure that ibandronic acid concentrate for solution for infusion is administered intravenously.

## 4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients.
- Caution is to be taken in patients with known hypersensitivity to other bisphosphonates.
- 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

*Osteonecrosis of the jaw (ONJ)*
Osteonecrosis of the jaw, generally associated with tooth extraction and/or local infection (including osteomyelitis) has been reported in patients with cancer receiving treatment regimens including primarily intravenously administered bisphosphonates. Many of these patients were also receiving chemotherapy and corticosteroids. Osteonecrosis of the jaw has also been reported in patients with osteoporosis receiving oral bisphosphonates.

A dental examination with appropriate preventive dentistry should be considered prior to treatment with bisphosphonates in patients with concomitant risk factors (e.g. cancer, chemotherapy, radiotherapy, corticosteroids, poor oral hygiene).

While on treatment, these patients should avoid invasive dental procedures if possible. For patients who develop osteonecrosis of the jaw while on bisphosphonate therapy, dental surgery may exacerbate the condition. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of osteonecrosis of the jaw. Clinical judgement of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

*Atypical fractures of the femur*
Atypical subtrochanteric and diaphyseal femoral fractures have been reported with bisphosphonate therapy, primarily in patients receiving long-term treatment for osteoporosis. These transverse or short oblique fractures can occur anywhere along the femur from just below the lesser trochanter to just above the supracondylar flare. These fractures occur after minimal or no trauma and some patients experience thigh or groin pain, often associated with imaging features of stress fractures, weeks to months before presenting with a completed femoral fracture. Fractures are often bilateral; therefore the contralateral femur should be examined in bisphosphonate-treated patients who have sustained a femoral shaft fracture. Poor healing of these fractures has also been reported. Discontinuation of bisphosphonate therapy in patients suspected to have an atypical femur fracture should be considered pending evaluation of the patient, based on an individual benefit risk assessment. During bisphosphonate treatment patients should be advised to report any thigh, hip or groin pain and any patient presenting with such symptoms should be evaluated for an incomplete femur fracture.

*Patients with renal impairment*
Clinical studies have not shown any evidence of deterioration in renal function with long term ibandronic acid therapy. Nevertheless, according to clinical assessment of the individual patient, it is recommended that renal function, serum calcium, phosphate and magnesium should be monitored in patients treated with ibandronic acid.

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

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

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

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

Interaction studies have only been performed in adults.

No interaction was observed when co-administered with melphalan/prednisolone in patients with multiple myeloma.

Other interaction studies in postmenopausal women have demonstrated the absence of any interaction potential with tamoxifen or hormone replacement therapy (oestrogen).

In relation to disposition, no drug interactions of clinical significance are likely. Ibandronic acid is eliminated by renal secretion only and does not undergo any biotransformation. The secretory pathway does not appear to include known acidic or basic transport systems involved in the excretion of other active substances. In addition, ibandronic acid does not inhibit the major human hepatic P450 isoenzymes and does not induce the hepatic cytochrome P450 system in rats. Plasma protein binding is low at therapeutic concentrations and ibandronic acid is therefore unlikely to displace other active substances.

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

In clinical studies, ibandronic acid has been administered concomitantly with commonly used antineoplastics, diuretics, antibiotics and analgesics without clinically apparent interactions occurring.

## 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 lactation.

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

No studies on the effects on the ability to drive and use machines have been performed.

## 4.8 Undesirable effects

Adverse reactions are ranked under heading of frequency, the most frequent first, using the following convention: very common ( ≥1/10), common ( ≥1/100 and <1/10), uncommon ( ≥1/1,000 and <1/100), rare ( ≥1/10,000 and <1/1,000), and very rare (<1/10,000).

*Treatment of tumour induced hypercalcaemia*
The safety profile for ibandronic acid in tumour-induced hypercalcaemia is derived from controlled clinical trials in this indication and after the intravenous administration of ibandronic acid at the recommended doses. Treatment was most commonly associated with a rise in body temperature. Occasionally, a flu-like syndrome consisting of fever, chills, bone and/or muscle ache-like pain was reported. In most cases no specific treatment was required and the symptoms subsided after a couple of hours/days.

**Table 1 Adverse Events in Controlled Clinical Trials in Tumour-Induced Hypercalcaemia after Treatment with Ibandronic acid**

| System Organ Class | Very common | Common | Uncommon | Rare | Very rare |
|---|---|---|---|---|---|
| **Immune system disorders** | | | | | Hypersensitivity |
| **Metabolism and nutritional disorders** | | Hypo-calcaemia** | | | |
| **Respiratory, thoracic, and mediastinal disorders** | | | | | Bronchospasm |
| **Skin and subcutaneous tissue disorders** | | | | | Angioneurotic oedema |
| **Musculo-skeletal and connective tissue disorders** | | Bone pain | Myalgia | | |
| **General disorders and administration site conditions** | Pyrexia | | Influenza-like illness**, rigors | | |

Note: Data for both the 2 mg and 4 mg doses of ibandronic acid are pooled.
**See further information below

*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.

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

Table 2 lists adverse drug reactions from the pivotal phase III study (152 patients treated with ibandronic acid 6 mg), i.e. adverse events with a remote, possible, or probable relationship to study medication, and from postmarketing experience.

**Table 2 Adverse Drug Reactions Occurring in Patients with Metastatic Bone Disease due to Breast Cancer Treated with Ibandronic acid 6 mg administered intravenously**

| System Organ Class | Very common | Common | Uncommon | Rare | Very rare |
|---|---|---|---|---|---|
| **Infections and infestations** | | Infection | Cystitis, vaginitis, oral candidiasis | | |
| **Neoplasms benign, malignant, and unspecified** | | | Benign skin neoplasm | | |
| **Blood and lymphatic system disorders** | | | Anaemia, blood dyscrasia | | |
| **Endocrine disorders** | | Parathyroid disorder | | | |
| **Metabolism and nutrition disorders** | | | Hypophosphataemia | | |
| **Psychiatric disorders** | | | Sleep disorder, anxiety, affection lability | | |
| **Nervous system disorders** | | Headache, dizziness, dysgeusia (taste perversion) | Cerbrovascular 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 | | |
| **Musculoskeletal and connective tissue disorders** | | Osteoarthritis, myalgia, arthralgia, joint disorder | | Atypical subtrochanteric and diaphyseal femoral fractures† (bisphosphonate class adverse reaction) | Osteonecrosis of jaw†** |
| **Renal and urinary** | | | Urinary retention, renal cyst | | |
| **Reproductive system and breast disorders** | | | Pelvic pain | | |
| **General disorders and administration site conditions** | | 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 postmarketing experience.

*Osteonecrosis of jaw*
Osteonecrosis of the jaw has been reported in patients treated by bisphosphonates. The majority of the reports refer to cancer patients, but such cases have also been reported in patients treated for osteoporosis. Osteonecrosis of the jaw is generally associated with tooth extraction and / or local infection (including osteomyelitis). Diagnosis of cancer, chemotherapy, radiotherapy, corticosteroids and poor oral hygiene are also deemed as risk factors (see section 4.4).

*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.

### 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: Drugs for treatment of bone diseases, bisphosphonate,
ATC Code: M05BA06

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

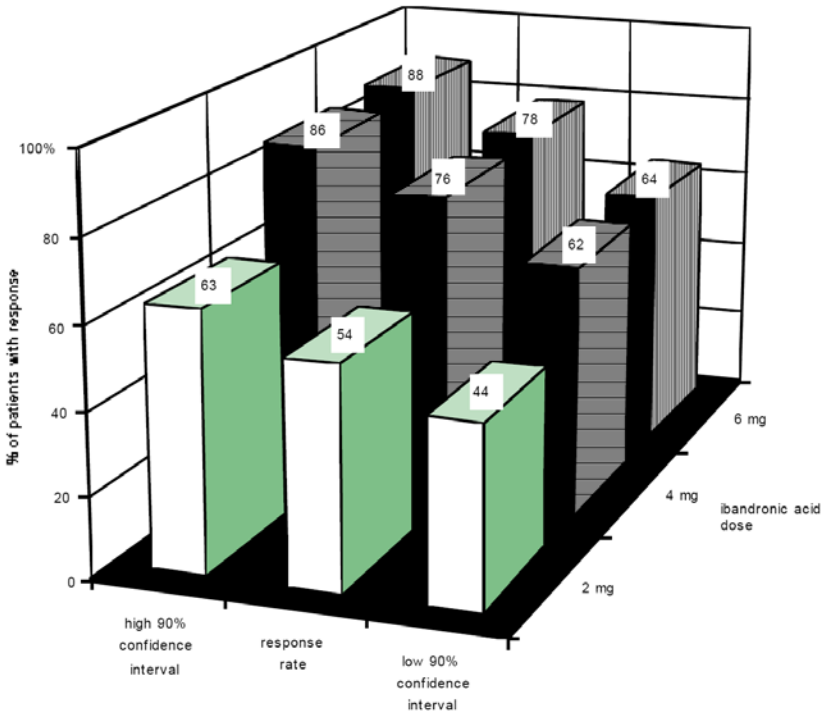
*In vivo*, ibandronic acid prevents experimentally-induced bone destruction caused by cessation of gonadal function, retinoids, tumours or tumour extracts. The inhibition of endogenous bone resorption has also been documented by $^{45}Ca$ kinetic studies and by the release of radioactive tetracycline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

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

Bone resorption due to malignant disease is characterized by excessive bone resorption that is not balanced with appropriate bone formation. Ibandronic acid selectively inhibits osteoclast activity, reducing bone resorption and thereby reducing skeletal complications of the malignant disease.

*Clinical studies in 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.




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 3.

**Table 3 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 4.

**Table 4 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*
The safety and efficacy of ibandronic acid in children and adolescents below age 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 drug-drug interaction 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.

*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*
There are no pharmacokinetic data for ibandronic acid in patients who have hepatic impairment. The liver has no significant role in the clearance of ibandronic acid since it is not metabolized but is cleared by renal excretion and by uptake into bone. Therefore dosage adjustment is not necessary in patients with hepatic impairment. Further, as protein binding of ibandronic acid is approximately 87% at therapeutic concentrations, hypoproteinaemia in severe liver disease is unlikely to lead to clinically significant increases in free plasma concentration.

*Elderly*
In a multivariate analysis, age was not found to be an independent factor of any of the pharmacokinetic parameters studied. As renal function decreases with age, this is the only factor that should be considered (see renal impairment section).

*Paediatric population*
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 drug (bisphosphonates). They include a decreased number of implantation sites, interference with natural delivery (dystocia), an increase in visceral variations (renal pelvis ureter syndrome) and teeth abnormalities in F1 offspring in rats.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Sodium chloride
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

2 years.

*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.

### 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 fluorotec plus rubber stopper and aluminium seals with pink flip-off cap. It is supplied as packs containing 1, 5 and 10 vials.
Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal

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

## 7. MARKETING AUTHORISATION HOLDER

Accord Healthcare Limited
Sage House
319, Pinner Road
North Harrow
Middlesex HA1 4 HF
United Kingdom

## 8. MARKETING AUTHORISATION NUMBER(S)

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

## 10. DATE OF REVISION OF THE TEXT

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

# ANNEX II

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

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

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

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

Name and address of the manufacturer(s) responsible for batch release

Accord Healthcare Ltd.
Ground Floor
Sage House
319 Pinner road
North Harrow, Middx HA1 4HF
United Kingdom

## B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

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

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

Pharmacovigilance system

The MAH must ensure that the system of pharmacovigilance presented in Module 1.8.1. of the Marketing Authorisation is in place and functioning before and whilst the medicinal product is on the market.

Risk Management Plan (RMP)

The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan as agreed in the Risk Management Plan presented in Module 1.8.2. of the Marketing Authorisation and any subsequent updates of the RMP agreed by the Committee for Medicinal Products for Human Use (CHMP).

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, an updated RMP should be submitted

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the European Medicines Agency.

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

Not applicable.

**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 2.25 mg ibandronate sodium monohydrate).

## 3. LIST OF EXCIPIENTS

Sodium chloride, sodium acetate trihydrate, glacial acetic acid and water for injections. See the package 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 Limited
Sage House
319, Pinner Road
North Harrow
Middlesex HA1 4 HF
United Kingdom

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

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

**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
I.V. 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 6.75 mg ibandronate sodium monohydrate).

## 3. LIST OF EXCIPIENTS

Sodium chloride, sodium acetate trihydrate, glacial acetic acid and water for injections. See the package 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 Limited
Sage House
319, Pinner Road
North Harrow
Middlesex HA1 4 HF
United Kingdom

## 12. MARKETING AUTHORISATION NUMBER(S)

## 13. BATCH NUMBER

Lot:

## 14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

**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
I.V. use

## 2. METHOD OF ADMINISTRATION

## 3. EXPIRY DATE

EXP:

## 4. BATCH NUMBER<, DONATION AND PRODUCT CODES>

Lot:

## CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6 mg/6 ml

## 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.**
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

**In this leaflet:**


## 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 indicated 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. BEFORE YOU RECEIVE IBANDRONIC ACID ACCORD

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

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

**Take special care with Ibandronic acid Accord**
- if you are allergic (hypersensitive) to any other bisphosphonates.
- if you have high or low levels of vitamin D or any other minerals.
- if you have kidney problems.

If any of the above apply to you (or you are not sure), talk to your doctor or pharmacist before receiving Ibandronic acid Accord.
If you are having dental treatment or surgery or know that you need some in the future, tell your dentist that you are being treated with Ibandronic acid Accord.

**Children and teenagers**
Ibandronic acid Accord should not be used in children and teenagers below age 18 years.

**Taking other medicines**
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including those obtained without a prescription. 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 any medicines.

**Driving and using machines**
It is not known if Ibandronic acid Accord affects your ability to drive, use machines or tools. Talk to your doctor first if you want to drive, use machines or tools.

**Important information about some of the ingredients**
This medicinal product 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.
- 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, than the recommended dose is 6 mg every 3-4 weeks, as an infusion to your vein over at least 15 minutes.
If you have raised calcium level in your blood due to a tumour than 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 to 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:**
- rash, itching, swelling of your face, lips, tongue and throat, with difficulty breathing. You may be having an allergic reaction to the medicine

- problems breathing.
- pain or sore in your mouth or jaw
- eye pain and inflammation (if prolonged).

**Other possible side effects**
**Very common** (affects more than 1 in 10 people)
- rise in body temperature.

**Common** (affects less than 1 in 10 people)
- stomach pain, indigestion, being sick or having diarrhoea
- low calcium or phosphate levels in your blood
- changes in blood test results such as Gamma GT or creatinine
- a heart problem called “bundle branch block”
- flu-like symptoms (including fever, chills, bone pain and aching muscles). These symptoms usually disappear within a couple of hours or days
- pain or stiffness in your 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** (affects 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”
- heart and circulatory problems (including palpitations, heart attack, hypertension 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
- 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
- hair loss
- pain or injury at the injection site
- weight loss

- kidney cyst.

**Rare** (affects less than 1 in 1000 people)
- eye pain or inflammation
- unusual fracture of the thigh bone particularly in patients on long-term treatment for osteoporosis may occur rarely. Contact your doctor if you experience pain, weakness or discomfort in your thigh, hip or groin as this may be an early indication of a possible fracture of the thigh bone.

**Very rare** (affects less than 1 in 10000 people)
- a condition involving exposed bone in the mouth called "osteonecrosis of the jaw".

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

## 5. HOW TO STORE IBANDRONIC ACID ACCORD

Keep this medicine out of the sight and reach of children.

Do not use Ibandronic acid Accord 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 Ibandronic acid Accord if you notice that the solution is not clear or contains particles.

## 6. FURTHER 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 colourless, clear solution.

It is supplied in:
**Ibandronic acid Accord 2 mg concentrate for solution for infusion**
6 ml, glass vial (type I) with fluorotec plus rubber stopper and aluminium seals with lavender flip-off cap.
**Ibandronic acid Accord 6 mg concentrate for solution for infusion**
6 ml, glass vial (type I) with fluorotec plus rubber stopper and aluminium seals with pink flip-off cap.

Pack size:
**Ibandronic acid Accord 2 mg concentrate for solution for infusion**
It is supplied as packs containing 1 vial.
**Ibandronic acid Accord 6 mg concentrate for solution for infusion**
It is supplied as packs containing 1, 5 and 10 vials. Not all pack sizes may be marketed.

**Marketing Authorisation Holder and Manufacturer**
Accord Healthcare Limited
Sage House
319, Pinner Road
North Harrow
Middlesex HA1 4 HF
United Kingdom

**This leaflet was last approved in**

**Other sources of information**

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

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.

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**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 time [1] | Infusion Volume [2] |
|---|---|---|
| ≥50 CLcr <80 | 6 mg / 15 minutes | 100 ml |
| ≥30 CLcr <50 | 4 mg / 1 hour | 500 ml |
| <30 | 2 mg / 1 hour | 500 ml |

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

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

**Dosage: 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) | = | 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.

**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:
- Hypercalcaemia - added to 500 ml isotonic sodium chloride solution or 500 ml 5 % dextrose solution and infused over 1-2 hours.
- 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 dosage section above

for patients with renal impairment.

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").

As the inadvertent intra-arterial administration of preparations not expressly recommended for this purpose as well as paravenous administration can lead to tissue damage, care must be taken to ensure that Ibandronic acid Accord concentrate for solution for infusion is administered intravenously.

**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.