SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ibandronic Acid 3mg/3ml Solution for Injection in pre-filled syringe

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One pre-filled syringe of 3 ml solution for injection contains 3 mg ibandronic acid (as 3.375 mg ibandronic acid, monosodium salt, monohydrate).
The concentration of ibandronic acid in the solution for injection is 1 mg per ml.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in pre-filled syringe.
Clear, colourless solution.

The pH of the solution is 4.9 – 5.5.

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 ibandronic acid or to any of the excipients listed in section 6.1.
- Hypocalcaemia (see section 4.4)

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.

Excipient(s)
Sodium
This medicine contains less than 1 mmol sodium (23 mg) per dose (3 ml), 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.

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 breast-feeding.

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 (MF4411).
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**
Immune system disorders		Asthma exacerbation	Hypersensitivity reaction	Anaphylactic reaction/shock*†
Nervous system disorders	Headache			
Eye disorders			Ocular inflammation*†	

System Organ Class	Common	Uncommon	Rare	Very rare
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† (bisphosphonates class adverse reaction)	Osteonecrosis of jaw*† osteonecrosis of the external auditory canal (bisphosphonate class adverse reaction)*†
General disorders and administration site conditions	Influenza like illness*, Fatigue	Injection site reactions, Asthenia		

*See further information below
†Identified in postmarketing 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.

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 Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

No specific information is available on the treatment of overdosage with ibandronic acid.

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 of 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 this is the only factor to take into consideration (see renal impairment section).

Paediatric population (see section 4.2 and section 5.1)
There are no data on the use of ibandronic acid in these age groups.

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. 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. Body weight gain was decreased in F1 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
Sodium hydroxide (E524) (for pH adjustment)
Acetic acid, glacial (E260)
Sodium acetate trihydrate
Water for injections.

6.2 Incompatibilities

This medical product must not be mixed with other medicinal products except those mentioned in section 6.6.

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 the container

Pre-filled syringes (3 ml) of colourless type I glass containing 3 ml of solution for injection.

Packs of 1 pre-filled syringe and 1 injection needle.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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 provider

7. MARKETING AUTHORISATION HOLDER

Teva UK Limited, Brampton Road, Hampden Park, Eastbourne, East Sussex BN22 9AG, UNITED KINGDOM

8. MARKETING AUTHORISATION NUMBER(S)

PL 00289/1759

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

27/02/2012

10. DATE OF REVISION OF THE TEXT

31/12/2020