

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ibandronic Acid Arrow 150 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 150 mg of Ibandronic Acid (as sodium ibandronate monohydrate).

Excipient: Contains 50.70 mg Sorbitol

For a full list of excipients, see Section 6.1

3 PHARMACEUTICAL FORM

Tablets

White to off-white, capsule shaped tablet with 'IN 150' on one side and '>' on the other side.

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

Posology

The recommended dose is one 150 mg tablet once a month. The tablet should preferably be taken on the same date each month.

Ibandronic Acid Tablets should be taken after an overnight fast (at least 6 hours) and 1 hour before the first food or drink (other than water) of the day (see section 4.5) or any other oral medicinal products or supplementation (including calcium).

In case a dose is missed, patients should be instructed to take one Ibandronic Acid 150 mg Tablet the morning after the tablet is remembered, unless the time to the next scheduled dose is within 7 days. Patients should then return to taking their dose once a month on their originally scheduled date. If the next scheduled dose is within 7 days, patients should wait until their next dose and then continue taking one tablet once a month as originally scheduled.

Patients should not take two tablets within the same week.

Patients should receive supplemental calcium and / or vitamin D if dietary intake is inadequate (see section 4.4 and section 4.5).

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

No dose adjustment is necessary for patients with mild or moderate renal impairment where creatinine clearance is equal or greater than 30 ml/min.

Ibandronic Acid Tablets are not recommended for patients with a creatinine clearance below 30 ml/min due to limited clinical experience (see section 4.4 and section 5.2).

Patients with hepatic impairment

No dose adjustment is required (see section 5.2).

Elderly population

No dose adjustment is required (see section 5.2).

Paediatric population

There is no relevant use of Ibandronic Acid Tablets in children, and ibandronic acid was not studied in the paediatric population.

Method of administration

For oral use.

Tablets should be swallowed whole with a glass of plain water (180 to 240 ml) while the patient is sitting or standing in an upright position. Patients should not lie down for 1 hour after taking Ibandronic Acid Tablets.

Plain water is the only drink that should be taken with Ibandronic Acid Tablets. Please note that some mineral waters may have a higher concentration of calcium and therefore, should not be used.

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

4.3 Contraindications

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

See also section 4.4.

4.4 Special warnings and precautions for use

Hypocalcaemia

Existing hypocalcaemia must be corrected before starting ibandronic acid therapy. Other disturbances of bone and mineral metabolism should also be effectively treated. Adequate intake of calcium and vitamin D is important in all patients

Gastrointestinal disorders

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

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

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

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

Since Nonsteroidal Anti-Inflammatory Drugs and bisphosphonates are both associated with gastrointestinal irritation, caution should be taken during concomitant administration.

Osteonecrosis of the jaw

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.

Renal impairment

Due to limited clinical experience, Ibandronic Acid Tablets are not recommended for patients with a creatinine clearance below 30 ml/min (see section 5.2).

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.

Sorbitol

This medicinal product contains sorbitol. Patients with rare hereditary problems of fructose intolerance should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Oral bioavailability of ibandronic acid is generally reduced in the presence of food. In particular, products containing calcium and other multivalent cations (such as aluminium, magnesium, iron), including milk, are likely to interfere with absorption of Ibandronic Acid Tablets, which is consistent with findings in animal studies. Therefore, patients should fast overnight (at least 6 hours) before taking Ibandronic Acid Tablets and continue fasting for 1 hour following intake of Ibandronic Acid Tablets (see section 4.2).

Calcium supplements, antacids and some oral medicinal products containing multivalent cations (such as aluminium, magnesium, iron) are likely to interfere with the absorption of Ibandronic Acid Tablets. Therefore, patients should not take other oral medicinal products for at least 6 hours before taking Ibandronic Acid Tablets and for 1 hour following intake of Ibandronic Acid Tablets.

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. Furthermore, plasma protein binding is approximately 85 % - 87 % (determined in vitro at therapeutic concentrations), and thus there is a low potential for interaction with other medicinal products due to displacement. Ibandronic acid is eliminated by renal excretion only and does not undergo any biotransformation. The secretory pathway appears not to include known acidic or basic transport systems involved in the excretion of other active substances.

In a two-year study in postmenopausal women with osteoporosis (BM 16549), the incidence of upper gastrointestinal events in patients concomitantly taking aspirin or NSAIDs was similar in patients taking ibandronic acid 2.5 mg daily or 150 mg once monthly after one and two years.

Of over 1500 patients enrolled in study BM 16549 comparing monthly with daily dosing regimens of ibandronic acid, 14 % and 18 % of patients used histamine (H₂) blockers or proton pump inhibitors after one and two years, respectively. Among these patients, the incidence of upper gastrointestinal events in the patients treated with ibandronic acid 150 mg once monthly was similar to that in patients treated with ibandronic acid 2.5 mg daily.

In healthy male volunteers and postmenopausal women, intravenous administration of ranitidine caused an increase in ibandronic acid bioavailability of about 20 %, probably as a result of reduced gastric acidity. However, since this increase is within the normal variability of the bioavailability of ibandronic acid, no dose adjustment is considered necessary when Ibandronic Acid Tablets are administered with H₂-antagonists or other active substances which increase gastric pH.

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

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

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 some reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Ibandronic Acid Tablets 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 Tablets should not be used during lactation.

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

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). The overall safety profile of ibandronic acid 2.5 mg daily in all these studies was similar to that of placebo.

In a two-year study in postmenopausal women with osteoporosis (BM 16549) the overall safety of ibandronic acid 150 mg once monthly and ibandronic acid 2.5 mg daily was similar. The overall proportion of patients who experienced an adverse reaction, was 22.7 % and 25.0 % for ibandronic acid 150 mg once monthly after one and two years, respectively. The majority of adverse reactions were mild to moderate in intensity. Most cases did not lead to cessation of therapy.

The most commonly reported adverse reaction was arthralgia.

Adverse reactions considered by investigators to be casually related to ibandronic acid are listed below by System Organ Class.

Frequencies are defined as common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), and rare ($\geq 1/10,000$ to $< 1/1,000$). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1: Adverse drug reactions occurring in postmenopausal women receiving ibandronic acid 150 mg once monthly or ibandronic acid 2.5mg daily in the phase III studies BM 16549 and MF4411 and in postmarketing experience.

System Organ Class	Common	Uncommon	Rare	Very rare
Immune system disorders			Hypersensitivity reaction	
Nervous system disorders	Headache	Dizziness		
Eye disorders			Ocular inflammation*†	
Gastrointestinal disorders*	Oesophagitis, Gastritis, Gastro oesophageal reflux disease, Dyspepsia, Diarrhoea, Abdominal pain, Nausea	Oesophagitis including oesophageal ulcerations or strictures and dysphagia, Vomiting, Flatulence	Duodenitis	
Skin and subcutaneous tissues disorders	Rash		Angioedema, Face oedema, Urticaria	
Musculoskeletal, connective tissue and bone disorders	Arthralgia, Myalgia, Musculoskeletal pain, Muscle cramp, Musculoskeletal stiffness	Back pain		Osteonecrosis of jaw*†
General disorders and administration site conditions	Influenza like illness*	Fatigue		

*See further information below

†Identified in postmarketing experience.

Gastrointestinal adverse events

Patients with a previous history of gastrointestinal disease including patients with peptic ulcer without recent bleeding or hospitalisation, and patients with dyspepsia or reflux controlled by medication were included in the once monthly treatment study. For these patients, there was no difference in the incidence of upper gastrointestinal adverse events with the 150 mg once monthly regimen compared to the 2.5 mg daily regimen.

Influenza-like illness

Transient, influenza-like symptoms have been reported with ibandronic acid 150mg once monthly, typically in association with the first dose. Such symptoms were generally of short duration, mild or moderate in intensity, and resolved during continuing treatment without requiring remedial measures. Influenza-like illness includes events reported as acute phase reaction or symptoms including myalgia, arthralgia, fever, chills, fatigue, nausea, loss of appetite, or bone pain.

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.

Post-marketing Experience

During post-marketing experience, the following reactions have been reported (frequency rare):
Atypical subtrochanteric and diaphyseal femoral fractures (bisphosphonate class adverse reaction)

4.9 Overdose

No specific information is available on the treatment of over dosage with Ibandronic Acid Tablets.

However, based on knowledge of this class of compounds, oral over-dosage may result in upper gastrointestinal adverse reactions (such as upset stomach, dyspepsia, oesophagitis, gastritis, or ulcer) or hypocalcaemia. Milk or antacids should be given to bind ibandronic acid, and any adverse reactions treated symptomatically. Owing to the risk of oesophageal irritation, vomiting should not be induced and the patient should remain fully upright.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for treatment of bone diseases, bisphosphonates, ATC code: M05B A06

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 experimentally induced bone destruction caused 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 mineralization 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)).

In a Phase 1 bioequivalence study conducted in 72 postmenopausal women receiving 150 mg orally every 28 days for a total of four doses, inhibition in serum CTX following the first dose was seen as early as 24 hours post-dose (median inhibition 28 %), with median maximal inhibition (69 %) seen 6 days later. Following the third and fourth dose, the median maximum inhibition 6 days post dose was 74 % with reduction to a median inhibition of 56 % seen 28 days following the fourth dose. With no further dosing, there is a loss of suppression of biochemical markers of bone resorption.

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 150 mg once monthly

Bone mineral density (BMD)

Ibandronic acid 150 mg once monthly was shown to be at least as effective as ibandronic acid 2.5 mg daily at increasing BMD in a two year, double-blind, multicentre study (BM 16549) of postmenopausal women 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).

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 16549.

	One year data in study BM 16549		Two year data in study BM 16549	
	ibandronic acid 2.5 mg daily (N = 318)	ibandronic acid 150 mg once monthly (N = 320)	ibandronic acid 2.5 mg daily (N = 294)	ibandronic acid 150 mg once monthly (N = 291)
Mean relative changes from baseline % [95% CI]				
Lumbar spine L2-L4 BMD	3.9 [3.4, 4.3]	4.9 [4.4, 5.3]	5.0 [4.4, 5.5]	6.6 [6.0, 7.1]
Total hip BMD	2.0 [1.7, 2.3]	3.1 [2.8, 3.4]	2.5 [2.1, 2.9]	4.2 [3.8, 4.5]
Femoral neck BMD	1.7 [1.3, 2.1]	2.2 [1.9, 2.6]	1.9 [1.4, 2.4]	3.1 [2.7, 3.6]
Trochanter BMD	3.2 [2.8, 3.7]	4.6 [4.2, 5.1]	4.0 [3.5, 4.5]	6.2 [5.7, 6.7]

Furthermore, ibandronic acid 150 mg once monthly was proven superior to ibandronic acid 2.5 mg daily for increases in lumbar spine BMD in a prospectively planned analysis at one year, $p=0.002$, and at two years, $p<0.001$.

At one year (primary analysis), 91.3 % ($p=0.005$) of patients receiving ibandronic acid 150 mg once monthly had a lumbar spine BMD increase above or equal to baseline (BMD responders), compared with 84.0 % of patients receiving ibandronic acid 2.5 mg daily. At two years, 93.5 % ($p=0.004$) and 86.4 % of patients receiving ibandronic acid 150 mg once monthly or ibandronic acid 2.5 mg daily, respectively, were responders.

For total hip BMD, 90.0 % ($p<0.001$) of patients receiving ibandronic acid 150 mg once monthly and 76.7 % of patients receiving ibandronic acid 2.5 mg daily had total hip BMD increases above or equal to baseline at one year. At two years 93.4 % ($p<0.001$) of patients receiving ibandronic acid 150 mg once monthly and 78.4 %, of patients

receiving ibandronic acid 2.5 mg daily had total hip BMD increases above or equal to baseline.

When a more stringent criterion is considered, which combines both lumbar spine and total hip BMD, 83.9 % ($p < 0.001$) and 65.7 % of patients receiving ibandronic acid 150 mg once monthly or ibandronic acid 2.5 mg daily, respectively, were responders at one year. At two years, 87.1 % ($p < 0.001$) and 70.5 %, of patients met this criterion in the 150 mg monthly and 2.5 mg daily arms respectively.

Biochemical markers of bone turn-over

Clinically meaningful reductions in serum CTX levels were observed at all time points measured, i.e. months 3, 6, 12 and 24. After one year (primary analysis) the median relative change from baseline was -76 % for ibandronic acid 150 mg once monthly and -67 % for ibandronic acid 2.5 mg daily. At two years the median relative change was -68 % and -62 %, in the 150 mg monthly and 2.5 mg daily arms respectively.

At one year, 83.5 % ($p = 0.006$) of patients receiving ibandronic acid 150 mg once monthly and 73.9 % of patients receiving ibandronic acid 2.5 mg daily were identified as responders (defined as a decrease ≥ 50 % from baseline). At two years 78.7 % ($p = 0.002$) and 65.6 % of patients were identified as responders in the 150 mg monthly and 2.5 mg daily arms respectively.

Based on the results of study BM 16549, ibandronic acid 150 mg once monthly is expected to be at least as effective in preventing fractures as ibandronic acid 2.5 mg daily.

Ibandronic acid 2.5 mg daily

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 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 % ($p = 0.011$). 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 . 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 ibandronate 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 treatment with 2.5 mg 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.

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

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 showed bone of normal quality and no indication of a mineralization defect.

Paediatric population

Ibandronic Acid Tablets were 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.

Absorption

The absorption of ibandronic acid in the upper gastrointestinal tract is rapid after oral administration and plasma concentrations increase in a dose-proportional manner up to 50 mg oral intake, with greater than dose-proportional increases seen above this dose. Maximum observed plasma concentrations were reached within 0.5 to 2 hours (median 1 hour) in the fasted state and absolute bioavailability was about 0.6 %. The extent of absorption is impaired when taken together with food or beverages (other than plain water). Bioavailability is reduced by about 90 % when

ibandronic acid is administered with a standard breakfast in comparison with bioavailability seen in fasted subjects. There is no meaningful reduction in bioavailability provided ibandronic acid is taken 60 minutes before the first food of the day. Both bioavailability and BMD gains are reduced when food or beverage is taken less than 60 minutes after ibandronic acid is ingested.

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 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

The absorbed fraction of 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 unabsorbed fraction of ibandronic acid is eliminated unchanged in the faeces.

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 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.

Pharmacokinetics in special clinical situations

Gender

Bioavailability and 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 are few 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.

No dose adjustment is necessary for patients with mild or moderate renal impairment (CL_{cr} equal or greater than 30 ml/min), as shown in study BM 16549 where the majority of patients had mild to moderate renal impairment.

Subjects with severe renal failure (CL_{cr} 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, 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 was not assessed in patients with end-stage renal disease managed by other than hemodialysis. The pharmacokinetics of ibandronic acid in these patients is unknown, and ibandronic acid should not be used under these circumstances.

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 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

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

There are no data on the use of Ibandronic Acid Arrow 150 mg Tablets 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

There was no evidence for a direct foetal toxic or teratogenic effect of ibandronic acid in orally treated rats and rabbits and there were no adverse effects on the development in F₁ offspring in rats at an extrapolated exposure of at least 35 times above human exposure. Adverse effects of 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

Sorbitol (E420)
Cellulose, microcrystalline
Silica, colloidal anhydrous
Croscarmellose sodium
Sodium stearyl fumarate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

There are no special precautions for storage.

6.5 Nature and contents of container

Aluminum (foil/foil) blisters containing 1 or 3 tablets. 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

Arrow ApS
Sankt Peders Strade 2, 1
4000 Roskilde
Denmark

8 MARKETING AUTHORISATION NUMBER

PA 1522/4/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 5th November 2010

10 DATE OF REVISION OF THE TEXT

December 2011