

## Summary of Product Characteristics for Pharmaceutical Products

### 1. Name of the medicinal product:

IBANDRO 150 mg film-coated tablets

(Ibandronic Acid Tablets 150 mg)

### 2. Qualitative and quantitative composition

#### Each film-coated tablet contains:

Ibandronic Acid ..... 150 mg

Excipient with known effect: lactose.

For the full list of excipients, see section 6.1.

### 3. Pharmaceutical form

Film-coated tablet.

A white, oblong, bisected on one side, film-coated tablet.

### 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 film-coated tablet once a month. The tablet should preferably be taken on the same date each month.

Ibandronic acid 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*

Ibandronic acid is 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).

No dose adjustment is necessary for patients with mild or moderate renal impairment where creatinine clearance is equal to 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 section 5.2).

### **Method of administration**

For oral use.

- Tablets should be swallowed whole with a glass of water (180 to 240 ml) while the patient is sitting or standing in an upright position. Water with a high concentration of calcium should not be used. If there is a concern regarding potentially high levels of calcium in the tap water (hard water), it is advised to use bottled water with a low mineral content.
- Patients should not lie down for 1 hour after taking ibandronic acid.
- Water is the only drink that should be taken with ibandronic acid. 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 listed in section 6.1.
- Hypocalcaemia (see section 4.4).
- Abnormalities of the oesophagus which delay oesophageal emptying such as stricture or achalasia.

- Inability to stand or sit upright for at least 60 minutes.

#### **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 irritation*

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 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 non-steroidal anti-inflammatory medicinal products 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.

#### 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.

#### *Renal impairment*

Due to limited clinical experience, ibandronic acid is not recommended for patients with a creatinine clearance below 30 ml/min (see section 5.2).

#### *Galactose intolerance*

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

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

### Medicinal product-food interaction

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

### Interactions with other medicinal products

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.

### Calcium supplements, antacids and some oral medicinal products containing multivalent cations

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. Therefore, patients should not take other oral medicinal products for at least 6 hours before taking ibandronic acid and for 1 hour following intake of ibandronic acid.

### Acetylsalicylic acid and NSAIDs

Since acetylsalicylic acid, non-steroidal anti-inflammatory medicinal products (NSAIDs) and bisphosphonates are associated with gastrointestinal irritation, caution should be taken during concomitant administration (see section 4.4).

### H2 blockers or proton pump inhibitors

Of over 1,500 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 is administered with H2-antagonists or other active substances which increase gastric pH.

## **4.6 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 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.

## **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 of the jaw, gastrointestinal irritation 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 (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 1,251 patients treated in 4 placebo-controlled clinical studies, with the large majority of patients coming from the pivotal three-year fracture study (MF 4411).

In 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. Most cases 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 ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $< 1/10$ ), uncommon ( $\geq 1/1,000$  to  $< 1/100$ ), rare ( $\geq 1/10,000$  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 drug reactions occurring in postmenopausal women receiving ibandronic acid 150 mg once monthly or ibandronic acid 2.5 mg daily in the phase III studies BM 16549 and MF 4411 and in post-marketing experience**

| System Organ Class                                          | Common                                                                                                   | Uncommon                                                                                         | Rare                                                       | Very rare                                                                                                     |
|-------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------|
| <b>Immune system disorders</b>                              |                                                                                                          | Asthma exacerbation                                                                              | Hypersensitivity reaction                                  | Anaphylactic reaction/shock*†                                                                                 |
| <b>Nervous system disorders</b>                             | Headache                                                                                                 | Dizziness                                                                                        |                                                            |                                                                                                               |
| <b>Eye disorders</b>                                        |                                                                                                          |                                                                                                  | Ocular inflammation*†                                      |                                                                                                               |
| <b>Gastrointestinal disorders*</b>                          | Oesophagitis, Gastritis, Gastro-oesophageal reflux disease, Dyspepsia, Diarrhoea, Abdominal pain, Nausea | Oesophagitis including oesophageal ulcerations or strictures and dysphagia, Vomiting, Flatulence | Duodenitis                                                 |                                                                                                               |
| <b>Skin and subcutaneous tissue disorders</b>               | Rash                                                                                                     |                                                                                                  | Angioedema, Face oedema, Urticaria                         | Stevens-Johnson syndrome†, Erythema multiforme†, Dermatitis bullous†                                          |
| <b>Musculoskeletal and connective tissue disorders</b>      | Arthralgia, Myalgia, Musculoskeletal pain, Muscle cramp, Musculoskeletal stiffness                       | Back pain                                                                                        | Atypical subtrochanteric and diaphyseal femoral fractures† | Osteonecrosis of jaw*†, Osteonecrosis of the external auditory canal (bisphosphonate class adverse reaction†) |
| <b>General disorders and administration site conditions</b> | Influenza-like illness*                                                                                  | Fatigue                                                                                          |                                                            |                                                                                                               |

\*See further information below.

† Identified in post-marketing experience.

## Description of selected adverse reactions

### *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*

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 the jaw*

Osteonecrosis of the jaw has been reported in patients treated with 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 to be 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.

### *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**

Healthcare professionals are asked to report any suspected adverse reactions via the Pharmacy and Poisons Board, Pharmacovigilance Electronic Reporting System (PvERS): <https://pv.pharmacyboardkenya.org>

## **4.9 Overdose**

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

However, based on knowledge of this class of compounds, oral overdosage 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: 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 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 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)).

In a phase I 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      |                                             |
|------------------------------------------------|--------------------------------------|---------------------------------------------|--------------------------------------|---------------------------------------------|
| Mean relative changes from baseline % [95% CI] | 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) |
| 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 turnover

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  $\geq 50$  % 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) |
|-----------------------------------------------------------------------|---------------------|--------------------------------------|
| <b>Relative risk reduction – new morphometric vertebral fractures</b> |                     | 62 % (40.9, 75.1)                    |
| <b>Incidence of new morphometric vertebral fractures</b>              | 9.56 % (7.5, 11.7)  | 4.68 % (3.2, 6.2)                    |
| <b>Relative risk reduction of clinical vertebral fracture</b>         |                     | 49 % (14.03, 69.49)                  |
| <b>Incidence of clinical vertebral fracture</b>                       | 5.33 % (3.73, 6.92) | 2.75 % (1.61, 3.89)                  |

|                                                                      | Placebo (N=974)      | ibandronic acid 2.5 mg daily (N=977) |
|----------------------------------------------------------------------|----------------------|--------------------------------------|
| <b>BMD – mean change relative to baseline lumbar spine at year 3</b> | 1.26 % (0.8, 1.7)    | 6.54 % (6.1, 7.0)                    |
| <b>BMD – mean change relative to baseline total hip at year 3</b>    | -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) |
|-----------------------------------------------------------------------|-----------------------|--------------------------------------|
| <b>Relative risk reduction – new morphometric vertebral fractures</b> |                       | 59 % (34.5, 74.3)                    |
| <b>Incidence of new morphometric vertebral fractures</b>              | 12.54 % (9.53, 15.55) | 5.36 % (3.31, 7.41)                  |
| <b>Relative risk reduction of clinical vertebral fracture</b>         |                       | 50 % (9.49, 71.91)                   |
| <b>Incidence of clinical vertebral fracture</b>                       | 6.97 % (4.67, 9.27)   | 3.57 % (1.89, 5.24)                  |
| <b>BMD – mean change relative to baseline lumbar spine at year 3</b>  | 1.13 % (0.6, 1.7)     | 7.01 % (6.5, 7.6)                    |
| <b>BMD – mean change relative to baseline total hip at year 3</b>     | -0.70 % (-1.1, -0.2)  | 3.59 % (3.1, 4.1)                    |

In the overall patient population of study MF 4411, 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 non-vertebral 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 mineralisation defect.

*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.

### *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 % to 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.

The secretory pathway appears not to include known acidic or basic transport systems involved in the excretion of other active substances. In addition, ibandronic acid does not inhibit the major human hepatic P450 isoenzymes and does not induce the hepatic cytochrome P450 system in rats.

#### *Pharmacokinetics in special 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<sub>cr</sub> equal to 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<sub>cr</sub> 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 haemodialysis. The pharmacokinetics of ibandronic acid in these patients is unknown, and ibandronic acid should not be used under these circumstances.

##### 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**

Not applicable

## **6. Pharmaceutical Particulars**

### **6.1 List of Excipients**

*Tablet core*

- Lactose
- Microcrystalline cellulose
- Povidone
- Sodium benzoate
- Crospovidone
- Potassium polacrilin
- Talc
- Magnesium stearate
- Colloidal silicon dioxide (light)

*Film coating*

- Hydroxypropyl methylcellulose (hypromellose)
- Macrogol 6000 (PEG-6000)
- Titanium dioxide
- Talc

### **6.2 Incompatibilities**

Not applicable.

### **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 Content of container**

One tablet in an alu-alu strip; one strip in a carton.

**6.6 Special precautions for disposal and other handling**

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

**7. Marketing Authorization Holder**

KRISHNA CHEMISTS LTD

**8. Marketing Authorization Number**

H2025/CTD10909/15632

**9. Date of first authorization/renewal of the authorization**

2025 May 26

**10. Date of revision of the text**

2025 May 26