Public Assessment Report

Decentralised Procedure

Ibandronic Acid 150mg Tablets

(sodium ibandronate monohydrate)

UK/H/2175/002/DC

UK licence no: PL 33786/0035

Arrow APS
LAY SUMMARY

On the 1st September 2010, the Medicine and Healthcare products Regulatory Agency (MHRA) granted Arrow ApS a Marketing Authorisation (licence) for the medicinal product Ibandronic Acid 150mg Tablets (PL 33786/0035). This licence was granted via the decentralised procedure (UK/H/2175/002/DC), with the UK as the Reference Member State (RMS) and Belgium, Cyprus, Czech Republic, Denmark, Germany, Finland, France, Hungary, Ireland, Italy, Malta, The Netherlands, Poland, Portugal, Slovenia, The Slovak Republic, Spain and Sweden as Concerned Member States (CMS).

Ibandronic Acid 150mg Tablets are used to treat a condition called osteoporosis (a thinning and weakening of bones, which is common in women after the menopause).

The active ingredient, sodium ibandronate monohydrate, belongs to a group of medicines called bisphosphates. They help to lower calcium loss from your bones and increase bone mass. This helps to prevent your bones breaking (fractures).

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of taking Ibandronic Acid 150mg Tablets outweigh the risks; hence a Marketing Authorisation has been granted.
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**Module 1**

<table>
<thead>
<tr>
<th><strong>Product Name</strong></th>
<th>Ibandronic Acid 150 mg Tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of Application</strong></td>
<td>Generic, Article 10.1</td>
</tr>
<tr>
<td><strong>Active Substance</strong></td>
<td>Sodium ibandronate monohydrate</td>
</tr>
<tr>
<td><strong>Form</strong></td>
<td>Tablets</td>
</tr>
<tr>
<td><strong>Strength</strong></td>
<td>150mg</td>
</tr>
</tbody>
</table>
| **Marketing Authorisation Holder** | Arrow ApS  
Hovedgaden 41, 2, 2970 Horsholm  
Denmark                       |
| **Reference Member State (RMS)** | UK                                        |
| **Concerned Member State (CMS)** | Belgium, Cyprus, Czech Republic, Denmark, Germany, Finland, France, Hungary, Ireland, Italy, Malta, The Netherlands, Poland, Portugal, Slovenia, The Slovak Republic, Spain and Sweden. |
| **Procedure Number**   | UK/H/2175/002/DC                                                    |
| **End of Procedure**   | 16<sup>th</sup> August 2010                                         |
Module 2
SUMMARY OF PRODUCT CHARACTERISTICS

The UK Summary of Product Characteristics (SmPC) for Ibandronic Acid 150mg Tablets (PL 33786/0035) is as follows:

1 NAME OF THE MEDICINAL PRODUCT
Ibandronic Acid 150 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 150 mg of Ibandronic Acid (as sodium ibandronate monohydrate).

Excipient: 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).

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

See also section 4.4.

4.4 Special warnings and precautions for use

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.

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

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).

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.

**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 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.

Lactation
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 (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), and rare (≥ 1/10,000 to < 1/1,000). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

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

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Frequency</th>
<th>Adverse reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune system disorders</td>
<td>Rare</td>
<td>Hypersensitivity reaction</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Common</td>
<td>Headache</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Dizziness</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Common</td>
<td>Oesophagitis, Gastritis, Gastro oesophageal reflux disease, Dyspepsia, Diarrhoea, Abdominal pain, Nausea</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Oesophagitis including oesophageal ulcerations or strictures and dysphagia, Vomiting, Flatulence</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
<td>Duodenitis</td>
</tr>
<tr>
<td>Skin and subcutaneous tissues disorders</td>
<td>Common</td>
<td>Rash</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
<td>Angioedema, Face oedema, Urticaria</td>
</tr>
<tr>
<td>Musculoskeletal, connective tissue and bone disorders</td>
<td>Common</td>
<td>Arthralgia, Myalgia, Musculoskeletal pain, Muscle cramp, Musculoskeletal stiffness</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Back pain</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Common</td>
<td>Influenza like illness*</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Fatigue</td>
</tr>
</tbody>
</table>
MedDRA version 7.1

* 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.

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.

Laboratory test findings
In the pivotal three-year study with ibandronic acid 2.5 mg daily (MF 4411) there was no difference compared with placebo for laboratory abnormalities indicative of hepatic or renal dysfunction, an impaired haematologic system, hypocalcaemia or hypophosphataemia. Similarly, no differences were noted between the groups in study BM 16549 after one and two years.

Post-marketing Experience
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).

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: 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>
<thead>
<tr>
<th></th>
<th>One year data in study BM 16549</th>
<th>Two year data in study BM 16549</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean relative changes from baseline %</td>
<td>ibandronic acid 2.5 mg daily (N = 318)</td>
<td>ibandronic acid 150 mg once monthly (N = 320)</td>
</tr>
<tr>
<td>Lumbar spine L2-L4 BMD</td>
<td>3.9 [3.4 , 4.3]</td>
<td>4.9 [4.4, 5.3]</td>
</tr>
<tr>
<td>Total hip BMD</td>
<td>2.0 [1.7, 2.3]</td>
<td>3.1 [2.8, 3.4]</td>
</tr>
<tr>
<td>Femoral neck BMD</td>
<td>1.7 [1.3, 2.1]</td>
<td>2.2 [1.9, 2.6]</td>
</tr>
<tr>
<td>Trochanter BMD</td>
<td>3.2 [2.8, 3.7]</td>
<td>4.6 [4.2, 5.1]</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>Placebo (N = 587)</th>
<th>Ibandronic acid 2.5 mg daily (N = 575)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Relative Risk Reduction</strong></td>
<td></td>
</tr>
<tr>
<td>New morphometric vertebral fractures</td>
<td>59% (34.5, 74.3)</td>
</tr>
<tr>
<td>Incidence of new morphometric vertebral fractures</td>
<td>12.54% (9.53, 15.55)</td>
</tr>
<tr>
<td>Relative risk reduction of clinical vertebral fracture</td>
<td>50% (9.49, 71.91)</td>
</tr>
<tr>
<td>Incidence of clinical vertebral fracture</td>
<td>6.97% (4.67, 9.27)</td>
</tr>
<tr>
<td>BMD – mean change relative to baseline lumbar spine at year 3</td>
<td>1.13% (0.6, 1.7)</td>
</tr>
<tr>
<td>BMD – mean change relative to baseline total hip at year 3</td>
<td>-0.70% (-1.1, -0.2)</td>
</tr>
</tbody>
</table>

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.

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.

Metabolism
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\text{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\text{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 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
No special requirements

7 MARKETING AUTHORISATION HOLDER
Arrow, ApS
Hovedgaden 41, 2,
2970 Horsholm
Denmark

8 MARKETING AUTHORISATION NUMBER(S)
PL 33786/0035

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
01/09/2010

10 DATE OF REVISION OF THE TEXT
01/09/2010
Module 3
Product Information Leaflet

### 1. WHAT IBANDRONIC ACID TABLETS ARE AND WHAT THEY ARE USED FOR

Ibandronic Acid Tablets belong to a group of medicines called bisphosphonates. The tablets contain ibandronic acid. The tablets do not contain hormones.

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

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

The earlier a woman reaches the menopause, the greater her risk of fractures in osteoporosis. Other things that can increase the risk of fractures include:
- Not enough calcium and vitamin D in the diet
- Smoking, or drinking too much alcohol
- Not enough working or other weight-bearing exercise
- A family history of osteoporosis.

Many people with osteoporosis have no symptoms. If you have no symptoms you may not know if you have the condition. However, osteoporosis makes you more likely to break bones if you fall or hurt yourself. A broken bone after the age of 50 may be a sign of osteoporosis. Osteoporosis can also cause back pain, height loss and a curved back.

Ibandronic acid prevents loss of bone from osteoporosis, and helps to rebuild bone. Therefore Ibandronic acid makes bones less likely to break.

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

### 2. BEFORE YOU TAKE IBANDRONIC ACID TABLETS

**Do not take Ibandronic Acid Tablets:**
- If you are allergic (hypersensitive) to ibandronic acid.
- If you are allergic to any of the other ingredients in the tablets (these are listed in Section 6, Further Information).
- If you have certain problems with your oesophagus (the tube connecting your mouth with your stomach) such as narrowing or difficulty swallowing.
- If you can't stand or sit upright for at least one hour (30 minutes) at a time.
- If you have, or had in the past, low blood calcium.

Please consult your doctor.

**Do not give Ibandronic Acid Tablets to children or adolescents.**

**Take special care with Ibandronic Acid Tablets:**
- Some people need to be especially careful while they're taking Ibandronic Acid Tablets. Check with your doctor.
- You may have some disturbances of mineral metabolism (such as vitamin D deficiency).
- If your kidneys are not functioning normally.
- If you have any swallowind or digestive problems.
- If you are undergoing dental treatment or will undergo dental surgery, tell your dentist that you are being treated with Ibandronic Acid Tablets.

Irritation, inflammation or ulceration of the oesophagus (the tube connecting your mouth with your stomach) can occur with symptoms of severe pain in the chest, severe pain after swallowing food or drink, severe nausea, or vomiting may occur especially if you do not drink a full glass of plain water and/or sit upright for at least one hour after taking Ibandronic Acid Tablets. If you develop these symptoms, stop taking Ibandronic Acid Tablets and tell your doctor straight away.

**Taking other medicines:**
- Please tell your doctor or pharmacist if you are taking, or have recently taken any other medicines, including medicines obtained without prescription. Especially:
  - Supplements containing calcium, magnesium, iron or aluminium, as they could possibly influence the effect of ibandronic acid.
  - Aspirin and other non-steroidal anti-inflammatory medicines (NSAIDs) (including ibuprofen, diclofenac sodium and naproxen) may irritate the stomach and intestine. Bisphosphonates (like ibandronic acid) may also do so. So be especially careful if you take painkillers or anti-inflammatory while you're taking ibandronic acid.

After swallowing your monthly Ibandronic Acid Tablet, wait at least 1 hour before taking any other medication, including indigestion tablets, calcium supplements, or vitamins.

**Taking Ibandronic Acid Tablets with food and drink:**
- Do not take Ibandronic Acid Tablets with food. Ibandronic acid is less effective if it's taken with food. You can drink plain water but no other drinks (see also Section 3, How to Take Ibandronic Acid Tablets).

**Pregnancy and breast-feeding:**
- Do not take Ibandronic Acid Tablets if you're pregnant or breast-feeding. If you're breast-feeding, you may need to stop in order to take Ibandronic Acid Tablets.

**Driving and using machines:**
- You can drive and use machines as it's very unlikely that Ibandronic Acid Tablets will affect your ability to drive and use machines.

**Important information about some of the ingredients of Ibandronic Acid Tablets:**
- Ibandronic Acid Tablets contain sorbitol. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.
3. HOW TO TAKE IBANDRONIC ACID TABLETS

Always take Ibandronic Acid Tablets exactly as your doctor has told you. If you're not sure about anything, ask your doctor or pharmacist.

The usual dose of Ibandronic Acid 150mg Tablets is one tablet once a month.

Taking your monthly tablet
It's important to follow these instructions carefully. They are designed to help your Ibandronic Acid Tablet reach your stomach quickly so it's less likely to cause irritation.

- Take one Ibandronic Acid 150mg Tablet once a month.
- Choose one day of the month that will be easy to remember. You can choose either the same date (such as the 1st of each month) or the same day (such as the first Sunday of each month) to take your Ibandronic Acid Tablet. Choose the date that best fits your routine.
- Take your Ibandronic Acid Tablet at least 6 hours after you last had anything to eat or drink except plain water.
- Take your Ibandronic Acid Tablet:
  - after you first get up for the day, and
  - before you have anything to eat or drink (on an empty stomach).
- Swallow your tablet with a full glass of plain water (at least 180 ml). Do not take your tablet with mineral water, fruit juice or any other drinks.
- Swallow your tablet whole - do not chew it, crush it or let it dissolve in your mouth.
- For the next four hours (60 minutes) after you've taken your tablet:
  - do not chew it, crush it or let it dissolve in your mouth.
  - do not eat anything.
  - do not drink anything (except plain water if you need it).
  - do not take any other medicines.
- After you've waited for an hour, you can have your first food and drink of the day. Once you've eaten, it's OK to lie down if you wish, and to take any other medication you need.

Do not take your tablet at bedtime or before you get up for the day.

Continuing to take Ibandronic Acid Tablets
It's important to keep taking Ibandronic Acid Tablets every month, as long as your doctor prescribes them for you. Ibandronic Acid Tablets can treat osteoporosis only as long as you keep taking them.

If you take too many Ibandronic Acid Tablets
If you've taken more than one tablet by mistake, drink a full glass of milk and talk to your doctor straight away.

Do not make yourself vomit, and do not lie down - this could cause Ibandronic Acid to irritate your oesophagus.

If you forget a dose
If you forget to take your tablet on the morning of your chosen day, do not take a tablet later in the day. Instead, consult your calendar and find out when your next scheduled dose is.

If your next scheduled dose is only 1 to 7 days away...
You should wait until the next scheduled dose is due and take it as normal. Then, continue taking one tablet once a month on the scheduled days you've marked on your calendar.

If your next scheduled dose is more than 7 days away...
You should take one tablet the morning after the day you remember, then, continue taking one tablet once a month on the scheduled days you've marked on your calendar.

Never take two Ibandronic Acid Tablets within the same week.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Ibandronic Acid Tablets can cause side effects, although not everybody gets them.

These side effects may occur with certain frequencies, which are defined as follows:
- very common: affects more than 1 user in 10
- common: affects 1 to 10 users in 100
- uncommon: affects 1 to 10 users in 1,000
- rare: affects 1 to 10 users in 10,000
- very rare: affects less than 1 user in 10,000
- not known: frequency cannot be estimated from the available data.

Common side effects are heartburn, indigestion, diarrhea, stomach ache, and nausea.

Ibandronic acid can also irritate the oesophagus, although you can usually avoid this by taking your dose as described in this leaflet. If you develop symptoms such as severe pain in the chest, severe pain after swallowing food or drink, severe nausea, or vomiting, stop taking Ibandronic Acid Tablets and tell your doctor straight away.

Other common side effects include rash, cramps in the muscles, pain in the muscles and joints, and headache.

It also includes flu-like symptoms (sore and pain, feeling of discomfort, fatigue) which are usually mild, short-lasting and disappear soon after you have taken the first dose. So you should be able to carry on taking Ibandronic Acid Tablets. Talk to your doctor if any effects become troublesome or last a long time.

Uncommon side effects are dizziness, back pain, tiredness (fatigue) and Tinitus (wind).

Rare side effects are swelling and itching of the face, lips and mouth, allergic (hypersensitivity) reactions, inflammation of the intestine and urticaria (a type of skin rash with red blisters).

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

5. HOW TO STORE IBANDRONIC ACID TABLETS

Keep out of the reach and sight of children.

There are no special storage precautions.

Do not use after the expiry date which is stated on the carton and blister after EXP. The expiry date refers to the last day of that month.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Ibandronic Acid Tablets contain:
- The active substance is ibandronic acid (each tablet contains 150mg of ibandronic acid as ibandronate sodium monohydrate).
- The other ingredients are tributyl citrate, microcrystalline cellulose, silica, colloidal anhydrous, croscarmellose sodium and sodium starch/hamarate.

What Ibandronic Acid Tablets look like and contents of the pack
The tablets are white or off-white, capsule shaped tablet with "IN 150" on one side and a "5" on the other side.

The tablets are available in blister packs of 1 or 3 tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder
Arrow ApS, Hervedgaden 41, 2, 2570 Holstebro, Denmark

Manufacturer:
Arrow Pharm (Malta) Limited, HR 62, Hair Fair Industrial Estate, Hair Fair, Malta.

This leaflet was last approved in 08/2010.
Module 4
Labelling

Carton
Module 5
Scientific discussion during initial procedure

I  INTRODUCTION
On 16th August 2010, Belgium, Cyprus, Czech Republic, Denmark, Germany, Finland, France, Hungary, Ireland, Italy, Malta, The Netherlands, Poland, Portugal, Slovenia, The Slovak Republic, Spain, Sweden and the UK agreed to grant a Marketing Authorisation (MA) to Arrow ApS for the medicinal product Ibandronic Acid 150mg Tablets. The MA was granted via a Decentralised Procedure (DCP), with the UK as Reference Member State (RMS UK/H/2175/02/DC). After the national phase, an MA was granted in the UK on 1st September 2010 (PL 33786/0035). This product is a prescription –only medicine.

This application was made under Article 10.1 of Directive 2001/83/EC for Ibandronic Acid 150mg Tablets, containing the known active substance sodium ibandronate monohydrate. The reference medicinal product for this application is Bonviva 150mg tablets (containing ibandronic acid), for which a marketing authorisation was first authorised on 25th June 1996 (EU/1/96/012/009; EU/1/96/012/010). This product was authorised via the centralised procedure and was marketed initially by Boehringer Mannheim, and later by Roche Limited following a centralised transfer of ownership on 23rd February 2004 (EU/1/03/265/003). The reference product has been authorised in the EEA for more than 10 years, so the period of data exclusivity has expired.

Ibandronic Acid is a third generation bisphosphonate which belongs to the group of nitrogen containing bisphosphonates. It acts selectively on bone tissue and specifically inhibits osteoclast activity without directly affecting bone formation. The 150 mg tablet of Ibandronic Acid is approved for use in the treatment of osteoporosis in postmenopausal women at increased risk of fracture. A reduction in the risk of vertebral fractures has been demonstrated.

The absolute bioavailability of ibandronic acid after oral doses is less than 1%. Absorption is decreased by food, especially by products containing calcium or other polyvalent cations. 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.

No new preclinical or clinical studies were conducted for this application, which is acceptable given that the application is for a generic version of a product that has been licensed for over 10 years. A bioequivalence study has been provided to support this application.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these product types at all sites responsible for the manufacture and assembly of these products. Evidence of compliance with GMP has been provided for the named manufacturing and assembly sites. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the community, the RMS has accepted copies of current GMP certificates or satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those
countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS considers that the pharmacovigilance system, as described by the MAH, fulfils the requirements and provides adequate evidence that the MAH has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country. The Marketing Authorisation Holder has provided adequate justification for not submitting a Risk Management Plan (RMP). As the application is for a generic version of an already authorised reference product, for which safety concerns requiring additional risk minimisation have not been identified, a risk minimisation system is not considered necessary. The reference product has been in use for many years and the safety profile of the active substance is well established.

The Marketing Authorisation Holder has provided adequate justification for not submitting an Environmental Risk Assessment (ERA). This is an application for a generic product and there is no reason to conclude that the marketing of this product will change the overall use pattern of the existing market.
II. ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Ibandronic Acid 150mg Tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>Sodium ibandronate monohydrate</td>
</tr>
<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Bisphosphonate M05BA06</td>
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<td>Pharmaceutical form and strength(s)</td>
<td>Tablets 150 mg</td>
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<td>Reference numbers for the Decentralised Procedure</td>
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</tr>
<tr>
<td>Reference Member State</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>Member States concerned</td>
<td>Belgium, Cyprus, Czech Republic, Denmark, Germany, Finland, France, Hungary, Ireland, Italy, Malta, The Netherlands, Poland, Portugal, Slovenia, The Slovak Republic, Spain and Sweden.</td>
</tr>
<tr>
<td>Marketing Authorisation Number(s)</td>
<td>PL 33786/0035</td>
</tr>
<tr>
<td>Name and address of the authorisation holder</td>
<td>Arrow ApS Hovedgaden 41, 2, 2970 Horsholm Denmark</td>
</tr>
</tbody>
</table>
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

DRUG SUBSTANCE

INN Sodium Ibandronate monohydrate

Chemical name:
[1-Hydroxy-3-(methylpentylamino) propylidene] bisphosphonic acid sodium salt

CAS: 138926-19-9

Structure:

![Chemical Structure](image)

Molecular Formula: C_{10}H_{15}O_8NNaP_2

Molecular Mass: 359.23

General Properties

Description: A white crystalline powder.


The active substance, sodium ibandronate monohydrate, is not the subject of a European Pharmacopeia (Ph. Eur.) or British Pharmacopeia monograph.

Manufacture

Synthesis of the drug substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised. Satisfactory certificates of analysis have been provided for all working standards. Batch analysis data are provided and comply with the proposed specification.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated, which support a suitable retest period when stored in the proposed packaging.
DRUG PRODUCT
Description and Composition

The finished product is presented as white to off-white, capsule shaped tablets with ‘IN 150’ on one side and ‘>’ on the other side. Each tablet contains 150mg of the active ingredient, ibandronic acid (as sodium ibandronate monohydrate).

Other ingredients consist of pharmaceutical excipients, namely sorbitol (E420), microcrystalline cellulose, colloidal anhydrous silica, croscarmellose sodium and sodium stearyl fumarate. An appropriate justification for the inclusion of each excipient has been provided. Satisfactory Certificates of Analysis have been provided for all excipients. Furthermore, no genetically modified organisms are used in the manufacture of any of the excipients.

Pharmaceutical Development
The aim of the pharmaceutical development programme was to develop a stable formulation for 150mg ibandronic acid tablets with similar physical and chemical characteristics to the innovator product, Bonviva 150 mg tablets (Roche Limited, UK).

Dissolution and Impurity Profiles
Comparative dissolution and impurity data were provided for the test and reference products. The dissolution and impurity profiles were found to be similar and were satisfactory.

Manufacture
A description and flow-chart of the manufacturing method has been provided.

In-process controls were considered appropriate considering the nature of the product and the method of manufacture. Process validation studies have been conducted and are accepted. Satisfactory analytical results from batches representative of commercial scale were provided.

Finished Product Specification
Finished product specifications are provided for both release and shelf-life, and are satisfactory; they provide an assurance of the quality and consistency of the finished product. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and adequately validated, as appropriate. Batch data are provided for the finished product, which demonstrate that the batches are compliant with the proposed release specifications. Certificates of Analysis have been provided for any reference standards used.

Container Closure System
The finished product is licensed for marketing in aluminium (foil/foil) blister strips, which are placed with the Patient Information Leaflet (PIL) into cardboard outer cartons in pack sizes of 1 or 3 tablets. The MAH has stated that not all pack sizes may be marketed and has committed to submit mock-ups for all packaging for assessment before those pack sizes are commercially marketed. All primary product packaging complies with Directive 2002/72/EC (as amended), and is suitable for contact with foodstuffs.

Stability
Finished product stability studies have been conducted in accordance with current guidelines and results were within the proposed specification limits. Based on the results, a shelf-life of
3 years has been set, which is satisfactory. This medicinal product does not require any special storage conditions.

**Bioequivalence Study**
A bioequivalence study was presented comparing the test product, Ibandronic Acid 150mg Tablets, to the reference product, Bonviva 150 mg tablets, Roche Limited, UK.

An evaluation of the bioequivalence study is found in the Clinical Aspects section.

**Quality Overall Summary**
A satisfactory quality overview is provided and has been prepared by an appropriately qualified expert. The *curriculum vitae* of the expert has been provided.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels**
The SmPC, PIL and labelling are pharmaceutically acceptable. Colour mock-ups of the labelling and PIL have been provided. The labelling is satisfactory and fulfils the statutory requirements for Braille.

The applicant has submitted results of PIL user testing. The results indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that the leaflet contains.

**MAA Form**
The MAA form is pharmaceutically satisfactory.

**Conclusion**
The test product corresponds to the current EU definition of a generic medicinal product because it complies with the criteria of having the same qualitative and quantitative composition in terms of the active substance and pharmaceutical form. On this basis and considering the bioequivalence data provided, the applicant’s claim that Ibandronic Acid 150mg Tablets is a generic medicinal product of Bonviva 150 mg tablets (EU/1/96/012/009; EU/1/96/012/010) Roche Limited, UK is justified.

There are no objections to approval of Ibandronic Acid 150mg Tablets from a pharmaceutical point of view.

**III.2 PRE-CLINICAL ASPECTS**
The pharmacodynamic, pharmacokinetic and toxicological properties of sodium ibandronate monohydrate are well-known. Therefore, no further studies are required and the applicant has provided none.

The pre-clinical overview was written by a suitably qualified person and is satisfactory. The *curriculum vitae* of the expert has been provided.

The SmPC is satisfactory from a pre-clinical viewpoint and is consistent with that for the reference product.

There are no objections to approval of Ibandronic Acid 150mg Tablets from a pre-clinical point of view.
III.3 CLINICAL ASPECTS

Clinical aspects

The application is supported by a bioequivalence study presented by the applicant, comparing the pharmacokinetic profiles of Ibandronic Acid 150 mg tablets (test) and Bonviva 150 mg tablets -Roche, UK (reference). The study was of an appropriate design and was conducted in accordance with the principles of Good Clinical Practice (GCP). Certificates of Analysis have been provided for both the test and reference products.

Pharmacokinetics

Methods:
The study was conducted as a randomized, single dose, laboratory-blinded, 2-period, 2-sequence, crossover study; to compare the oral bioavailability of the proposed Ibandronic Acid 150 mg Tablets (Arrow) with that of the reference product Bonviva 150 mg tablets (Roche Limited), in 90 healthy volunteers under fasting conditions.

Subjects received the test product (Ibandronic Acid 150 mg tablet) and the reference product (Bonviva 150 mg Tablet), each on one occasion, according to the randomisation list. A single oral dose was administered to each subject under fasting conditions, in each study period. Drug administrations in each subject were separated by a wash-out period of 21 days.

Blood samples were collected prior to and up to 36 hours after each drug administration. The samples were analysed for ibandronate in human plasma, using the HPLC method using MS/MS detection.

The pharmacokinetic parameters of this trial were \( C_{\text{max}} \), \( T_{\text{max}} \), \( \text{AUC}_{\text{t}} \), \( \text{AUC}_{\infty} \), \( \text{AUC}_{\text{T/}\infty} \), \( K_{\text{el}} \) and \( T_{1/2\text{el}} \).

The parameter \( T_{\text{max}} \) was to be analysed using a non-parametric approach. All other un-transformed and ln-transformed pharmacokinetic parameters were to be statistically analysed using a random Analysis of Variance (ANOVA) model. The sequence, period and treatment effects were to be assessed at the two-sided 5% level. Furthermore, the 90% confidence interval for the exponential of the difference in LS means between the Test and Reference product (Test to Reference ratio of geometric LS means) was to be calculated for the ln-transformed parameters.

The ratio of geometric LS means with corresponding 90% confidence interval calculated from the exponential of the difference between the Test and Reference product for the ln-transformed parameters \( C_{\text{max}} \), \( \text{AUC}_{\text{T}} \) and \( \text{AUC}_{\infty} \) were all to be within the 80.00 to 125.00 % bioequivalence range.

Results:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>( \text{AUC}_{0-t} ) ng·h/ml</th>
<th>( \text{AUC}_{\text{t/}\infty} ) ng·h/ml</th>
<th>( C_{\text{max}} ) ng/ml</th>
<th>( t_{\text{max}} ) h</th>
<th>( T_{1/2\text{el}} ) h</th>
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<tbody>
<tr>
<td>Test</td>
<td>361.990</td>
<td>387.053</td>
<td>85.728</td>
<td>1.00</td>
<td>24.64</td>
</tr>
<tr>
<td>Reference</td>
<td>363.553</td>
<td>390.152</td>
<td>86.940</td>
<td>1.00</td>
<td>24.80</td>
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<tr>
<td>*Ratio (90% CI)</td>
<td>95.87 (86-106.86)</td>
<td>95.91 (86.24-106.67)</td>
<td>94.17 (83.09-106.73)</td>
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The results presented show that the criteria used to assess bioequivalence between the Test and Reference formulations have been fulfilled. The Test to Reference ratio and the corresponding 90% confidence interval, of geometric LS means for the $C_{\text{max}}$, $AUC_T$ and $AUC_{\infty}$ were within the acceptance range of 80.00 to 125.00%.

**Pharmacodynamics**
No new data have been submitted and none are required.

**Clinical efficacy**
No new data have been submitted and none are required. The reference product is established and the application depends upon the ability to demonstrate bioequivalence. Efficacy is reviewed in the clinical overview. The efficacy of Ibandronic acid is well-established from its extensive use in clinical practice.

**Clinical safety**
The bioequivalence study has not highlighted any new safety concerns. There were no serious adverse events or deaths during the course of the study. No subject was withdrawn from the study for safety reasons.

**PRODUCT INFORMATION:**
**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels**
The SmPC and PIL are clinically acceptable, and consistent with those for the reference product. The labelling is clinically acceptable and in-line with current requirements.

**Expert Report**
A satisfactory clinical overview is provided, and has been prepared by an appropriately qualified expert. The *curriculum vitae* of the expert has been provided.

**Conclusion**
The bioequivalence study was of an appropriate design and demonstrates the bioequivalence of the test (Ibandronic Acid 150mg Tablets) and reference (Bonviva 150 mg tablets, Roche Limited, UK) products within the agreed acceptance limits.

Sufficient clinical information has been submitted to support this application. When used as indicated, the product has a favourable benefit-to-risk ratio. A Marketing Authorisation was therefore granted.
IV OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY
The important quality characteristics of Ibandronic Acid 150mg Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRE-CLINICAL
No new pre-clinical data were submitted and none are required for an application of this type.

EFFICACY
Bioequivalence has been demonstrated between the applicant’s Ibandronic Acid 150mg Tablets, and the reference product, Bonviva 150 mg tablets (Roche Limited, UK).

No new or unexpected safety concerns arise from this application.

PRODUCT LITERATURE
The SmPC and PIL are acceptable, and consistent with those for the reference product. The labelling is acceptable and in-line with current requirements.

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

The approved labelling artwork complies with statutory requirements. In line with current legislation, the name of the product in Braille appears in the outer packaging and sufficient space has been included for a standard UK pharmacy dispensing label.

BENEFIT/RISK ASSESSMENT
The quality of the product is acceptable, and no new preclinical or clinical safety concerns have been identified. The qualitative and quantitative assessment supports the claim that the applicant’s Ibandronic Acid 150mg Tablets and the reference product Bonviva 150 mg tablets (Roche Limited, UK) are interchangeable. Extensive clinical experience with sodium ibandronate monohydrate is considered to have demonstrated the therapeutic value of the active substance. The benefit/risk ratio is therefore considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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