Public Assessment Report

Decentralised Procedure

IBANDRONATE APOTEX 50MG FILM-COATED TABLETS

UK/H/1867/001/DC
UK licence no: PL 27583/0097

APOTEX EUROPE BV
IBANDRONATE APOTEX 50MG FILM-COATED TABLETS

LAY SUMMARY

On 5th January 2010, the UK granted Apotex Europe BV a licence for the medicinal product Ibandronate Apotex 50mg Film-Coated Tablets (PL 27583/0097). This licence was granted via the decentralised procedure (UK/H/1867/001/DC), with the UK as reference member state (RMS) and Belgium, Czech Republic, Germany, Hungary, Ireland and Luxembourg as concerned member states (CMS).

Ibandronate Apotex 50mg Film-Coated Tablets is used to treat the symptoms of skeletal events if you have breast cancer or a condition known as bone metastases. These can be pathological fractures or problems with bones requiring radiotherapy or surgery.

The active ingredient ibandronate sodium belongs to a group of medicines called bisphosphonates. They help to lower calcium loss from your bones. This helps to prevent your bones breaking (fractures) and other bone problems (skeletal events), which can happen when you have cancer cells in your bones.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Ibandronate Apotex 50mg Film-Coated 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>Ibandronate Apotex 50mg Film-Coated Tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of Application</strong></td>
<td>Generic application, Article 10.1</td>
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<tr>
<td><strong>Active Substance</strong></td>
<td>Ibandronate sodium</td>
</tr>
<tr>
<td><strong>Form</strong></td>
<td>50mg film-coated tablets</td>
</tr>
<tr>
<td><strong>Strength</strong></td>
<td>50mg</td>
</tr>
<tr>
<td><strong>MA Holder</strong></td>
<td>Apotex Europe BV, Darwinweg 20, 2333 CR Leiden, The Netherlands</td>
</tr>
<tr>
<td><strong>RMS</strong></td>
<td>UK</td>
</tr>
<tr>
<td><strong>CMS</strong></td>
<td>Belgium, Czech Republic, Germany, Hungary, Ireland and Luxembourg</td>
</tr>
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<td><strong>Procedure Number</strong></td>
<td>UK/H/1867/001/DC</td>
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<tr>
<td><strong>Timetable</strong></td>
<td>Day 210 – 19th October 2009</td>
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Module 2

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Ibandronate Apotex, 50 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains ibandronate sodium (as propylene glycol solvate) equivalent to 50 mg of ibandronic acid.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet.

White to off-white, oval, biconvex film-coated tablets, engraved “APO” on one side, “IBA 50” on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Ibandronic acid is indicated for the prevention of skeletal events (pathological fractures, bone complications requiring radiotherapy or surgery) in patients with breast cancer and bone metastases.

4.2 Posology and method of administration
Ibandronic acid therapy should only be initiated by physicians experienced in the treatment of cancer.

For oral use.

The recommended dose is one 50 mg film-coated tablet daily.

Ibandronate Film-coated tablets should be taken after an overnight fast (at least 6 hours) and before the first food or drink of the day. Medicinal products and supplements (including calcium) should similarly be avoided prior to taking Ibandronate Film-coated tablets. Fasting should be continued for at least 30 minutes after taking the tablet. Plain water may be taken at any time during the course of ibandronic acid treatment.

- The tablets should be swallowed whole with a full glass of plain water (180 to 240 ml) while the patient is standing or sitting in an upright position.
- Patients should not lie down for 60 minutes after taking Ibandronate.
- Patients should not chew or suck the tablet because of a potential for oropharyngeal ulceration.
- Plain water is the only drink that should be taken with Ibandronate. Please note that some mineral waters may have a higher concentration of calcium and therefore should not be used.

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

Patients with renal impairment:
No dosage adjustment is necessary for patients with mild or moderate renal impairment where creatinine clearance is equal to or greater than 30 ml/min. Below 30 ml/min creatinine clearance, the recommended dose is 50 mg once weekly. See dosing instructions, above.

Elderly:
No dose adjustment is necessary.

Children and adolescents:
Ibandronate is not recommended for patients below age 18 years due to insufficient data on safety and efficacy.

4.3 Contraindications
- Hypersensitivity to ibandronic acid or to any of the excipients.
- Ibandronic acid should not be used in children.
4.4 Special warnings and precautions for use

Caution is indicated in patients with known hypersensitivity to other bisphosphonates.

Hypocalcaemia and other disturbances of bone and mineral metabolism should be effectively treated before starting ibandronic acid therapy. Adequate intake of calcium and vitamin D is important in all patients. Patients should receive supplemental calcium and/or vitamin D if dietary intake is inadequate.

Oral bisphosphonates have been associated with dysphagia, oesophagitis and oesophageal or gastric ulcers. Therefore, patients should pay particular attention to the dosing instructions (see section 4.2).

Physicians should be alert to signs or symptoms signalling a possible oesophageal reaction during therapy, and patients should be instructed to discontinue ibandronic acid and seek medical attention if they develop symptoms of oesophageal irritation such as new or worsening dysphagia, pain on swallowing, retrosternal pain, or heartburn.

Since NSAIDS are associated with gastrointestinal irritation, caution should be taken during concomitant oral medication with ibandronic acid.

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

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.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

Drug-Food Interactions

Products containing calcium and other multivalent cations (such as aluminium, magnesium, iron), including milk and food, are likely to interfere with absorption of Ibandronate Film-coated tablets. Therefore, with such products, including food, intake must be delayed at least 30 minutes following oral administration.

Bioavailability was reduced by approximately 75% when Ibandronate Film-coated tablets were administered 2 hours after a standard meal. Therefore, it is recommended that the tablets should be taken after an overnight fast (at least 6 hours) and fasting should continue for at least 30 minutes after the dose has been taken (see section 4.2).

Drug-Drug Interactions

When co-administered with melphalan/prednisolone in patients with multiple myeloma, no interaction was observed.

Other interaction studies in postmenopausal women have demonstrated the absence of any interaction potential with tamoxifen or hormone replacement therapy (oestrogen).
In healthy male volunteers and postmenopausal women, intravenous ranitidine caused an increase in ibandronic acid bioavailability of about 20% (which is within the normal variability of the bioavailability of ibandronic acid), probably as a result of reduced gastric acidity. However, no dosage adjustment is required when ibandronic acid is administered with H2-antagonists or other drugs that increase gastric pH.

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

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

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

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 reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Therefore, ibandronic acid 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 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 profile of ibandronic acid is derived from controlled clinical trials in the approved indication and after the oral administration of ibandronic acid at the recommended dose.

In the pooled database from the 2 pivotal phase III trials (286 patients treated with ibandronic acid 50 mg), the proportion of patients who experienced an adverse reaction with a possible or probable relationship to ibandronic acid was 27%.

Adverse reactions are ranked under heading of frequency, the most frequent first, using the following convention:

- very common (≥ 10%)
- common (≥ 1% and < 10%)
- uncommon (≥ 0.1% and < 1%)
- rare (≥ 0.01% and < 0.1%)
- very rare (≤ 0.01%)

Table 1 lists common adverse reactions from the pooled phase III trials. Adverse reactions that are equally frequent in both active and placebo or more frequent in placebo-treated patients are excluded.
<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Placebo p. o. daily (n=277 patients) No. (%)</th>
<th>Ibandronic acid 50 mg p. o. daily (n=286 patients) No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Metabolism and Nutrition Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypocalcaemia</td>
<td>14 (5.1)</td>
<td>27 (9.4)</td>
</tr>
<tr>
<td><strong>Gastrointestinal Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>13 (4.7)</td>
<td>20 (7.0)</td>
</tr>
<tr>
<td>Nausea</td>
<td>4 (1.4)</td>
<td>10 (3.5)</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>2 (0.7)</td>
<td>6 (2.1)</td>
</tr>
<tr>
<td>Oesophagitis</td>
<td>2 (0.7)</td>
<td>6 (2.1)</td>
</tr>
<tr>
<td><strong>General Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthenia</td>
<td>2 (0.7)</td>
<td>4 (1.4)</td>
</tr>
</tbody>
</table>

Adverse drug reactions occurring at a frequency < 1%:
The following list provides information on adverse drug reactions reported in study MF 4414 and MF 4434 occurring more frequently with ibandronic acid 50 mg than with placebo:

**Investigations:**
Uncommon: blood parathyroid hormone increased

**Blood and Lymphatic System Disorders:**
Uncommon: anaemia

**Nervous System Disorders:**
Uncommon: paraesthesia, dysgeusia (taste perversion)

**Gastrointestinal Disorders:**
Uncommon: haemorrhage, duodenal ulcer, gastritis, dysphagia, abdominal pain, dry mouth

**Renal and Urinary Disorders:**
Uncommon: azotaemia (uraemia)

**Skin and Subcutaneous Tissue Disorders:**
Uncommon: pruritus

**General Disorders:**
Uncommon: chest pain, influenza-like illness, malaise, pain

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 case of overdose has been reported.

No specific information is available on the treatment of overdosage with ibandronic acid. However, oral overdosage may result in upper gastrointestinal events, such as upset stomach, heartburn, oesophagitis, gastritis or ulcer. Milk or antacids should be given to bind ibandronic acid. 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: Bisphosphonate

ATC Code: M05B A06

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

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

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

Bone resorption due to malignant disease is characterised by excessive bone resorption that is not balanced with appropriate bone formation. Ibandronic acid selectively inhibits osteoclast activity, reducing bone resorption and thereby reducing skeletal complications of the malignant disease. Clinical studies in patients with breast cancer and bone metastases have shown that there is a dose dependent inhibitory effect on bone osteolysis, expressed by markers of bone resorption, and a dose dependent effect on skeletal events.

Prevention of skeletal events in patients with breast cancer and bone metastases with ibandronic acid 50 mg tablets was assessed in two randomised placebo controlled phase III trials with duration of 96 weeks. Female patients with breast cancer and radiologically confirmed bone metastases were randomised to receive placebo (277 patients) or 50 mg ibandronic acid (287 patients). The results from these trials are summarised below.

Primary Efficacy Endpoints:
The primary endpoint of the trials was the skeletal morbidity period rate (SMPR). This was a composite endpoint which had the following skeletal related events (SREs) as sub-components:
- radiotherapy to bone for treatment of fractures/impending fractures
- surgery to bone for treatment of fractures
- vertebral fractures
- non-vertebral fractures

The analysis of the SMPR was time-adjusted and considered that one or more events occurring in a single 12 week period could be potentially related. Multiple events were therefore, counted only once in any given 12 week period for the purposes of the analysis. Pooled data from these studies demonstrated a significant advantage for ibandronic acid 50 mg p. o. over placebo in the reduction in SREs measured by the SMPR (p=0.041). There was also a 38 % reduction in the risk of developing an SRE for ibandronic acid treated patients when compared with placebo (relative risk 0.62, p=0.003).

Efficacy results are summarised in Table 2.

| Table 2 Efficacy Results (Breast Cancer Patients with Metastatic Bone Disease) |
|---------------------------------|-----------------|-----------------|
| Placebo n=277                  | Ibandronic acid 50 mg n=287 | p-value |
| SMPR (per patient year)        | 1.15            | 0.99            | p=0.041 |
| SRE relative risk              | -               | 0.62            | p=0.003 |
**Secondary Efficacy Endpoints:**
A statistically significant improvement in bone pain score was shown for ibandronic acid 50 mg compared to placebo. The pain reduction was consistently below baseline throughout the entire study and accompanied by a significantly reduced use of analgesics compared to placebo. The deterioration in Quality of Life and WHO performance status was significantly less in ibandronic acid treated patients compared with placebo. Urinary concentrations of the bone resorption marker CTx (C-terminal telopeptide released from type I collagen) were significantly reduced in the ibandronic acid group compared to placebo. This reduction in urinary CTx levels was significantly correlated with the primary efficacy endpoint SMPR (Kendall-tau-b (p< 0.001)). A tabular summary of the secondary efficacy results is presented in Table 3.

### Table 3 Secondary Efficacy Results (Breast Cancer Patients with Metastatic Bone Disease)

<table>
<thead>
<tr>
<th></th>
<th>Placebo n=277</th>
<th>Ibandronic acid 50 mg n=287</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone pain *</td>
<td>0.20</td>
<td>-0.10</td>
<td>p=0.001</td>
</tr>
<tr>
<td>Analgesic use *</td>
<td>0.85</td>
<td>0.60</td>
<td>p=0.019</td>
</tr>
<tr>
<td>Quality of Life *</td>
<td>-26.8</td>
<td>-8.3</td>
<td>p=0.032</td>
</tr>
<tr>
<td>WHO performance score *</td>
<td>0.54</td>
<td>0.33</td>
<td>p=0.008</td>
</tr>
<tr>
<td>Urinary CTx **</td>
<td>10.95</td>
<td>-77.32</td>
<td>p=0.001</td>
</tr>
</tbody>
</table>

* Mean change from baseline to last assessment.
** Median change from baseline to last assessment.

### 5.2 Pharmacokinetic properties

**Absorption:**
The absorption of ibandronic acid in the upper gastrointestinal tract is rapid after oral administration. 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. When taken 30 minutes before a meal, the reduction in bioavailability is approximately 30%. There is no meaningful reduction in bioavailability provided ibandronic acid is taken 60 minutes before a meal.

Bioavailability was reduced by approximately 75% when ibandronic acid tablets were administered 2 hours after a standard meal. Therefore, it is recommended that the tablets should be taken after an overnight fast (minimum 6 hours) and fasting should continue for at least 30 minutes after the dose has been taken (see section 4.2).

**Distribution:**
After initial systemic exposure, ibandronic acid rapidly binds to bone or is excreted into urine. In humans, the apparent terminal volume of distribution is at least 90 l and the amount of dose reaching the bone is estimated to be 40-50% of the circulating dose. Protein binding in human plasma is approximately 87% at therapeutic concentrations, and thus drug-drug interaction due to displacement is unlikely.

**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%) 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 and dependent on dose and assay sensitivity, but the apparent terminal half-life is generally in the range of 10-60 hours. However, early plasma levels fall quickly, reaching 10% of peak values within 3 and 8 hours after intravenous or oral administration respectively.
Total clearance of ibandronic acid is low with average values in the range 84-160 ml/min. Renal clearance (about 60 ml/min in healthy postmenopausal females) accounts for 50-60% of total clearance and is related to creatinine clearance. The difference between the apparent total and renal clearances is considered to reflect the uptake by bone.

Pharmacokinetics in Special Populations

**Gender:**
Bioavailability and pharmacokinetics of ibandronic acid are similar in both men and women.

**Race:**
There is no evidence for clinically relevant interethnic differences between Asians and Caucasians in ibandronic acid disposition. There are only very few data available on patients with African origin.

**Patients with renal impairment:**
Renal clearance of ibandronic acid in patients with various degrees of renal impairment is linearly related to creatinine clearance (CLcr). No dosage adjustment is necessary for patients with mild or moderate renal impairment (CLcr ≥ 30 ml/min). Subjects with severe renal impairment (CLcr ≤ 30 ml/min) receiving oral administration of 10 mg ibandronic acid daily for 21 days, had 2 - 3 fold higher plasma concentrations than subjects with normal renal function. Total clearance of ibandronic acid was reduced to 44 ml/min in the subjects with severe renal impairment.

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 impairment. However, there was no reduction in tolerability associated with the increase in exposure. Reduction of the oral dose to one 50 mg tablet once weekly is recommended in patients with severe renal impairment (CLcr < 30 ml/min) (see section 4.2).

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

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

**Children and adolescents:**
There are no data on the use of ibandronic acid in patients less than 18 years old.

### 5.3 Preclinical safety data

Effects in non-clinical studies were observed only at exposures sufficiently in excess of the maximum human exposure indicating little relevance to clinical use. As with other bisphosphonates, the kidney was identified to be the primary target organ of systemic toxicity.

**Mutagenicity/Carcinogenicity:**
No indication of carcinogenic potential was observed. Tests for genotoxicity revealed no evidence of genetic activity for ibandronic acid.

**Reproductive toxicity:**
No evidence of direct foetal toxicity or teratogenic effects was observed for ibandronic acid in intravenously or orally treated rats and rabbits. Adverse effects of ibandronic acid in reproductive toxicity studies in the rat were those expected for this class of drugs (bisphosphonates). They include a decreased number of implantation sites, interference with natural delivery (dystocia), an increase in visceral variations (renal pelvis ureter syndrome) and teeth abnormalities in F1 offspring in rats.
6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
- Microcrystalline cellulose
- Crospovidone (E1202)
- Magnesium stearate (E572)
- Colloidal anhydrous silica

Tablet coat:
- Hypromellose (E464)
- Macrogol

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years.

6.4 Special precautions for storage
Store below 25°C.

6.5 Nature and contents of container
PVC/PVdC- Aluminium blisters: 14, 28, 30, 84 tablets.
HDPE tablet container with a PP cap closure: 30, 100 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Apotex Europe BV
Darwinweg 20
2333 CR Leiden
The Netherlands

8 MARKETING AUTHORISATION NUMBER(S)
PL 27583/0097

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
05/01/2010

10 DATE OF REVISION OF THE TEXT
05/01/2010
Module 3

PAR Ibandronate Apotex 50mg Film-Coated Tablets

Package Leaflet: Information for the User
Ibandronate Apotex, 50 mg film-coated tablets
(ibandronic acid)

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Ibandronate is and what it is used for
2. Before you take Ibandronate
3. How to take Ibandronate
4. Possible side effects
5. How to store Ibandronate
6. Further information

1. WHAT IBANDRONATE IS AND WHAT IT IS USED FOR

Ibandronate belongs to a group of medicines called bisphosphonates. They help to lower calcium loss from your bones. This helps to prevent your bones breaking (fractures) and other bone problems (skeletal events) which can happen when you have cancer cells in your bones.

Ibandronate is used to treat the symptoms of skeletal events if you have breast cancer or a condition known as bone metastases. These can be pathological fractures or problems with bones requiring radiotherapy or surgery.

2. BEFORE YOU TAKE IBANDRONATE

During treatment your blood may be monitored to ensure that you are receiving the correct dose of Ibandronate.

If you are undergoing dental treatment or will undergo dental surgery, tell your dentist that you are being treated with Ibandronate.

Do not take Ibandronate if:
- you are allergic (hypersensitive) to Ibandronic acid or to any of the other ingredients in this medicine (listed in section 6).
- Do not take this medicine if this applies to you. If you are not sure, talk to your doctor or pharmacist before taking Ibandronate.

Children
Ibandronate should not be taken by children under the age of 18.

Take special care with Ibandronate
Check with your doctor or pharmacist before taking your medicine if:
- you are allergic (hypersensitive) to other medicines called 'bisphosphonates'.
- you have low levels of calcium in your blood (= hypocalcaemia).
- you have low levels of magnesium in your blood (= hypomagnesaemia).
- you have any other mineral problems such as vitamin D deficiency.
- you have severe kidney disease (renal insufficiency i.e. creatinine clearance <30 ml/min).
- you are taking NSAIDs (non steroidal anti-inflammatory drugs) such as Ibuprofen and naproxen as this may cause a reaction in your stomach or intestine.
- you have had problems in the past with your oesophagus (the tube that connects your mouth to your stomach).
- you become aware of any signs or symptoms suggesting a possible reaction of the oesophagus (this may include pain in your chest, heartburn, pain after swallowing food or drink).
- If this is the case, you should speak to your doctor without delay.
- you have problems with your jaw or are under dental treatment or will undergo dental surgery tell your dentist that you are being treated with Ibandronate.
- If any of the above apply to you (or you are not sure), talk to your doctor or pharmacist before taking Ibandronate.

Tests:
Your doctor may do regular blood tests while you are taking this medicine. This is to check that your kidneys are working properly.

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines. This includes medicines you get without a prescription. It also includes vitamins containing calcium, iron, aluminium and magnesium.

No interaction was observed when Ibandronic acid was administered concomitantly with tamoxifen, or melphalan/ prednisolone.

When administered with H2-antagonists or other drugs that increase gastric pH Ibandronate absorption may be slightly increased but no dose adjustment is needed.

Do not take this medicine and tell your doctor or pharmacist if:
- you are taking a type of antibiotic called an 'aminoglycoside' such as gentamicin.

Do not take Ibandronate if this applies to you. If you are not sure, talk to your doctor or pharmacist before taking Ibandronate.

When to take your other medicines:
- Do not take any other medicines or food supplements for at least 6 hours before taking Ibandronate.
- Once you have taken Ibandronate wait 30 minutes before taking any other medicines including indigestion tablets/ medicine, calcium supplements and vitamins.

Taking Ibandronate with food and drink
Your Ibandronate tablets should be taken after an overnight fast (at least 6 hours) and before the first food or drink of the day. Medications and supplements (including calcium) should similarly be avoided prior to taking Ibandronate tablets. Fastening, including avoiding other medication and supplements should be continued for at least 30 minutes after taking the tablet. Plain water may be taken at any time during the course of Ibandronate treatment.

Pregnancy and breast-feeding
Do not take Ibandronate if:
- you are pregnant.
- you are breast-feeding.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
Ibandronate should not affect your ability to drive. Do not drive or use any tools or machines until you know how Ibandronate affects you. Ask your doctor or pharmacist if you are unsure.

3. HOW TO TAKE IBANDRONATE

Always take Ibandronate exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Taking the medicine
- Do not eat, drink or take any other medicines or food supplements for at least 6 hours before taking this medicine.
- Take your tablets in the morning.
- Swallow the tablets whole with a full glass of plain water, while sitting up.
- Do not chew, suck or allow your tablet to dissolve in your mouth.
- Once you have taken Ibandronate, wait 30 minutes before eating, drinking or taking any other medicines or food supplements.
- Do not lie down for one hour after taking the tablets.
How much medicine to take
- The usual dose for adults and the elderly is one tablet (50 mg) each day.
- If you have kidney problems then your doctor may tell you to take one tablet (50 mg) each week.

If you take more Ibandronate than you should
- Drink a glass of milk.
- Do not make yourself vomit, and do not lie down.
- Talk to a doctor or go to hospital straight away.
- Take the medicine pack with you.

If you forget to take Ibandronate
If you forget to take a dose of this medicine, wait until the next morning to take Ibandronate.
- If you are taking a tablet each day, skip the missed dose completely.
- If you are taking a tablet only once a week, take the missed dose the next morning. You will then need to wait a whole week before you take your next dose. This means your regular day to take your dose on will change.

Do not take a double dose to make up for a forgotten dose.

If you stop taking Ibandronate
Do not stop taking Ibandronate without talking to your doctor. If you stop taking Ibandronate it could make your problem worse.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Ibandronate can cause side effects, although not everybody gets them. The following side effects may happen with this medicine:

Common (affects less than 1 in 10 people):
- indigestion or heartburn
- stomach pain
- feeling sick
- lower levels of calcium in your blood (shown in blood tests)
- feeling weak
- inflammation of the oesophagus (the tube that connects your pharynx (throat) with your stomach.

Uncommon (affects less than 1 in 100 people):
- high levels of substances called ‘parathyroid hormone’ or ‘uric’ in your blood (shown in blood tests)
- a blood problem such as anaemia (low haemoglobin levels – shown in blood tests) in which you feel tired
- itching or tingling sensation (paresthesia)
- taste disturbance or a dry mouth
- swelling of your stomach (gastritis) or bleeding ulcers of the stomach and the intestine
- difficulty swallowing
- flu like symptoms or feeling unwell
- pain
- chest pain.

It is not known how many people will get the following:
- problems with the jaw, swelling, inflammation or pain (osteonecrosis). This often occurs if you have weak bones (osteoporosis).

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

5. HOW TO STORE Ibandronate

- Keep out of the reach and sight of children.
- Store below 25 °C.

Do not use Ibandronate after the expiry date which is stated on the carton, blister and bottle 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.

5. FURTHER INFORMATION

What Ibandronate contains
- The active substance is ibandronic acid. Each tablet contains ibandronate sodium (as propylene glycol solvate) equivalent to 50 mg ibandronic acid.
- The other ingredients are microcrystalline cellulose, croscarmellose sodium, magnesium stearate (E572), colloidal anhydrous silica, hypromellose (E464) and macrogol.

What Ibandronate looks like and contents of the pack
- The tablets are white to off-white, oval, biconvex film-coated tablets, with “AP” on one side and “IBA 50” on the other side.
- The tablets are available in blisters of 14, 28, 30 or 64 tablets and tablet containers of 80 and 100 tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Marketing authorisation holder
Aptex Europe B.V.
Danneveld 20
2333 CR Leiden
The Netherlands

Manufacturer
Aptex Nederland B.V.
Archimedesweg 2
2935 CN Leiden
The Netherlands

Distributor:
Aptex UK Ltd.
6 Ridgeway Court,
Grovebury Road, Leighton Buzzard,
Bedfordshire, LU7 4SF, United Kingdom

This medicinal product is authorised in the member states of the EEA under the following names:

<table>
<thead>
<tr>
<th>Member State</th>
<th>Medicinal product name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belgium</td>
<td>Ibandronate Apotex</td>
</tr>
<tr>
<td>Czech Republic</td>
<td>Ibandronate Apotex 50 mg potable tablet</td>
</tr>
<tr>
<td>Germany</td>
<td>Ibandronate Apotex 50 mg Filmtabletten</td>
</tr>
<tr>
<td>Hungary</td>
<td>Ibandronat Apotex</td>
</tr>
<tr>
<td>Ireland</td>
<td>Ibandronate Apotex</td>
</tr>
<tr>
<td>Luxembourg</td>
<td>Ibandronate Apotex</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>Ibandronate Apotex</td>
</tr>
</tbody>
</table>

This leaflet was last approved in October 2009.
Module 5
Scientific discussion during initial procedure

I INTRODUCTION

On 19th October 2009, Belgium, the Czech Republic, Germany, Hungary, Ireland, Luxembourg and the UK agreed to grant a marketing authorisation to Apotex Europe BV for the medicinal product Ibandronate Apotex 50mg Tablets (UK/H/1867/001/DC). The licences were granted via the Decentralised Procedure (DCP), with the UK as Reference Member State. After the national phase, a licence was granted in the UK on 5th January 2010 (PL 27583/0097).

This application was made under Article 10.1 of Directive 2001/83 EC for Ibandronic Acid Apotex 50mg Tablets, containing the known active substance ibandronic acid. The reference medicinal product for this application is Bondronat 50mg Film-Coated Tablets (Roche Registrations Ltd), which has been licenced in at least one member state for over 10 years.

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

Ibandronic acid is indicated for the prevention of skeletal events (pathological fractures, bone complications requiring radiotherapy or surgery) in patients with breast cancer and bone metastases.

The drug product corresponds to the current EU definition for generic medicinal product because it complies with the criteria of having the same qualitative and quantitative composition in terms of active substance, the same dosage form, and bioequivalence has been demonstrated between the drug product and an appropriate reference medicinal product.

The bioequivalence study was conducted in accordance with current Good Clinical Practice.

A formal Environmental Risk Assessment has not been performed as the product is intended for generic substitution. Hence no increase in environmental risk is to be expected compared to that of the reference product.

An acceptable justification for not submitting a European Risk Management Plan has been provided. Other documentation relating to pharmacovigilance system have been provided.

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP certificates of satisfactory inspection summary reports, ‘close-out letters’ issued by the inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those non-Community sites.
## II. ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Ibandronate Apotex 50mg Film-Coated Tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name(s) of the active substance(s) (USAN)</td>
<td>Ibandronate sodium</td>
</tr>
<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Bisphosphonates (M05B A06)</td>
</tr>
<tr>
<td>Pharmaceutical form and strength(s)</td>
<td>50mg Film-Coated Tablets</td>
</tr>
<tr>
<td>Reference numbers for the Mutual Recognition Procedure</td>
<td>UK/H/1867/001/DC</td>
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<tr>
<td>Reference Member State</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>Member States concerned</td>
<td>Belgium, Czech Republic, Germany, Hungary, Ireland and Luxembourg</td>
</tr>
<tr>
<td>Marketing Authorisation Number(s)</td>
<td>PL 27583/0097</td>
</tr>
<tr>
<td>Name and address of the authorisation holder</td>
<td>Apotex Europe BV, Darwinweg 20, 2333 CR Leiden, The Netherlands</td>
</tr>
</tbody>
</table>
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

DRUG SUBSTANCE

INN: Ibandronate sodium
Chemical Names: monosodium {1-hydroxy-3-[methyl(pentyl)amino]-1-phosphonopropyl}phosphonate propylene glycolate

Structure:

```
H3C
\|\n\|\nN \|\nCH3
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Molecular formula: C$_9$H$_{22}$NO$_7$P$_2$Na • CH$_3$CH(OH)CH$_2$OH
Molecular weight: 319.23
Physical form: A white to off-white powder, soluble in water, practically insoluble in organic solvents

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. No materials of animal or human origin are used in the production of the active substance.

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. All impurities have been appropriately characterised and certificates of analysis have been provided for any working standards used. Batch analysis data are provided that comply with the proposed specification.

Suitable specifications for all materials used in the active substance packaging have been provided. The primary packaging meets the requirements for materials in contact with food.

Appropriate stability data have been generated, from studies carried out in accordance with ICH conditions. A suitable retest period has been set, based on the stability data provided.

DRUG PRODUCT

Other ingredients

Other ingredients consist of pharmaceutical excipients microcrystalline cellulose, crospovidone (E1202), magnesium stearate (E572), colloidal anhydrous silica, hypromellose (E464) and macrogol. All excipients are controlled to their respective European Pharmacopoeia monograph specifications. Satisfactory certificates of analysis have been provided for all excipients. None of the excipients used contain materials of animal or human origin.

Pharmaceutical Development

Suitable pharmaceutical development data have been provided for this application. Comparable dissolution and impurity profile are provided for this product versus the originator product.
Manufacture
A description and flow-chart of the manufacturing method have been provided. In-process controls are satisfactory based on process validation data and controls on the finished product. Process validation has been carried out on batches of the product. The results appear satisfactory.

Finished product specification
The finished product specification is satisfactory. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

Container Closure System
The finished product is supplied in polyvinylchloride/polyvinylidene chloride/aluminium blisters in pack sizes of 14, 28, 30 and 84 tablets and a high-density polyethylene container with a polypropylene cap in pack sizes of 30 and 100 tablets.

Specifications and Certificates of Analysis for the primary packaging material have been provided. These are satisfactory. All primary packaging is controlled to European Pharmacopoeia standards and complies with current guidelines concerning materials in contact with food.

Stability
Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing.

Based on the results, a shelf-life of 2 years has been set, with the storage instructions “Store below 25°C”.

Summary of Product Characteristics (SPC), Patient Information Leaflet (PIL) and Labelling
The SPC, PIL and labelling are pharmaceutically satisfactory. The marketing authorisation holder has committed to submitting mock-ups of the patient information leaflet and labels to the relevant regulatory authorities before marketing the product in any member state.

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 it contains.

MAA Form
The MAA form is pharmaceutically satisfactory.

Expert Report
The pharmaceutical expert report is written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Conclusion
It is recommended that a Marketing Authorisation is granted for this application.
III.2 NON-CLINICAL ASPECTS
Pharmacodynamic, pharmacokinetic and toxicological properties of ibandronate sodium are well-known. As ibandronate sodium is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required.

ENVIRONMENTAL RISK ASSESSMENT
There is no environmental risk assessment statement included in the application. This is acceptable for a generic product.

SUMMARY OF PRODUCT CHARACTERISTICS (SPC)
The SPC is satisfactory from a preclinical viewpoint.

NON-CLINICAL EXPERT REPORT
The non-clinical expert report has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

OVERALL CONCLUSION ON THE NON-CLINICAL PART
The applicant has provided an adequate review of the available non-clinical data. There were no new non-clinical data identified in the literature review that would change the risk-benefit analysis for ibandronate sodium.

III.3 CLINICAL ASPECTS
Pharmacokinetics
With the exception of the bioequivalence study, no new data have been submitted and none are required for an application of this type. The bioequivalence study was conducted in line with Good Clinical Practice and the Declaration of Helsinki.

Bioequivalence
A randomised, open-label, two-treatment, two-sequence, two-period, two-way crossover, single-dose bioequivalence study to compare Ibandronate Apotex 50mg Film-Coated Tablets (test) versus Bondronat 50mg Film-Coated Tablets (reference) in healthy fasted volunteers.

A single dose of 100mg (2 tablets) of test or reference study drug was administered with a glass of water after an overnight fast. Blood samples were taken pre- and up to 120 hours post dose. Each treatment arm was separated by a 4-week washout period.
Results
The pharmacokinetic results for active ibandronate sodium are presented below:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Apotex 100 mg (test)</th>
<th>Bondronat 100 mg (reference)</th>
<th>Ratio (%)</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (pg/ml)</td>
<td>46426.0 (74)</td>
<td>42402.0 (60)</td>
<td>105.6</td>
<td>94.1 – 119.0</td>
</tr>
<tr>
<td>AUC$_{0-t}$ (pg.hr/ml)</td>
<td>200663.6 (54)</td>
<td>199035.9 (52)</td>
<td>100.2</td>
<td>90.4 – 111.0</td>
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<tr>
<td>AUC$_{0-\infty}$ (pg.hr/ml)</td>
<td>212933.8 (53)</td>
<td>209501.9 (52)</td>
<td>100.7</td>
<td>90.8 – 111.6</td>
</tr>
<tr>
<td>$t_{\text{max}}$ (hr)</td>
<td>1.00 (65)</td>
<td>1.00 (65)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>$K_e$ (h$^{-1}$)</td>
<td>0.01331 (16)</td>
<td>0.01411 (14)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>$t_{\text{distribute}}$ (hr)</td>
<td>53.57 (18)</td>
<td>50.02 (13)</td>
<td>-</td>
<td>-</td>
</tr>
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</table>

* for $t_{\text{max}}$ values are medians. LS estimates of geometric means for $C_{\text{max}}$, AUC$_{0-t}$, AUC$_{0-\infty}$ and LS estimates of arithmetic means for $t_{\text{max}}$, $K_e$, $t_{\text{distribute}}$.

Conclusions
The 90% confidence intervals for the test/reference lie within the acceptance criteria specified in the CPMP/EWP/QWP/1401/98 Notes for Guidance on the Investigation of Bioavailability and Bioequivalence. Bioequivalence of the test product to the reference formulation has been satisfactorily demonstrated in accordance with CHMP criteria.

Pharmacodynamics
No new data have been submitted and none are required for an application of this type.

Clinical efficacy
No new data have been submitted and none are required for an application of this type.

Clinical safety
Ibandronate sodium has an acceptable adverse events profile. No new safety concerns arise from the bioequivalence study and the safety profiles of this product versus the reference product (Bondronat 50mg Film-Coated Tablets) are similar.

Summary of Product Characteristics (SPC), Patient Information Leaflet (PIL) and labelling
The SPC, PIL and labelling are medically satisfactory and consistent with those for the reference product.

Clinical Expert Report
The clinical expert report is written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

MAA Form
The MAA Form is medically satisfactory.

Clinical Conclusion
The grant of a Marketing Authorisation is recommended.
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT
QUALITY
The important quality characteristics of Ibandronate Apotex 50mg Film-Coated 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.

PRECLINICAL
The preclinical data submitted have not revealed any evidence of potential risks to human health from treatment with Ibandronate Apotex 50mg Film-Coated Tablets beyond those already described.

EFFICACY
No new data have been submitted and none are required for an application of this type.

Ibandronate Apotex 50mg Film-Coated Tablets is a generic version of Bondronat 50mg Film-Coated Tablets (Roche Registrations Ltd). The use of the reference product is well-established in the UK. Both products contain the same quantitative and qualitative composition of the active ingredient, ibandronate sodium.

In the bioequivalence study, the 90% confidence intervals for the test/reference lie within the acceptance criteria specified in the CPMP/EWP/QWP/1401/98 Notes for Guidance on the Investigation of Bioavailability and Bioequivalence. Bioequivalence of the test product to the reference formulation has been satisfactorily demonstrated in accordance with CHMP criteria.

No new safety data are supplied or required for this generic application. Ibandronate sodium has a well-established side-effect profile and is generally well-tolerated.

The SPC, PIL and labelling are satisfactory.

BENEFIT-RISK ASSESSMENT
The quality of the product is acceptable, and no new preclinical or clinical safety concerns have been identified. The data supplied supports the claim that the applicant’s product and the innovator product are interchangeable. Extensive clinical experience with ibandronate sodium is considered to have demonstrated the therapeutic value of the compound. The risk-benefit is, therefore, considered to be positive.
## Module 6

### STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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