1. **NAME OF THE MEDICINAL PRODUCT**

Ibandronic Acid Teva 50 mg film-coated tablets

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each film-coated tablet contains 50 mg ibandronic acid (as ibandronate sodium monohydrate).

For a full list of excipients, see section 6.1.

3. **PHARMACEUTICAL FORM**

Film-coated tablet.

White, biconvex, capsule-shaped film-coated tablets, engraved “50” on one side and plain on the other.

4. **CLINICAL PARTICULARS**

4.1 **Therapeutic indications**

Ibandronic Acid Teva 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 Teva 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.

Ibandronic Acid Teva 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 Ibandronic Acid Teva 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 Teva 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 Ibandronic Acid Teva.
- Patients should not chew, suck or crush the tablet because of a potential for oropharyngeal ulceration.
- Plain water is the only drink that should be taken with Ibandronic Acid Teva. 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 renal impairment (CLcr ≥50 and <80 mL/min).

For patients with moderate renal impairment (CLcr ≥30 and <50 mL/min) a dosage adjustment to one 50 mg film-coated tablet every second day is recommended (see section 5.2).

For patients with severe renal impairment (CLcr <30 mL/min) the recommended dose is one 50 mg film-coated tablet once weekly. See dosing instructions, above.

**Elderly**

No dose adjustment is necessary.

**Children and adolescents**

Ibandronic Acid Teva is not recommended for patients below age 18 years due to insufficient data on safety and efficacy.

### 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.

Ibandronic Acid Teva 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 Teva 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.

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 Teva 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 hospitalization, 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 and be able to comply with the dosing instructions (see section 4.2).

Physicians should be alert to any signs or symptoms signaling a possible oesophageal reaction and patients should be instructed to discontinue Ibandronic Acid Teva 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 NSAIDS are associated with gastrointestinal irritation, caution should be taken during concomitant oral medication with Ibandronic Acid Teva.

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 Teva.

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 Ibandronic Acid Teva. Therefore, with such products, including food, intake must be delayed at least 30 minutes following oral administration.

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 (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 tamoxifien 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 Teva 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

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 Teva should not be used during pregnancy.

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 Teva 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 1 Adverse Reactions Reported Commonly and Greater than Placebo

<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>Metabolism and Nutrition Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypocalcaemia</td>
<td>14 (5.1)</td>
<td>27 (9.4)</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</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>General Disorders</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:

Uncommon:
- Blood and Lymphatic System Disorders: anaemia
- Nervous System Disorders: paraesthesia, dysgeusia (taste perversion)
- Gastrointestinal Disorders: haemorrhage, duodenal ulcer, gastritis, dysphagia, abdominal pain, dry mouth
- Skin and Subcutaneous Tissue Disorders: pruritus
- Renal and Urinary Disorders: azotaemia (uraemia)
- General Disorders: chest pain, influenza-like illness, malaise, pain
- Investigations: blood parathyroid hormone increased

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 Teva. 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 Teva. 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: M05BA06
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 $^{45}$Ca 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 characterized 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 randomized 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)**

<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>SMPR (per patient year)</td>
<td>1.15</td>
<td>0.99</td>
<td>$p=0.041$</td>
</tr>
<tr>
<td>SRE relative risk</td>
<td>-</td>
<td>0.62</td>
<td>$p=0.003$</td>
</tr>
</tbody>
</table>

**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>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Ibandronic acid 50 mg</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 metabolized 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
Exposure to ibandronic acid in patients with various degree of renal impairment is related to creatinine clearance (CLcr). 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 (CLcr ≥ 80 mL/min). Total clearance of ibandronic acid was reduced to 44 ml/min in the subjects with severe renal impairment compared with 129 mL/min in subjects with normal renal function. No dosage adjustment is necessary for patients with mild renal impairment (CLcr ≥ 50 and <80 mL/min). For patients with moderate renal impairment (CLcr ≥ 30 and <50 mL/min) or severe renal impairment (CLcr < 30 mL/min) an adjustment in the dose is recommended (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 metabolized 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:
Cellulose microcrystalline,
Povidone K-30,
Crosponive (type A),
Silica colloidal anhydrous,
Stearic acid.

Tablet coating:
Opadry white YS-1-7003:
Titanium dioxide (E171),
Hypromellose,
Macrogol 400,
Polysorbate 80.

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container
PVC/Aclar/PVC – Aluminium blisters in cardboard boxes of 28 or 84 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7. MARKETING AUTHORISATION HOLDER
Teva Pharma B.V.
8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

DD/MM/YYYY

10. DATE OF REVISION OF THE TEXT

MM/YYYY

1. NAME OF THE MEDICINAL PRODUCT

Ibandronic Acid Teva 150 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 150 mg ibandronic acid (as ibandronate sodium monohydrate).

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.
White, biconvex, capsule-shaped film-coated tablets, engraved “I150” on one side and plain on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of osteoporosis in postmenopausal women at increased risk of fracture (see section 5.1). A reduction in the risk of vertebral fractures has been demonstrated, efficacy on femoral neck fractures has not been established.

4.2 Posology and method of administration

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

Ibandronic Acid Teva 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 Teva 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 sections 4.4 and 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 Teva is not recommended for patients with a creatinine clearance below 30 ml/min due to limited clinical experience (see sections 4.4 and 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 Teva in children, and Ibandronic Acid Teva 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 Teva. Plain water is the only drink that should be taken with Ibandronic Acid Teva. 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 Teva 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 Teva 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 Ibandronic Acid Teva therapy. Other disturbances of bone and mineral metabolism should also be effectively treated. Adequate intake of calcium and vitamin D is important in all patients.

Renal impairment
Due to limited clinical experience, Ibandronic Acid Teva is 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.

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 Teva, which is consistent with findings in animal studies. Therefore, patients should fast overnight (at least 6 hours) before taking Ibandronic Acid Teva and continue fasting for 1 hour following intake of Ibandronic Acid Teva (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 Teva. Therefore, patients should not take other oral medicinal products for at least 6 hours before taking Ibandronic Acid Teva and for 1 hour following intake of Ibandronic Acid Teva.

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 Teva is 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 Teva 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 Teva 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 (MF 4411). 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 causally related to ibandronic acid are listed below by System Organ Class.

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

Table 1: Adverse reactions occurring in postmenopausal women receiving ibandronic acid 150 mg once monthly or ibandronic acid 2.5 mg daily in phase III studies BM 16549 and MF 4411.
<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</td>
<td>Common</td>
<td>Rash</td>
</tr>
<tr>
<td>disorders</td>
<td></td>
<td>Angioedema, Face oedema, Urticaria</td>
</tr>
<tr>
<td>Musculoskeletal, connective tissue</td>
<td>Common</td>
<td>Arthralgia, Myalgia, Musculoskeletal pain, Muscle cramp, Musculoskeletal stiffness</td>
</tr>
<tr>
<td>and bone disorders</td>
<td>Uncommon</td>
<td>Back pain</td>
</tr>
<tr>
<td>General disorders and</td>
<td>Common</td>
<td>Influenza-like illness*</td>
</tr>
<tr>
<td>administration site conditions</td>
<td>Uncommon</td>
<td>Fatigue</td>
</tr>
</tbody>
</table>

MedDRA version 7.1

* Transient, influenza-like symptoms have been reported with ibandronic acid 150 mg 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 a 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 Teva. However, based on a 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 Teva, 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: M05BA06

Mechanism of action
Ibandronic acid is a highly potent bisphosphonate belonging to the nitrogen-containing group of bisphosphonates, which act selectively on bone tissue and specifically inhibit osteoclast activity without directly affecting bone formation. It does not interfere with osteoclast recruitment. Ibandronic acid leads to progressive net gains in bone mass and a decreased incidence of fractures through the reduction of elevated bone turnover towards premenopausal levels in postmenopausal women.

Pharmacodynamic effects
The pharmacodynamic action of ibandronic acid is inhibition of bone resorption. In vivo, ibandronic acid prevents experimentally induced bone destruction caused by cessation of gonadal function, retinoids, tumours or tumour extracts. In young (fast growing) rats, the endogenous bone resorption is also inhibited, leading to increased normal bone mass compared with untreated animals. Animal models confirm that ibandronic acid is a highly potent inhibitor of osteoclastic activity. In growing rats, there was no evidence of impaired mineralization even at doses greater than 5,000 times the dose required for osteoporosis treatment.

Both daily and intermittent (with prolonged dose-free intervals) long-term administration in rats, dogs and monkeys was associated with formation of new bone of normal quality and maintained or increased mechanical strength even at doses in the toxic range. In humans, the efficacy of both daily and intermittent administration with a dose-free interval of 9-10 weeks of ibandronic acid was confirmed in a clinical trial (MF 4411), in which ibandronic acid demonstrated anti-fracture efficacy.

In animal models ibandronic acid produced biochemical changes indicative of dose-dependent inhibition of bone resorption, including suppression of urinary biochemical markers of bone collagen degradation (such as deoxypyridinoline, and cross-linked N-telopeptides of type I collagen (NTX)).

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

Clinical efficacy
Independent risk factors, for example, low BMD, age, the existence of previous fractures, a family history of fractures, high bone turnover and low body mass index should be considered in order to identify women at increased risk of osteoporotic fractures.

Ibandronic acid 150 mg once monthly
Bone mineral density (BMD)
Ibandronic acid 150 mg once monthly was shown to be at least as effective as ibandronic acid 2.5 mg
daily at increasing BMD in a two year, double-blind, multicentre study (BM 16549) of
postmenopausal women with osteoporosis (lumbar spine BMD T score below -2.5 SD at baseline).
This was demonstrated in both the primary analysis at one year and in the confirmatory analysis at two
years endpoint (Table 2).

Table 2: Mean relative change from baseline of lumbar spine, total hip, femoral neck and trochanter
BMD after one year (primary analysis) and two years of treatment (Per-Protocol Population) in study
BM 16549.

<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</td>
<td>Ibandronic acid 2.5 mg daily</td>
<td>Ibandronic acid 150 mg once</td>
</tr>
<tr>
<td>from baseline % [95% CI]</td>
<td>(N=318)</td>
<td>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>
<tr>
<td></td>
<td>5.0 [4.4, 5.5]</td>
<td>4.0 [3.5, 4.5]</td>
</tr>
<tr>
<td></td>
<td>6.6 [6.0, 7.1]</td>
<td>6.2 [5.7, 6.7]</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 a 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 morphometric vertebral fractures</td>
<td>9.56% (7.5, 11.7)</td>
<td>4.68% (3.2, 6.2)</td>
</tr>
<tr>
<td>Relative risk reduction of clinical vertebral fracture</td>
<td></td>
<td>49% (14.03, 69.49)</td>
</tr>
<tr>
<td>Incidence of clinical vertebral fracture</td>
<td>5.33% (3.73, 6.92)</td>
<td>2.75% (1.61, 3.89)</td>
</tr>
<tr>
<td>BMD – mean change relative to baseline lumbar spine at year 3</td>
<td>1.26% (0.8, 1.7)</td>
<td>6.54% (6.1, 7.0)</td>
</tr>
<tr>
<td>BMD – mean change relative to baseline total hip at year 3</td>
<td>-0.69% (-1.0, -0.4)</td>
<td>3.36% (3.0, 3.7)</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**
In the overall patient population of the study MF 4411, no reduction was observed for non-vertebral fractures, however daily ibandronic acid appeared to be effective in a high-risk subpopulation (femoral neck BMD T-score < -3.0), where a non-vertebral fracture risk reduction of 69% was observed.

Daily 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 (CLcr 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 (CLcr less than 30 ml/min) receiving daily oral administration of 10 mg ibandronic acid for 21 days, had 2-3 fold higher plasma concentrations than subjects with normal renal function and total clearance of ibandronic acid was 44 ml/min. After intravenous administration of 0.5 mg, 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 sections 4.2 and 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 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

**Tablet core:**
- Cellulose microcrystalline,
- Povidone K-30,
- Crosprotivone (type A),
- Silica colloidal anhydrous,
- Stearic acid.

**Tablet coating:**
- Opadry white YS-1-7003:
  - Titanium dioxide (E171),
  - Hypromellose,
  - Macrogol 400,
  - Polysorbate 80.

#### 6.2 Incompatibilities

Not applicable.

#### 6.3 Shelf life

2 years

#### 6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

#### 6.5 Nature and contents of container
PVC/Aclar/PVC – Aluminium blisters in cardboard boxes of 1 or 3 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Teva Pharma B.V.
Computerweg 10
3542 DR Utrecht
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

DD/MM/YYYY

10. DATE OF REVISION OF THE TEXT

MM/YYYY

Detailed information on this medicinal product is available on the website of the European Medicines Agency [http://www.ema.europa.eu/]
ANNEX II

A. MANUFACTURING AUTHORISATION HOLDERS RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION
A. MANUFACTURING AUTHORISATION HOLDERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

Teva Pharmaceutical Works Private Limited Company
Pallagi út 13
HU-4042 Debrecen
Hungary

TEVA Pharmaceutical Works Private Limited Company
H-2100 Gödöllő
Táncsics Mihály út 82
Hungary

TEVA UK Ltd
Brampton Road, Hampden Park
Eastbourne, East Sussex,
BN22 9AG
United Kingdom

Pharmachemie B.V.
Swensweg 5,
2031 GA Haarlem
The Netherlands

Teva Czech Industries s.r.o.
Ostravska 29/305
747 70 Opava-Komarov
Czech Republic

TEVA Santé SA
Rue Bellocier,
89107 Sens
France

PLIVA Krakow Zaklady Farmaceutyczne SA
ul. Mogilska 80
31-546 Krakow
Poland

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.
B. CONDITIONS OF THE MARKETING AUTHORISATION

- CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER

Medicinal product subject to medical prescription

- CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

Not applicable

- OTHER CONDITIONS

Pharmacovigilance system

The MAH must ensure that the system of pharmacovigilance, as described in version 7.0 presented in Module 1.8.1. of the Marketing Authorisation Application, is in place and functioning before and whilst the product is on the market.

PSURs

The proposed generic product Ibandronic Acid Teva 150 mg film-coated tablets should follow an annual PSUR submission scheme, in line with that of Bonviva.

The proposed generic product Ibandronic Acid Teva 50 mg film-coated tablet should follow a 3-yearly PSUR submission scheme, in line with that of Bondronat.
ANNEX III

LABELLING AND PACKAGE LEAFLET
A. LABELLING
<table>
<thead>
<tr>
<th>PARTICULARS TO APPEAR ON THE OUTER PACKAGING</th>
</tr>
</thead>
<tbody>
<tr>
<td>OUTER CARTON</td>
</tr>
<tr>
<td>1. NAME OF THE MEDICINAL PRODUCT</td>
</tr>
<tr>
<td>Ibandronic Acid Teva 50 mg film-coated tablets</td>
</tr>
<tr>
<td>ibandronic acid</td>
</tr>
<tr>
<td>2. STATEMENT OF ACTIVE SUBSTANCE</td>
</tr>
<tr>
<td>Each film-coated tablet contains 50 mg ibandronic acid (as ibandronate sodium monohydrate)</td>
</tr>
<tr>
<td>3. LIST OF EXCIPIENTS</td>
</tr>
<tr>
<td>4. PHARMACEUTICAL FORM AND CONTENTS</td>
</tr>
<tr>
<td>Film-coated tablet</td>
</tr>
<tr>
<td>28 film-coated tablets</td>
</tr>
<tr>
<td>84 film-coated tablets</td>
</tr>
<tr>
<td>5. METHOD AND ROUTE OF ADMINISTRATION</td>
</tr>
<tr>
<td>Oral use</td>
</tr>
<tr>
<td>Do not suck , chew or crush the tablets</td>
</tr>
<tr>
<td>Read the package leaflet before use</td>
</tr>
<tr>
<td>6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN</td>
</tr>
<tr>
<td>Keep out of the reach and sight of children.</td>
</tr>
<tr>
<td>7. OTHER SPECIAL WARNING(S), IF NECESSARY</td>
</tr>
<tr>
<td>8. EXPIRY DATE</td>
</tr>
<tr>
<td>EXP</td>
</tr>
<tr>
<td>9. SPECIAL STORAGE CONDITIONS</td>
</tr>
</tbody>
</table>
10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Teva Pharma B.V.
Computerweg 10,
3542 DR Utrecht,
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Ibandronic Acid Teva 50 mg film-coated tablets
### MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

#### BLISTERS

1. **NAME OF THE MEDICINAL PRODUCT**
   
   Ibandronic Acid Teva 50 mg film-coated tablets
   ibandronic acid

2. **NAME OF THE MARKETING AUTHORISATION HOLDER**
   
   Teva Pharma B.V.

3. **EXPIRY DATE**
   
   EXP

4. **BATCH NUMBER**
   
   Lot

5. **OTHER**
   
   Mon
   Tue
   Wed
   Thu
   Fri
   Sat
   Sun
PARTICULARS TO APPEAR ON THE OUTER PACKAGING
OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Ibandronic Acid Teva 150 mg film-coated tablets
ibandronic acid

2. STATEMENT OF ACTIVE SUBSTANCE

Each film-coated tablet contains 150 mg ibandronic acid (as ibandronate sodium monohydrate)

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

1 film-coated tablet
3 film-coated tablets

5. METHOD AND ROUTE OF ADMINISTRATION

Once monthly tablet
Do not suck, chew or crush the tablet
Read the package leaflet before use

Month 1 __/__/__
Month 2 __/__/__
Month 3 __/__/__
Note down the date you take your tablet

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Teva Pharma B.V.
Computerweg 10,
3542 DR Utrecht,
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Ibandronic Acid Teva 150 mg film-coated tablets
### MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

#### BLISTERS

1. **NAME OF THE MEDICINAL PRODUCT**

Ibandronic Acid Teva 150 mg film-coated tablets
ibandronic acid

2. **NAME OF THE MARKETING AUTHORISATION HOLDER**

Teva Pharma B.V.

3. **EXPIRY DATE**

EXP

4. **BATCH NUMBER**

Lot

5. **OTHER**
B. PACKAGE LEAFLET
Ibandronic Acid Teva 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 Ibandronic Acid Teva is and what it is used for
2. Before you take Ibandronic Acid Teva
3. How to take Ibandronic Acid Teva
4. Possible side effects
5. How to store Ibandronic Acid Teva
6. Further information

1. WHAT IBANDRONIC ACID TEVA IS AND WHAT IT IS USED FOR

The active substance of Ibandronic Acid Teva, ibandronic acid, belongs to the group of medicines known as bisphosphonates. It inhibits increased loss of calcium from the bones (bone resorption), and prevents bone complications and fractures related to the spread of cancer cells into bone.

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

2. BEFORE YOU TAKE IBANDRONIC ACID TEVA

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

If you are under dental treatment or will undergo dental surgery, tell your dentist that you are being treated with Ibandronic Acid Teva.

Do not take Ibandronic Acid Teva
- if you are allergic (hypersensitive) to ibandronic acid or any of the other ingredients of Ibandronic Acid Teva.
- 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 (60 minutes) at a time
- if you have, or had in the past low blood calcium. Please consult your doctor.

Do not give Ibandronic Acid Teva to children.

Take special care with Ibandronic Acid Teva
if you know or believe that you may have:
- allergies to other bisphosphonates,
- other disturbances of mineral metabolism (such as vitamin D deficiency),
- moderate kidney disease (creatinine clearance ≥30 and <50 mL/min) or severe kidney disease (renal insufficiency i.e. creatinine clearance <30 mL/min),

or when
- you have any swallowing or digestive problems

Irritation, inflammation or ulceration of the oesophagus (the tube that connects your mouth with your stomach) often with symptoms of severe pain in the chest, severe pain after swallowing food and/or drink, severe nausea, or vomiting may occur, especially if you do not drink a full glass of plain water and/or if you lie down within an hour of taking Ibandronic Acid Teva. If you develop these symptoms, stop taking Ibandronic Acid Teva 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 a prescription, or are taking supplements containing calcium, magnesium, iron or aluminium.

No interaction was observed when ibandronic acid was administered in combination with tamoxifen (used in the treatment of breast cancer), or melphalan/prednisolone.

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

Take special care if you are also taking non-steroidal anti-inflammatory drugs (NSAIDs), since both types of medicinal products (NSAIDs and bisphosphonates) may cause irritation to the stomach and intestine.

After taking your Ibandronic Acid Teva tablet, wait at least 30 minutes before taking any other medication of the day, including indigestion tablets/medicine, calcium supplements and vitamins.

**Taking Ibandronic Acid Teva with food and drink**
Your Ibandronic Acid Teva tablet 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, aluminium, magnesium and iron) should similarly be avoided prior to taking Ibandronic Acid Teva. Fasting, 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 Ibandronic Acid Teva treatment.

**Pregnancy and breast-feeding**
Do not take Ibandronic Acid Teva if you are pregnant or if you are breast-feeding.

**Driving and using machines**
The effects of Ibandronic Acid Teva on the ability to drive or to use machines has not been studied.

3. **HOW TO TAKE IBANDRONIC ACID TEVA**

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

The usual dose of Ibandronic Acid Teva is one tablet per day. If you have kidney problems, your doctor may reduce your dose to one tablet every second day in case of moderate kidney disease or to one tablet per week in case of severe kidney disease.

To reduce possible irritation, it is important that you follow the instructions below:
- Take Ibandronic Acid Teva BEFORE taking your first food, drink or other medicinal products of the day.
- Take your Ibandronic Acid Teva tablet with a full glass of plain water only (about 200 ml).
- Do not take your tablet with any drink other than plain water.
- Do not chew, suck, crush or allow the tablet to dissolve in your mouth.
- After taking your Ibandronic Acid Teva tablet, wait at least 30 minutes before taking your first food, beverage, or other medication of the day.
- You should remain in an upright (sitting or standing) position while taking Ibandronic Acid Teva and remain upright for 60 minutes after taking your tablet. If you do not stay upright (standing or sitting), some of the medicine could leak back into your oesophagus.
- It is important to continue taking Ibandronic Acid Teva for as long as your doctor prescribes the medicine, Ibandronic Acid Teva can help with your condition only if you continue to take the tablets.

If you take more Ibandronic Acid Teva than you should
If you take too many tablets by mistake, drink a full glass of milk and contact your doctor immediately.
Do not make yourself vomit, and do not lie down.

If you forget to take Ibandronic Acid Teva
Do not take a double dose to make up for a forgotten tablet. Return to taking one tablet per day the following day, as usual.

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

4. POSSIBLE SIDE EFFECTS

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

The following terms are used to describe how often side effects have been reported:

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>very common:</td>
<td>affects more than 1 user in 10</td>
</tr>
<tr>
<td>common:</td>
<td>affects 1 to 10 users in 100</td>
</tr>
<tr>
<td>uncommon:</td>
<td>affects 1 to 10 users in 1,000</td>
</tr>
<tr>
<td>rare:</td>
<td>affects 1 to 10 users in 10,000</td>
</tr>
<tr>
<td>very rare:</td>
<td>affects less than 1 user in 10,000</td>
</tr>
<tr>
<td>not known:</td>
<td>frequency cannot be estimated from the available data</td>
</tr>
</tbody>
</table>

• Common:
  - indigestion,
  - nausea,
  - abdominal pain,
  - oesophagitis (inflammation of the gullet),
  - tiredness,
  - low calcium levels in the blood.

Ibandronic Acid Teva 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 Teva and tell your doctor straight away.

• Uncommon:
  - strange taste,
  - paraesthesia (tingling sensation)
  - dry mouth,
- bleeding gastrointestinal ulcer,
- difficulty swallowing,
- gastritis,
- itching,
- chest pain,
- flu-like symptoms,
- feeling unwell and pain,
- anaemia (low hemoglobin in the blood),
- high levels of urea and high levels of parathyroid hormone have been reported from blood tests.

• Not known:
- jaw problems associated with delayed healing and infection, often following tooth extraction.

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.

5. HOW TO STORE IBANDRONIC ACID TEVA

Keep out of the reach and sight of children.

This medicinal product does not require any special storage conditions.

Do not use Ibandronic Acid Teva after the expiry date which is stated on the blister and carton 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 Teva contains
- The active substance is ibandronic acid.
  Each film-coated tablet contains 50 mg ibandronic acid (as ibandronate sodium monohydrate).
- The other ingredients are: tablet core: cellulose microcrystalline, povidone K-30, crospovidone (type A), silica colloidal anhydrous, stearic acid; tablet coating: titanium dioxide (E171), hypromellose, macrogol 400, polysorbate 80.

What Ibandronic Acid Teva looks like and contents of the pack
- The Ibandronic Acid Teva film-coated tablets are white, biconvex, capsule-shaped, engraved “50” on one side and plain on the other.
- Ibandronic Acid Teva comes in blisters (PVC/Aclar/PVC – Aluminium) in cartons of 28 or 84 tablets.

  Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:

Teva Pharma B.V.,
Computerweg 10,
3542 DR Utrecht,
The Netherlands
Manufacturer:

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Hungary

Teva Pharmaceutical Works Private Limited Company
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Hungary

Teva UK Ltd
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Pharmachemie B.V
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Teva Czech Industries s.r.o
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Czech Republic

PLIVA Krakow Zaklady Farmaceutyczne SA
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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Teva UK Limited
Tel: +44 1323 501 111

This leaflet was last approved in {MM/YYYY}.

Detailed information on this medicine is available on the European Medicines Agency web site:
http://www.ema.europa.eu/
Ibandronic Acid Teva 150 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 Ibandronic Acid Teva is and what it is used for
2. Before you take Ibandronic Acid Teva
3. How to take Ibandronic Acid Teva
4. Possible side effects
5. How to store Ibandronic Acid Teva
6. Further information

1. WHAT IBANDRONIC ACID TEVA IS AND WHAT IT IS USED FOR

Ibandronic Acid Teva belongs to a group of medicines called bisphosphonates. It contains ibandronic acid. It does not contain hormones.
Ibandronic Acid Teva may reverse bone loss by stopping more loss of bone and increasing bone mass in most women who take it, even though they will not be able to see or feel a difference. Ibandronic Acid Teva 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 Teva 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 walking 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 Teva prevents loss of bone from osteoporosis, and helps to rebuild bone. Therefore Ibandronic Acid Teva makes bone 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; walking or any other weight-bearing exercise; not smoking; and not drinking too much alcohol.
2. BEFORE YOU TAKE IBANDRONIC ACID TEVA

Do not take Ibandronic Acid Teva
- if you are allergic (hypersensitive) to ibandronic acid or any of the other ingredients of Ibandronic Acid Teva.
- 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 (60 minutes) at a time.
- if you have, or had in the past low blood calcium.

Please consult your doctor if any of the above apply.

Do not give Ibandronic Acid Teva to children or adolescents.

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

Irritation, inflammation or ulceration of the oesophagus (the tube that connects your mouth with your stomach) often with symptoms of severe pain in the chest, severe pain after swallowing food and/or drink, severe nausea, or vomiting may occur, especially if you do not drink a full glass of plain water and/or if you lie down within an hour of taking Ibandronic Acid Teva. If you develop these symptoms, stop taking Ibandronic Acid Teva 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 a prescription. Especially:
- supplements containing calcium, magnesium, iron or aluminium, as they could possibly influence the effects of Ibandronic Acid Teva;
- 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 Teva) may also do so. So be especially careful if you take painkillers or anti-inflammatories while you’re taking Ibandronic Acid Teva.

After swallowing your monthly Ibandronic Acid Teva tablet, wait for 1 hour before taking any other medication, including indigestion tablets, calcium supplements, or vitamins.

Taking Ibandronic Acid Teva with food and drink
Do not take Ibandronic Acid Teva with food or milk. Ibandronic Acid Teva is less effective if it’s taken with food.
You can drink plain water but no other drinks (see section 3. How to take Ibandronic Acid Teva).

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

Driving and using machines
You can drive and use machines as it’s very unlikely that Ibandronic Acid Teva will affect your ability to drive and use machines.
3. HOW TO TAKE IBANDRONIC ACID TEVA

Always take Ibandronic Acid Teva 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 Teva 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 Teva tablet reach your stomach quickly, so it’s less likely to cause irritation.

- Take one Ibandronic Acid Teva 150 mg 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 Teva tablet. Choose the date that best fits your routine.
- Take your Ibandronic Acid Teva tablet at least 6 hours after you last had anything to eat or drink except plain water.

- Take your Ibandronic Acid Teva 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, milk, fruit juice or any other drinks.

- Swallow your tablet whole — do not chew it, crush it, suck it or let it dissolve in your mouth.

- For the next hour (60 minutes) after you’ve taken your tablet
  - do not lie down; if you do not stay upright (standing or sitting), some of the medicine could leak back into your oesophagus

- 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 (other than water). 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.

If you take more Ibandronic Acid Teva than you should
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 Teva to irritate your oesophagus.

If you forget to take Ibandronic Acid Teva
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 next 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 Teva tablets within the same week.

If you stop taking Ibandronic Acid Teva
It’s important to keep taking Ibandronic Acid Teva every month, as long as your doctor prescribes it for you.
Ibandronic Acid Teva can treat osteoporosis only as long as you keep taking it.

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

4. POSSIBLE SIDE EFFECTS

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

The following terms are used to describe how often side effects have been reported:

<table>
<thead>
<tr>
<th>Term</th>
<th>Description</th>
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</thead>
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</tr>
<tr>
<td>not known</td>
<td>frequency cannot be estimated from the available data</td>
</tr>
</tbody>
</table>

- heartburn,
- indigestion,
- diarrhoea,
- stomach ache,
- nausea.

Ibandronic Acid Teva 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, 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 (aches and pains, feeling of discomfort, fatigue) which are usually mild, are short-lasting and disappear soon after you have taken the first dose. So you should be able to carry on taking Ibandronic Acid Teva. Talk to your doctor if any effects become troublesome or last a long time.
• Uncommon:
  - dizziness,
  - back pain,
  - flatulence.

• Rare:
  - swelling and itching of the face, lips and mouth.

• Not known:
  - jaw problems associated with delayed healing and infection, often following tooth extraction

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.

5. HOW TO STORE IBANDRONIC ACID TEVA

Keep out of the reach and sight of children.

This medicinal product does not require any special storage conditions.

Do not use Ibandronic Acid Teva after the expiry date which is stated on the blister and carton 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 Teva contains

- The active substance is ibandronic acid.
  Each film-coated tablet contains 150 mg ibandronic acid (as ibandronate sodium monohydrate).
- The other ingredients are: tablet core: cellulose microcrystalline, povidone K-30, crospovidone (type A), silica colloidal anhydrous, stearic acid; tablet coating: titanium dioxide (E171), hypromellose, macrogol 400, polysorbate 80.

What Ibandronic Acid Teva looks like and contents of the pack

- The Ibandronic Acid Teva film-coated tablets are white, biconvex, capsule-shaped, engraved “1150” on one side and plain on the other.
- Ibandronic Acid Teva comes in blisters (PVC/Aclar/PVC – Aluminium) in cartons of 1 or 3 tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:

Teva Pharma B.V.,
Computerweg 10,
3542 DR Utrecht,
The Netherlands
Manufacturer:

Teva Pharmaceutical Works Private Limited Company
Pallagi út 13, 4042 Debrecen
Hungary

Teva Pharmaceutical Works Private Limited Company
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/