ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

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 sodium monohydrate).

For the 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 in adults 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.

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

Special populations
Hepatic impairment
No dose adjustment is required (see section 5.2).

Renal impairment
No dose 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 population (> 65 years)
No dose adjustment is necessary (see section 5.2).

Paediatric population
The safety and efficacy of Ibandronic Acid Teva in children and adolescents below the age of 18 years have not been established. No data are available. (see sections 5.1 and 5.2).

Method of administration

For oral use.

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. Water may be taken at any time during the course of Ibandronic Acid Teva treatment (see section 4.5). Water with a high concentration of calcium should not be used. If there is concern regarding potentially high levels of calcium in the tap water (hard water), it is advised to use bottled water with a low mineral content.

- The tablets should be swallowed whole with a full glass of 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.

- Water is the only drink that should be taken with Ibandronic Acid Teva.

4.3 Contraindications

- Hypersensitivity to ibandronic acid or to any of the excipients listed in section 6.1.
- Hypocalcaemia
- Abnormalities of the oesophagus which delay oesophageal emptying such as stricture or achalasia
- Inability to stand or sit upright for at least 60 minutes

4.4 Special warnings and precautions for use

Patients with disturbances of bone and mineral metabolism
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.

Gastrointestinal irritation
Orally administered bisphosphonates may cause local irritation of the upper gastrointestinal mucosa. Because of these possible irritant effects and a potential for worsening of the underlying disease, caution should be used when Ibandronic Acid 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.

Acetylsalicylic acid and NSAIDs
Since acetylsalicylic acid, Nonsteroidal Anti-Inflammatory medicinal products (NSAIDs) and bisphosphonates are associated with gastrointestinal irritation, caution should be taken during concomitant administration.

Osteonecrosis of the jaw
Osteonecrosis of the jaw (ONJ) has been reported very rarely in the post-marketing setting in patients receiving Ibandronic Acid Teva for oncology indications (see section 4.8).

The start of treatment or of a new course of treatment should be delayed in patients with unhealed open soft tissue lesions in the mouth.

A dental examination with preventive dentistry and an individual benefit-risk assessment is recommended prior to treatment with Ibandronic Acid Teva in patients with concomitant risk factors.

The following risk factors should be considered when evaluating a patient's risk of developing ONJ:
- Potency of the medicinal product that inhibit bone resorption (higher risk for highly potent compounds), route of administration (higher risk for parenteral administration) and cumulative dose of bone resorption therapy.
- Cancer, co-morbid conditions (e.g. anaemia, coagulopathies, infection), smoking.
- Concomitant therapies: corticosteroids, chemotherapy, angiogenesis inhibitors, radiotherapy to head and neck.
- Poor oral hygiene, periodontal disease, poorly fitting dentures, history of dental disease, invasive dental procedures e.g. tooth extractions.

All patients should be encouraged to maintain good oral hygiene, undergo routine dental check-ups, and immediately report any oral symptoms such as dental mobility, pain or swelling, or non-healing of sores or discharge during treatment with Ibandronic Acid Teva. While on treatment, invasive dental procedures should be performed only after careful consideration and be avoided in close proximity to Ibandronic Acid Teva administration.

The management plan of the patients who develop ONJ should be set up in close collaboration between the treating physician and a dentist or oral surgeon with expertise in ONJ. Temporary interruption of Ibandronic Acid Teva treatment should be considered until the condition resolves and contributing risk factors are mitigated where possible.

Osteonecrosis of the external auditory canal
Osteonecrosis of the external auditory canal has been reported with bisphosphonates, mainly in association with long-term therapy. Possible risk factors for osteonecrosis of the external auditory canal include steroid use and chemotherapy and/or local risk factors such as infection or trauma. The possibility of osteonecrosis of the external auditory canal should be considered in patients receiving bisphosphonates who present with ear symptoms including chronic ear infections.

Atypical fractures of the femur
Atypical subtrochanteric and diaphyseal femoral fractures have been reported with bisphosphonate therapy, primarily in patients receiving long-term treatment for osteoporosis. These transverse or short oblique fractures can occur anywhere along the femur from just below the lesser trochanter to just above the supracondylar flare. These fractures occur after minimal or no trauma and some patients experience thigh or groin pain, often associated with imaging features of stress fractures, weeks to months before presenting with a completed femoral fracture. Fractures are often bilateral; therefore the contralateral femur should be examined in bisphosphonate-treated patients who have sustained a femoral shaft fracture. Poor healing of these fractures has also been reported.

Discontinuation of bisphosphonate therapy in patients suspected to have an atypical femur fracture should be considered pending evaluation of the patient, based on an individual benefit risk assessment.

During bisphosphonate treatment patients should be advised to report any thigh, hip or groin pain and any patient presenting with such symptoms should be evaluated for an incomplete femur fracture (see section 4.8).

Atypical fractures of other long bones
Atypical fractures of other long bones, such as the ulna and tibia have also been reported in patients receiving long-term treatment. As with atypical femoral fractures, these fractures occur after minimal, or no trauma and some patients experience prodromal pain prior to presenting with a completed fracture. In cases of ulna fracture, this may be associated with repetitive stress loading associated with the long-term use of walking aids (see section 4.8).

Renal function
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.

Patients with known hypersensitivity to other bisphosphonates
Caution is to be taken in patients with known hypersensitivity to other bisphosphonates.

Excipient(s)
Sodium
This medicine contains less than 1 mmol sodium (23 mg) per film-coated tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Medicinal product-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 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 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).

Interactions with other medicinal products
Metabolic interactions are not considered likely, since ibandronic acid does not inhibit the major human hepatic P450 isoenzymes and has been shown not to induce the hepatic cytochrome P450 system in rats (see section 5.2). Ibandronic acid is eliminated by renal excretion only and does not undergo any biotransformation.

H_2-antagonists or other medicinal products that increase gastric pH.
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 medicinal products that increase gastric pH.

Acetylsalicylic acid and NSAIDs
Since acetylsalicylic acid, Nonsteroidal Anti-Inflammatory medicinal products (NSAIDs) and bisphosphonates are associated with gastrointestinal irritation, caution should be taken during concomitant administration (see section 4.4).

Aminoglycosides

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

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data from the use of ibandronic acid in pregnant women. Studies in rats have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Therefore, Ibandronic Acid Teva should not be used during pregnancy.

Breast-feeding
It is not known whether ibandronic acid is excreted in human milk. Studies in lactating rats have demonstrated the presence of low levels of ibandronic acid in the milk following intravenous administration. Ibandronic Acid Teva should not be used during lactation.

Fertility
There are no data on the effects of ibandronic acid in humans. In reproductive studies in rats by the oral route, ibandronic acid decreased fertility. In studies in rats using the intravenous route, ibandronic acid decreased fertility at high daily doses (see section 5.3).

4.7 Effects on ability to drive and use machines

On the basis of the pharmacodynamic and pharmacokinetic profile and reported adverse reactions, it is expected that Ibandronic Acid Teva has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile
The most serious reported adverse reactions are anaphylactic reaction/shock, atypical fractures of the femur, osteonecrosis of the jaw, gastrointestinal irritation, and ocular inflammation (see paragraph "Description of selected adverse reactions" and section 4.4). Treatment was most frequently associated with a decrease in serum calcium to below normal range (hypocalcaemia), followed by dyspepsia.

Tabulated list of adverse reactions
Table 1 lists adverse reactions from 2 pivotal phase III studies (Prevention of skeletal events in patients with breast cancer and bone metastases: 286 patients treated with ibandronic acid 50 mg administered orally), and from post-marketing experience.

Adverse reactions are listed according to MedDRA system organ class and frequency category. Frequency categories are defined using the following convention: very common (≥1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1 Adverse Drug Reactions Reported for Oral Administration of Ibandronic Acid

System Organ Class	Common	Uncommon	Rare	Very rare	Not known
Blood and lymphatic system disorders		Anaemia			

System Organ Class	Common	Uncommon	Rare	Very rare	Not known
Immune system disorders				Hypersensitivity†, bronchospasm†, angioedema†, anaphylactic reaction/shock†*	Asthma exacerbation
Metabolism and nutrition disorders	Hypocalcaemia*				
Nervous system disorders		Paraesthesia, dysgeusia (taste perversion)			
Eye disorders			Ocular inflammation†*		
Gastrointestinal disorders	Oesophagitis, abdominal pain, dyspepsia, nausea	Haemorrhage, duodenal ulcer, gastritis, dysphagia, dry mouth			
Skin and subcutaneous tissue disorders		Pruritus		Stevens-Johnson syndrome†, erythema multiforme†, dermatitis bullous†	
Musculoskeletal and connective tissue disorders			Atypical subtrochanteric and diaphyseal femoral fractures†	Osteonecrosis of jaw†*, osteonecrosis of the external auditory canal (bisphosphonate class adverse reaction)†	Atypical fractures of long bones other than the femur
Renal and urinary disorders		Azotaemia (uraemia)			
General disorders and administration site conditions	Asthenia	Chest pain, influenza-like illness, malaise, pain			
Investigations		Blood parathyroid hormone increased			

*See further information below
†Identified in postmarketing experience.

Description of selected adverse reactions

Hypocalcaemia
Decreased renal calcium excretion may be accompanied by a fall in serum phosphate levels not requiring therapeutic measures. The serum calcium level may fall to hypocalcaemic values.

Osteonecrosis of jaw
Cases of osteonecrosis of the jaw have been reported, predominantly in cancer patients treated with medicinal products that inhibit bone resorption, such as ibandronic acid (see section 4.4.) Cases of ONJ have been reported in the post-marketing setting for ibandronic acid.

Atypical subtrochanteric and diaphyseal femoral fractures
Although the pathophysiology is uncertain, evidence from epidemiological studies suggests an increased risk of atypical subtrochanteric and diaphyseal femoral fractures with long-term bisphosphonate therapy for postmenopausal osteoporosis, particularly beyond three to five years of use. The absolute risk of atypical subtrochanteric and diaphyseal long bone fractures (bisphosphonate class adverse reaction) remains very low.

Ocular inflammation
Ocular inflammation events such as uveitis, episcleritis and scleritis have been reported with ibandronic acid. In some cases, these events did not resolve until the ibandronic acid was discontinued.

Anaphylactic reaction/shock
Cases of anaphylactic reaction/shock, including fatal events, have been reported in patients treated with intravenous ibandronic acid.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

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. Due to the risk of oesophageal irritation, vomiting should not be induced and the patient should remain fully upright.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Medicinal products for treatment of bone diseases, 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 a 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)

	All Skeletal Related Events (SREs)		
	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)

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

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

Paediatric population (see section 4.2 and section 5.2)
The safety and efficacy of Ibandronic Acid Teva in children and adolescents below the age of 18 years have not been established. No data are available.

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 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 interaction with other medicinal products, due to displacement is unlikely.

Biotransformation
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.

The secretory pathway of renal elimination 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.

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 (see section 4.2)
There are no pharmacokinetic data for ibandronic acid in patients who have hepatic impairment. The liver has no significant role in the clearance of ibandronic acid 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 (see section 4.2)
In a multivariate analysis, age was not found to be an independent factor of any of the pharmacokinetic parameters studied. As renal function decreases with age, this is the only factor to take into consideration (see renal impairment section).

Paediatric population (see sections 4.2 and 5.1)
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. In reproductive studies in rats by the oral route effects on fertility consisted of increased preimplantation losses at dose levels of 1 mg/kg/day and higher. In reproductive studies in rats by the intravenous route, ibandronic acid decreased sperm counts at doses of 0.3 and 1 mg/kg/day and decreased fertility in males at 1 mg/kg/day and in females at 1.2 mg/kg/day. Adverse effects of ibandronic acid in reproductive toxicity studies in the rat were those expected for this class of medicinal products (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
Crospovidone (type A)
Silica colloidal anhydrous
Stearic acid

Tablet coating:
Opadry white YS-1-7003:
Titanium dioxide (E 171)
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

Any unused medicinal product or waste material should be disposed of in accordance with local requirements. The release of pharmaceuticals in the environment should be minimized.

7. MARKETING AUTHORISATION HOLDER

Teva B.V.
Swensweg 5

2031 GA Haarlem
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/642/001	28 film-coated tablets in PVC/Aclar/PVC – Aluminium blisters in cardboard boxes
EU/1/10/642/002	84 film-coated tablets in PVC/Aclar/PVC – Aluminium blisters in cardboard boxes

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17 September 2010
Date of latest renewal: 25 June 2015

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu/

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 sodium monohydrate).

For the 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).

The optimal duration of bisphosphonate treatment for osteoporosis has not been established. The need for continued treatment should be re-evaluated periodically based on the benefits and potential risks of Ibandronic Acid Teva on an individual patient basis, particularly after 5 or more years of use.

Special populations
Renal impairment
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).

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

Hepatic impairment
No dose adjustment is required (see section 5.2).

Elderly population (>65 years)
No dose adjustment is required (see section 5.2).

Paediatric population
There is no relevant use of Ibandronic Acid Teva in children below 18 years, and Ibandronic Acid Teva was not studied in this population (see section 5.1 and section 5.2).

Method of administration
For oral use.

- Tablets should be swallowed whole with a glass of water (180 to 240 ml) while the patient is sitting or standing in an upright position. Water with a high concentration of calcium should not be used. If there is a concern regarding potentially high levels of calcium in the tap water (hard water), it is advised to use bottled water with a low mineral content.
- Patients should not lie down for 1 hour after taking Ibandronic Acid Teva.
- Water is the only drink that should be taken with Ibandronic Acid Teva.
- Patients should not chew or suck the tablet, because of a potential for oropharyngeal ulceration.

4.3 Contraindications

- Hypersensitivity to ibandronic acid or to any of the excipients listed in section 6.1
- Hypocalcaemia
- Abnormalities of the oesophagus which delay oesophageal emptying such as stricture or achalasia
- Inability to stand or sit upright for at least 60 minutes

4.4 Special warnings and precautions for use

Hypocalcaemia
Existing hypocalcaemia must be corrected before starting Ibandronic Acid 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.

Gastrointestinal irritation
Orally administered bisphosphonates may cause local irritation of the upper gastrointestinal mucosa. Because of these possible irritant effects and a potential for worsening of the underlying disease, caution should be used when Ibandronic Acid 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 reactions 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 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 Nonsteroidal Anti-Inflammatory medicinal products and bisphosphonates are both associated with gastrointestinal irritation, caution should be taken during concomitant administration.

Osteonecrosis of the jaw
Osteonecrosis of the jaw (ONJ) has been reported very rarely in the post-marketing setting in patients receiving Ibandronic Acid Teva for osteoporosis (see section 4.8).

The start of treatment or of a new course of treatment should be delayed in patients with unhealed open soft tissue lesions in the mouth.

A dental examination with preventive dentistry and an individual benefit-risk assessment is recommended prior to treatment with Ibandronic Acid Teva in patients with concomitant risk factors.

The following risk factors should be considered when evaluating a patient's risk of developing ONJ:
- Potency of the medicinal product that inhibit bone resorption (higher risk for highly potent compounds), route of administration (higher risk for parenteral administration) and cumulative dose of bone resorption therapy.
- Cancer, co-morbid conditions (e.g. anaemia, coagulopathies, infection), smoking.
- Concomitant therapies: corticosteroids, chemotherapy, angiogenesis inhibitors, radiotherapy to head and neck.
- Poor oral hygiene, periodontal disease, poorly fitting dentures, history of dental disease, invasive dental procedures e.g. tooth extractions.

All patients should be encouraged to maintain good oral hygiene, undergo routine dental check-ups, and immediately report any oral symptoms such as dental mobility, pain or swelling, or non-healing of sores or discharge during treatment with Ibandronic Acid Teva. While on treatment, invasive dental procedures should be performed only after careful consideration and be avoided in close proximity to Ibandronic Acid Teva administration.

The management plan of the patients who develop ONJ should be set up in close collaboration between the treating physician and a dentist or oral surgeon with expertise in ONJ. Temporary interruption of Ibandronic Acid Teva treatment should be considered until the condition resolves and contributing risk factors are mitigated where possible.

Osteonecrosis of the external auditory canal
Osteonecrosis of the external auditory canal has been reported with bisphosphonates, mainly in association with long-term therapy. Possible risk factors for osteonecrosis of the external auditory canal include steroid use and chemotherapy and/or local risk factors such as infection or trauma. The possibility of osteonecrosis of the external auditory canal should be considered in patients receiving bisphosphonates who present with ear symptoms including chronic ear infections.

Atypical fractures of the femur
Atypical subtrochanteric and diaphyseal femoral fractures have been reported with bisphosphonate therapy, primarily in patients receiving long-term treatment for osteoporosis. These transverse or short oblique fractures can occur anywhere along the femur from just below the lesser trochanter to just above the supracondylar flare. These fractures occur after minimal or no trauma and some patients experience thigh or groin pain, often associated with imaging features of stress fractures, weeks to months before presenting with a completed femoral fracture. Fractures are often bilateral; therefore the contralateral femur should be examined in bisphosphonate-treated patients who have sustained a femoral shaft fracture. Poor healing of these fractures has also been reported. Discontinuation of bisphosphonate therapy in patients suspected to have an atypical femur fracture should be considered pending evaluation of the patient, based on an individual benefit risk assessment.

During bisphosphonate treatment patients should be advised to report any thigh, hip or groin pain and any patient presenting with such symptoms should be evaluated for an incomplete femur fracture (see section 4.8).

Atypical fractures of other long bones
Atypical fractures of other long bones, such as the ulna and tibia have also been reported in patients receiving long-term treatment. As with atypical femoral fractures, these fractures occur after minimal, or no trauma and some patients experience prodromal pain prior to presenting with a completed fracture. In cases of ulna fracture, this may be associated with repetitive stress loading associated with the long-term use of walking aids (see section 4.8).

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).

Excipient(s)
Sodium
This medicine contains less than 1 mmol sodium (23 mg) per film-coated tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Medicinal product-Food Interaction
Oral bioavailability of ibandronic acid is generally reduced in the presence of food. In particular, products containing calcium, including milk and other multivalent cations (such as aluminium, magnesium, iron), are likely to interfere with absorption of Ibandronic Acid 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).

Interactions with other medicinal products
Metabolic interactions are not considered likely, since ibandronic acid does not inhibit the major human hepatic P450 isoenzymes and has been shown not to induce the hepatic cytochrome P450 system in rats (see section 5.2). Ibandronic acid is eliminated by renal excretion only and does not undergo any biotransformation.

Calcium supplements, antacids and some oral medicinal products containing multivalent cations
Calcium supplements, antacids and some oral medicinal products containing multivalent cations (such as aluminium, magnesium, iron) are likely to interfere with the absorption of Ibandronic Acid 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.

Acetylsalicylic acid and NSAIDs
Since Acetylsalicylic acid, Nonsteroidal Anti-Inflammatory medicinal products (NSAIDs) and bisphosphonates are associated with gastrointestinal irritation, caution should be taken during concomitant administration (see section 4.4).

H2 blockers or proton pump inhibitors
Of over 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.

4.6 Fertility, pregnancy and lactation

Pregnancy
Ibandronic Acid Teva is only for use in postmenopausal women and must not be taken by women of childbearing potential.

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.

Breast-feeding
It is not known whether ibandronic acid is excreted in human milk. Studies in lactating rats have demonstrated the presence of low levels of ibandronic acid in the milk following intravenous administration. Ibandronic Acid Teva should not be used during breast-feeding.

Fertility
There are no data on the effects of ibandronic acid from humans. In reproductive studies in rats by the oral route, ibandronic acid decreased fertility. In studies in rats using the intravenous route, ibandronic acid decreased fertility at high daily doses (see section 5.3).

4.7 Effects on ability to drive and use machines

On the basis of the pharmacodynamic and pharmacokinetic profile and reported adverse reactions, it is expected that Ibandronic Acid Teva has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile
The most serious reported adverse reactions are anaphylactic reaction/shock, atypical fractures of the femur, osteonecrosis of the jaw, gastrointestinal irritation, ocular inflammation, (see paragraph “Description of selected adverse reactions” and section 4.4).

The most frequently reported adverse reactions are arthralgia and influenza-like symptoms. These symptoms are typically in association with the first dose, generally of short duration, mild or moderate in intensity, and usually resolve during continuing treatment without requiring remedial measures (see paragraph “Influenza like illness”).

Tabulated list of adverse reactions
In table 1 a complete list of known adverse reactions is presented. The safety of oral treatment with ibandronic acid 2.5 mg daily was evaluated in 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).

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

Adverse reactions are listed according to MedDRA system organ class and frequency category. Frequency categories are defined using the following convention: very common (≥1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare

(<1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1: Adverse reactions occurring in postmenopausal women receiving ibandronic acid 150 mg once monthly or ibandronic acid 2.5 mg daily in the phase III studies BM 16549 and MF 4411 and in post-marketing experience.

System Organ Class	**Common**	**Uncommon**	**Rare**	**Very rare**	**Not known**
Immune system disorders		Asthma exacerbation	Hypersensitivity reaction	Anaphylactic reaction/shock*†	
Metabolism and nutrition disorders		Hypocalcaemia†			
Nervous system disorders	Headache	Dizziness			
Eye disorders			Ocular inflammation*†		
Gastrointestinal disorders*	Oesophagitis, Gastritis, Gastro oesophageal reflux disease, Dyspepsia, Diarrhoea, Abdominal pain, Nausea	Oesophagitis including oesophageal ulcerations or strictures and dysphagia, Vomiting, Flatulence	Duodenitis		
Skin and subcutaneous tissues disorders	Rash		Angioedema, Face oedema, Urticaria	Stevens-Johnson syndrome†, Erythema multiforme†, Dermatitis bullous†	
Musculoskeletal and connective tissue disorders	Arthralgia, Myalgia, Musculoskeletal pain, Muscle cramp, Musculoskeletal stiffness	Back pain	Atypical subtrochanteric and diaphyseal femoral fractures†	Osteonecrosis of jaw*†, Osteonecrosis of the external auditory canal (bisphosphonate class adverse reaction)†	Atypical fractures of long bones other than the femur
General disorders and administration site conditions	Influenza like illness*	Fatigue			

*See further information below
†Identified in post-marketing experience.

Description of selected adverse reactions

Gastrointestinal adverse reactions

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

Influenza-like illness
Influenza-like illness includes events reported as acute phase reaction or symptoms including myalgia, arthralgia, fever, chills, fatigue, nausea, loss of appetite, or bone pain.

Osteonecrosis of jaw
Cases of osteonecrosis of the jaw have been reported, predominantly in cancer patients treated with medicinal products that inhibit bone resorption, such as ibandronic acid (see section 4.4.) Cases of ONJ have been reported in the post-marketing setting for ibandronic acid.

Atypical subtrochanteric and diaphyseal femoral fractures
Although the pathophysiology is uncertain, evidence from epidemiological studies suggests an increased risk of atypical subtrochanteric and diaphyseal femoral fractures with long-term bisphosphonate therapy for postmenopausal osteoporosis, particularly beyond three to five years of use. The absolute risk of atypical subtrochanteric and diaphyseal long bone fractures (bisphosphonate class adverse reaction) remains very low.

Ocular inflammation
Ocular inflammation events such as uveitis, episcleritis and scleritis have been reported with ibandronic acid. In some cases, these events did not resolve until the ibandronic acid was discontinued.

Anaphylactic reaction/shock
Cases of anaphylactic reaction/shock, including fatal events, have been reported in patients treated with intravenous ibandronic acid.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

No specific information is available on the treatment of overdose with Ibandronic Acid Teva. However, based on a knowledge of this class of compounds, oral overdose 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: Medicinal products for treatment of bone diseases, bisphosphonates, ATC code: M05-BA06

Mechanism of action
Ibandronic acid is a highly potent bisphosphonate belonging to the nitrogen-containing group of bisphosphonates, which act selectively on bone tissue and specifically inhibit osteoclast activity without directly affecting bone formation. It does not interfere with osteoclast recruitment. Ibandronic

acid leads to progressive net gains in bone mass and a decreased incidence of fractures through the reduction of elevated bone turnover towards premenopausal levels in postmenopausal women.

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

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

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

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

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

Ibandronic acid 150 mg once monthly

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

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

	One year data in study BM 16549		Two year data in study BM 16549	
Mean relative changes from baseline % [95 % CI]	Ibandronic acid 2.5 mg daily (N=318)	Ibandronic acid 150 mg once monthly (N=320)	Ibandronic acid 2.5 mg daily (N=294)	Ibandronic acid 150 mg once monthly (N=291)
Lumbar spine L2-L4 BMD	3.9 [3.4, 4.3]	4.9 [4.4, 5.3]	5.0 [4.4, 5.5]	6.6 [6.0, 7.1]

Total hip BMD	2.0 [1.7, 2.3]	3.1 [2.8, 3.4]	2.5 [2.1, 2.9]	4.2 [3.8, 4.5]
Femoral neck BMD	1.7 [1.3, 2.1]	2.2 [1.9, 2.6]	1.9 [1.4, 2.4]	3.1 [2.7, 3.6]
Trochanter BMD	3.2 [2.8, 3.7]	4.6 [4.2, 5.1]	4.0 [3.5, 4.5]	6.2 [5.7, 6.7]

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

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

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

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

Biochemical markers of bone turn-over

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

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

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

Ibandronic acid 2.5 mg daily

In the initial three-year, randomised, double-blind, placebo-controlled, fracture study (MF 4411), a statistically significant and medically relevant decrease in the incidence of new radiographic morphometric and clinical vertebral fractures was demonstrated (table 3). In this study, ibandronic acid was evaluated at oral doses of 2.5 mg daily and 20 mg intermittently as an exploratory regimen. Ibandronic acid was taken 60 minutes before the first food or drink of the day (post-dose fasting period). The study enrolled women aged 55 to 80 years, who were at least 5 years postmenopausal, who had a BMD at lumbar spine of 2 to 5 SD below the premenopausal mean (T-score) in at least one vertebra [L1-L4], and who had one to four prevalent vertebral fractures. All patients received 500 mg calcium and 400 IU vitamin D daily. Efficacy was evaluated in 2,928 patients. Ibandronic acid 2.5 mg administered daily, showed a statistically significant and medically relevant reduction in the incidence of new vertebral fractures. This regimen reduced the occurrence of new radiographic vertebral

fractures by 62 % (p=0.0001) over the three year duration of the study. A relative risk reduction of 61 % was observed after 2 years (p=0.0006). No statistically significant difference was attained after 1 year of treatment (p=0.056). The anti-fracture effect was consistent over the duration of the study. There was no indication of a waning of the effect over time. The incidence of clinical vertebral fractures was also significantly reduced by 49 % (p=0.011). The strong effect on vertebral fractures was furthermore reflected by a statistically significant reduction of height loss compared to placebo (p<0.0001).

Table 3: Results from 3 years fracture study MF 4411 (%, 95 % CI)

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

The treatment effect of ibandronic acid was further assessed in an analysis of the subpopulation of patients who at baseline had a lumbar spine BMD T-score below –2.5. The vertebral fracture risk reduction was very consistent with that seen in the overall population.

Table 4: Results from 3 years fracture study MF 4411 (%, 95 % CI) for patients with lumbar spine BMD T-score below –2.5 at baseline

	Placebo (N=587)	Ibandronic acid 2.5 mg daily (N=575)
Relative Risk Reduction New morphometric vertebral fractures		59 % (34.5, 74.3)
Incidence of new morphometric vertebral fractures	12.54 % (9.53, 15.55)	5.36 % (3.31, 7.41)
Relative risk reduction of clinical vertebral fracture		50 % (9.49, 71.91)
Incidence of clinical vertebral fracture	6.97 % (4.67, 9.27)	3.57 % (1.89, 5.24)
BMD – mean change relative to baseline lumbar spine at year 3	1.13 % (0.6, 1.7)	7.01 % (6.5, 7.6)
BMD – mean change relative to baseline total hip at year 3	-0.70 % (-1.1, -0.2)	3.59 % (3.1, 4.1)

In the overall patient population of the study 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.

Paediatric population (see section 4.2 and section 5.2)
Ibandronic acid was not studied in the paediatric population, therefore no efficacy or safety data are available for this patient population.

5.2 Pharmacokinetic properties

The primary pharmacological effects of ibandronic acid on bone are not directly related to actual plasma concentrations, as demonstrated by various studies in animals and humans.

Absorption
The absorption of ibandronic acid in the upper gastrointestinal tract is rapid after oral administration and plasma concentrations increase in a dose-proportional manner up to 50 mg oral intake, with greater than dose-proportional increases seen above this dose. Maximum observed plasma concentrations were reached within 0.5 to 2 hours (median 1 hour) in the fasted state and absolute bioavailability was about 0.6 %. The extent of absorption is impaired when taken together with food or beverages (other than water). Bioavailability is reduced by about 90 % when ibandronic acid is administered with a standard breakfast in comparison with bioavailability seen in fasted subjects. There is no meaningful reduction in bioavailability provided ibandronic acid is taken 60 minutes before the first food of the day. Both bioavailability and BMD gains are reduced when food or beverage is taken less than 60 minutes after ibandronic acid is ingested.

Distribution
After initial systemic exposure, ibandronic acid rapidly binds to bone or is excreted into urine. In humans, the apparent terminal volume of distribution is at least 90 l and the amount of dose reaching the bone is estimated to be 40-50 % of the circulating dose. Protein binding in human plasma is approximately 85 %-87 % (determined *in vitro* at therapeutic concentrations), and thus there is a low potential for interaction with other medicinal products due to displacement.

Biotransformation
There is no evidence that ibandronic acid is metabolised in animals or humans.

Elimination
The absorbed fraction of ibandronic acid is removed from the circulation via bone absorption (estimated to be 40-50% in postmenopausal women) and the remainder is eliminated unchanged by the kidney. The unabsorbed fraction of ibandronic acid is eliminated unchanged in the faeces.

The range of observed apparent half-lives is broad, the apparent terminal half-life is generally in the range of 10-72 hours. As the values calculated are largely a function of the duration of study, the dose used, and assay sensitivity, the true terminal half-life is likely to be substantially longer, in common with other bisphosphonates. Early plasma levels fall quickly reaching 10 % of peak values within 3 and 8 hours after intravenous or oral administration respectively.

Total clearance of ibandronic acid is low with average values in the range 84-160 ml/min. Renal clearance (about 60 ml/min in healthy postmenopausal females) accounts for 50-60 % of total clearance and is related to creatinine clearance. The difference between the apparent total and renal clearances is considered to reflect the uptake by bone.

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

Pharmacokinetics in special clinical situations

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

Race
There is no evidence for any clinically relevant inter-ethnic differences between Asians and Caucasians in ibandronic acid disposition. There are few data available on patients of African origin.

Patients with renal impairment
Renal clearance of ibandronic acid in patients with various degrees of renal impairment is linearly related to creatinine clearance.

No dose adjustment is necessary for patients with mild or moderate renal impairment (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 (see section 4.2)
There are no pharmacokinetic data for ibandronic acid in patients who have hepatic impairment. The liver has no significant role in the clearance of ibandronic acid which is not metabolised but is cleared by renal excretion and by uptake into bone. Therefore dose adjustment is not necessary in patients with hepatic impairment.

Elderly population (see section 4.2)
In a multivariate analysis, age was not found to be an independent factor of any of the pharmacokinetic parameters studied. As renal function decreases with age this is the only factor to take into consideration (see renal impairment section).

Paediatric population (see section 4.2 and section 5.1)
There are no data on the use of ibandronic acid in these age groups.

5.3 Preclinical safety data

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. In reproductive studies in rats by the oral route effects on fertility consisted of increased preimplantation losses at dose levels of 1 mg/kg/day and higher. In reproductive studies in rats by the intravenous route, ibandronic acid decreased sperm counts at doses of 0.3 and 1 mg/kg/day and decreased fertility in males at 1 mg/kg/day and in females at 1.2 mg/kg/day. 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
Crospovidone (type A)
Silica colloidal anhydrous
Stearic acid

Tablet coating:
Opadry white YS-1-7003:
Titanium dioxide (E 171)
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

Any unused medicinal product or waste material should be disposed of in accordance with local requirements. The release of pharmaceuticals in the environment should be minimized.

7. MARKETING AUTHORISATION HOLDER

Teva B.V.

Swensweg 5
2031 GA Haarlem
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/642/003	1 film-coated tablet in PVC/Aclar/PVC – Aluminium blister in cardboard boxes
EU/1/10/642/004	3 film-coated tablets in PVC/Aclar/PVC – Aluminium blisters in cardboard boxes

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17 September 2010
Date of latest renewal: 25 June 2015

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu/

ANNEX II

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

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

A. MANUFACTURERS 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

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 Operations Poland Sp.z.o.o
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 OR RESTRICTIONS REGARDING SUPPLY AND USE

Ibandronic Acid Teva 50 mg: Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

Ibandronic Acid Teva 150 mg: Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

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

- **Risk management plan (RMP)**

  Not applicable.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Ibandronic Acid Teva 50 mg film-coated tablets
ibandronic acid

2. STATEMENT OF ACTIVE SUBSTANCE

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

28 film-coated tablets
84 film-coated tablets

5. METHOD AND ROUTE OF ADMINISTRATION

Do not suck, chew or crush the tablets.

Read the package leaflet before use.

Oral use

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

Keep out of the sight and reach 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 B.V.
Swensweg 5
2031 GA Haarlem
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/642/001 28 film-coated tablets
EU/1/10/642/002 84 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Ibandronic Acid Teva 50 mg film-coated tablets

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Ibandronic Acid Teva 50 mg film-coated tablets
ibandronic acid

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Teva 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 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

Do not suck, chew or crush the tablet.
Once monthly tablet.
Note down the date you take your tablet.
Month 1 __/__/__
Month 2 __/__/__
Month 3 __/__/__

Read the package leaflet before use.

Oral use

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

Keep out of the sight and reach 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 B.V.
Swensweg 5
2031 GA Haarlem
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/642/003 1 film-coated tablet
EU/1/10/642/004 3 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Ibandronic Acid Teva 150 mg film-coated tablets

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Ibandronic Acid Teva 150 mg film-coated tablets
ibandronic acid

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Teva B.V.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

3 film-coated tablets pack
Month 1
Month 2
Month 3

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Ibandronic Acid Teva 50 mg film-coated tablets
ibandronic acid

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- 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 only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Ibandronic Acid Teva is and what it is used for

Ibandronic Acid Teva contains the active substance ibandronic acid. This belongs to a group of medicines called bisphosphonates.

Ibandronic Acid Teva is used in adults and prescribed to you if you have breast cancer that has spread to your bones (called bone "metastases").

- It helps to prevent your bones from breaking (fractures).
- It also helps to prevent other bone problems that may need surgery or radiotherapy.

Ibandronic Acid Teva works by reducing the amount of calcium that is lost from your bones. This helps to stop your bones from getting weaker.

2. What you need to know before you take Ibandronic Acid Teva

Do not take Ibandronic Acid Teva
- if you are allergic to ibandronic acid or any of the other ingredients of this medicine (listed in section 6)
- if you have problems with your food pipe/gullet (oesophagus) such as narrowing or difficulty swallowing
- if you cannot stand or sit upright for at least one hour (60 minutes) at a time
- if you have or ever had low calcium in your blood.

Do not take this medicine if any of the above apply to you. If you are not sure, talk to your doctor or pharmacist before taking Ibandronic Acid Teva.

Warnings and precautions
A side effect called osteonecrosis of the jaw (ONJ) (bone damage in the jaw) has been reported very rarely in the post-marketing setting in patients receiving Ibandronic Acid Teva for cancer-related conditions. ONJ can also occur after stopping treatment.

It is important to try and prevent ONJ developing as it is a painful condition that can be difficult to treat. In order to reduce the risk of developing osteonecrosis of the jaw, there are some precautions you should take.

Before receiving treatment, tell your doctor/nurse (health care professional) if:
- you have any problems with your mouth or teeth such as poor dental health, gum disease or a planned tooth extraction.
- you do not receive routine dental care or have not had a dental check up for a long time.
- you are a smoker (as this may increase the risk of dental problems).
- you have previously been treated with a bisphosphonate (used to treat or prevent bone disorders).
- you are taking medicines called corticosteroids (such as prednisolone or dexamethasone).
- you have cancer.

Your doctor may ask you to undergo a dental examination before starting treatment with Ibandronic Acid Teva.

While being treated, you should maintain good oral hygiene (including regular teeth brushing) and receive routine dental check-ups. If you wear dentures you should make sure these fit properly. If you are under dental treatment or will undergo dental surgery (e.g. tooth extractions), inform your doctor about your dental treatment and tell your dentist that you are being treated with Ibandronic Acid Teva.

Contact your doctor and dentist immediately if you experience any problems with your mouth or teeth such as loose teeth, pain or swelling, non-healing of sores or discharge, as these could be signs of osteonecrosis of the jaw.

Atypical fractures of the long bones, such as in the forearm bone (ulna) and the shinbone (tibia), have also been reported in patients receiving long-term treatment with Ibandronate. These fractures occur after minimal, or no trauma and some patients experience pain in the area of the fracture prior to presenting with a completed fracture.

Talk to your doctor or pharmacist before taking Ibandronic Acid Teva:
- if you are allergic to any other bisphosphonates
- if you have any swallowing or digestion problems
- if you have high or low blood levels of vitamin D or any other minerals
- if you have kidney problems.

Irritation, inflammation or ulceration of the gullet/food pipe (oesophagus) 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 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 (see sections 3 and 4).

Children and adolescents
Ibandronic Acid Teva should not be used in children and adolescents below the age of 18 years.

Other medicines and Ibandronic Acid Teva
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This is because Ibandronic Acid Teva can affect the way some other medicines work. Also some other medicines can affect the way Ibandronic Acid Teva works.

In particular, tell your doctor or pharmacist if you are taking any of the following medicines:
- supplements containing calcium, magnesium, iron or aluminium
- acetylsalicylic acid and non-steroidal anti-inflammatory medicines called “NSAIDs”, such as ibuprofen or naproxen. This is because NSAIDs and Ibandronic Acid Teva can both irritate your stomach and gut

- a type of antibiotic injection called “aminoglycoside” such as gentamicin. This is because aminoglycosides and Ibandronic Acid Teva can both lower the amount of calcium in your blood.

Taking medicines that reduce stomach acid such as cimetidine and ranitidine, may slightly increase the effects of Ibandronic Acid Teva.

Ibandronic Acid Teva with food and drink
Do not take Ibandronic Acid Teva with food or any other drinks except water as Ibandronic Acid Teva is less effective if it is taken with food or drink (see section 3).

Take Ibandronic Acid Teva with at least 6 hours after you had last had anything to eat, drink or any other medicines or supplements (e.g. products containing calcium (milk), aluminium, magnesium and iron) except water. After taking your tablet, wait at least 30 minutes. Then you can have your first food and drink, and take any medicines or supplements (see section 3).

Pregnancy and breast-feeding
Do not take Ibandronic Acid Teva if you are pregnant, planning to get pregnant or if you are breast-feeding. Ask your doctor or pharmacist for advice before taking this medicine.

Driving and using machines
You can drive and use machines as it’s expected that Ibandronic Acid Teva has no or negligible effect on your ability to drive and use machines. Talk to your doctor first if you want to drive, use machine or tools.

Ibandronic Acid Teva contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per film-coated tablet, that is to say essentially ‘sodium-free’.

3. How to take Ibandronic Acid Teva

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Take your tablet at least 6 hours after you had last had anything to eat, drink or any other medicines or supplements except water. Water with a high concentration of calcium should not be used. If there is concern regarding potentially high levels of calcium in the tap water (hard water), it is advised to use bottled water with a low mineral content.

Your doctor may do regular blood tests while you are taking Ibandronic Acid Teva. This is to check that you are being given the right amount of medicine.

Taking this medicine
It is important that you take Ibandronic Acid Teva at the right time and in the right way. This is because it can cause irritation, inflammation or ulcers in your food pipe/gullet (oesophagus).

You can help stop this happening by doing the following:

- Take your tablet as soon as you get up for the day before having your first food, drink, any medicine or supplements.

- Take your tablet with a full glass of water only (about 200 mL). Do not take your tablet with any drink other than water.

- Swallow the tablet whole. Do not chew, suck or crush the tablet. Do not let the tablet dissolve in your mouth.

- After taking your tablet, wait at least 30 minutes. Then you can have your first food and drink, and take any medicines or supplements.

- Stay upright (sitting or standing) while taking your tablet and for the next hour (60 minutes). Otherwise, some of the medicine could leak back into your food pipe/gullet (oesophagus).

How much to take
The usual dose of Ibandronic Acid Teva is one tablet each day. If you have moderate kidney problems, your doctor may reduce your dose to one tablet every other day. If you have severe kidney problems, your doctor may reduce your dose to one tablet each week.

If you take more Ibandronic Acid Teva than you should
If you take too many tablets talk to a doctor or go to hospital straight away. Drink a full glass of milk before you go. Do not make yourself sick. Do not lie down.

If you forget to take Ibandronic Acid Teva
Do not take a double dose to make up for a forgotten dose. If you are taking a tablet each day, skip the missed dose completely. Then carry on as usual the next day. If you are taking a tablet every other day or once a week, ask your doctor or pharmacist for advice.

If you stop taking Ibandronic Acid Teva
Keep taking Ibandronic Acid Teva for as long as your doctor tells you. This is because the medicine will only work if it is taken all the time.

Continuing to receive Ibandronic Acid Teva

It's important to keep receiving Ibandronic Acid Teva every month, as long as your doctor prescribes it for you. After 3-5 years of receiving Ibandronic Acid Teva, please consult with your doctor whether you should continue to receive Ibandronic Acid Teva.

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

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Talk to a nurse or a doctor straight away if you notice any of the following serious side effects, you may need urgent medical treatment:

Common (may affect up to 1 in 10 people):
- feeling sick, heartburn and discomfort in swallowing (inflammation of your gullet/food pipe)

Uncommon (may affect less than 1 in 100 people):
- severe stomach pain. This could be a sign of an ulcer of the first section of the bowel (duodenum) that is bleeding, or that your stomach is inflamed (gastritis)

Rare (may affect up to 1 in 1,000 people):
- persistent eye pain and inflammation
- new pain, weakness or discomfort in your thigh, hip or groin. You may have early signs of a possible unusual fracture of the thigh bone.

Very rare (may affect up to 1 in 10,000 people):
- pain or sore in your mouth or jaw. You may have early signs of severe jaw problems (necrosis [dead bone tissue] in the jaw bone).

- Talk to your doctor if you have ear pain, discharge from the ear, and/or an ear infection. These could be signs of bone damage in the ear.
- itching, swelling of your face, lips, tongue and throat, with difficulty breathing. You may be having a serious, potentially life threatening allergic reaction.
- severe adverse skin reactions.

Not known (frequency cannot be estimated from the available data):
- asthma attack

Other possible side effects

Common (may affect up to 1 in 10 people):
- tummy pain, indigestion
- low calcium levels in your blood
- weakness.

Uncommon (may affect less than 1 in 100 people):
- chest pain
- itching or tingling skin (paraesthesia)
- flu-like symptoms, feeling generally unwell or in pain
- dry mouth, strange taste in your mouth or difficulty swallowing
- anaemia(bloodlessness)
- high levels of urea or high levels of parathyroid hormone in your blood.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Ibandronic Acid Teva

Keep this medicine out of the sight and reach of children.

Do not use this medicine 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.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Ibandronic Acid Teva contains
- The active substance is ibandronic acid. Each film-coated tablet contains 50 mg ibandronic acid (as 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 (E 171), 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 B.V.
Swensweg 5
2031 GA Haarlem
The Netherlands

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

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 Operations Poland Sp.z.o.o
ul. Mogilska 80
31-546 Krakow
Poland

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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

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

Package leaflet: Information for the patient

Ibandronic Acid Teva 150 mg film-coated tablets
ibandronic acid

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- 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 only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

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 the active substance ibandronic acid. 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 postmenopausal 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.

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. What you need to know before you take Ibandronic Acid Teva

Do not take Ibandronic Acid Teva
- If you are allergic to ibandronic acid or any of the other ingredients of this medicine (listed in section 6).

- If you have certain problems with your gullet/food pipe (oesophagus) 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.

Warnings and precautions
A side effect called osteonecrosis of the jaw (ONJ) (bone damage in the jaw) has been reported very rarely in the post-marketing setting in patients receiving Ibandronic Acid Teva for osteoporosis. ONJ can also occur after stopping treatment.

It is important to try and prevent ONJ developing as it is a painful condition that can be difficult to treat. In order to reduce the risk of developing osteonecrosis of the jaw, there are some precautions you should take.

Atypical fractures of the long bones, such as in the forearm bone (ulna) and the shinbone (tibia), have also been reported in patients receiving long-term treatment with Ibandronate. These fractures occur after minimal, or no trauma and some patients experience pain in the area of the fracture prior to presenting with a completed fracture.

Before receiving treatment, tell your doctor/nurse (health care professional) if:
- you have any problems with your mouth or teeth such as poor dental health, gum disease or a planned tooth extraction.
- you do not receive routine dental care or have not had a dental check up for a long time.
- you are a smoker (as this may increase the risk of dental problems).
- you have previously been treated with a bisphosphonate (used to treat or prevent bone disorders).
- you are taking medicines called corticosteroids (such as prednisolone or dexamethasone).
- you have cancer.

Your doctor may ask you to undergo a dental examination before starting treatment with Ibandronic Acid Teva.

While being treated, you should maintain good oral hygiene (including regular teeth brushing) and receive routine dental check-ups. If you wear dentures you should make sure these fit properly. If you are under dental treatment or will undergo dental surgery (e.g. tooth extractions), inform your doctor about your dental treatment and tell your dentist that you are being treated with Ibandronic Acid Teva.

Contact your doctor and dentist immediately if you experience any problems with your mouth or teeth such as loose teeth, pain or swelling, non-healing of sores or discharge, as these could be signs of osteonecrosis of the jaw.

Some people need to be especially careful while they're taking Ibandronic Acid Teva. Talk to your doctor before taking Ibandronic Acid Teva:
- 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.

Irritation, inflammation or ulceration of the gullet/food pipe (oesophagus) 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 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 (see section 3).

Children and adolescents
Do not give Ibandronic Acid Teva to children or adolescents below 18 years.

Other medicines and Ibandronic Acid Teva

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Especially:

- **Supplements containing calcium, magnesium, iron or aluminium**, as they could possibly influence the effects of Ibandronic Acid Teva.
- Acetylsalicylic acid and other non-steroidal anti-inflammatory medicines (NSAIDs) (including ibuprofen, diclofenac sodium and naproxen) may irritate the stomach and intestine. 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.

Ibandronic Acid Teva with food and drink
Do not take Ibandronic Acid Teva with food. Ibandronic Acid Teva is less effective if it's taken with food.

You can drink water but no other drinks.

After you have taken Ibandronic Acid Teva, please wait for 1 hour before you can have your first food and further drinks. (see 3. How to take Ibandronic Acid Teva).

Pregnancy and breast-feeding
Ibandronic Acid Teva is for use only by postmenopausal women and must not be taken by women who could still have a baby.

Do not take Ibandronic Acid Teva if you are pregnant or breast feeding. Ask your doctor or pharmacist for advice before taking this medicine.

Driving and using machines
You can drive and use machines as it's expected that Ibandronic Acid Teva has no or negligible effect on your ability to drive and use machines.

Ibandronic Acid Teva contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per film-coated tablet, that is to say essentially 'sodium-free'.

3. How to take Ibandronic Acid Teva

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

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 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 water** (at least 180 ml).

Do not take your tablet with water with a high concentration of calcium, fruit juice or any other drinks. If there is a concern regarding potentially high levels of calcium in the tap water (hard water), it is advised to use bottled water with a low mineral content.

- **Swallow your tablet whole,** — do not chew it, crush 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 water if you need it)
  - **do not take any other medicines**

- After you've waited for an hour, you can have your first food and drink of the day. Once you've eaten, it's OK to lie down if you wish, and to take any other medication you need.

Continuing to take Ibandronic Acid Teva
It's important to keep taking Ibandronic Acid Teva every month, as long as your doctor prescribes it for you. After 3-5 years of using Ibandronic Acid Teva, please consult with your doctor whether you should continue to take Ibandronic Acid Teva.

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 you forgot to take your tablet on your chosen day and your next scheduled dose is only 1 to 7 days away…**

  Never take two Ibandronic Acid Teva tablets within the same week. 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 you forgot to take your tablet on your chosen day and 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.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Talk to a nurse or a doctor straight away if you notice any of the following serious side effects - you may need urgent medical treatment:

Uncommon (may affect up to 1 in 100 people):
- severe pain in the chest, severe pain after swallowing food or drink, severe nausea, or vomiting, difficulty in swallowing. You may have a severe inflammation of your gullet/food pipe, possibly with sores or constriction of the gullet/food pipe

Rare (may affect up to 1 in 1000 people):
- itching, swelling of your face, lips, tongue and throat, with difficulty breathing.
- persistent eye pain and inflammation
- new pain, weakness or discomfort in your thigh, hip or groin. You may have early signs of a possible unusual fracture of the thigh bone

Very rare (may affect up to 1 in 10,000 people):
- pain or sore in your mouth or jaw. You may have early signs of severe jaw problems (necrosis [dead bone tissue] in the jaw bone)
- Talk to your doctor if you have ear pain, discharge from the ear, and/or an ear infection. These could be signs of bone damage in the ear.
- serious, potentially life-threatening allergic reaction
- severe adverse skin reactions

Other possible side effects

Common (may affect up to 1 in 10 people):
- headache
- heartburn, discomfort in swallowing, stomach or tummy pain (may be due to an inflammation of the stomach), indigestion, nausea, having, diarrhoea (loose bowels)
  muscle cramps, stiffness of your joints and limbs
- flu-like symptoms, including fever, shaking and shivering, feeling of discomfort, bone pain and aching muscles and joints. Talk to a nurse or doctor if any effects become troublesome or last more than a couple of days
- rash

Uncommon (may affect up to 1 in 100 people):
- dizziness
- flatulence (farting, feeling bloated)
- back pain
- feeling tired and exhausted
- asthma attacks
- symptoms of low blood calcium levels (hypocalcaemia) including muscle cramps or spasms and/or tingling sensation in the fingers or around the mouth

Rare (may affect up to 1 in 1000 people):
- inflammation of the duodenum (first section of the bowel) causing stomach pain
- hives

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Ibandronic Acid Teva

Keep this medicine out of the sight and reach of children.

Do not use this medicine 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.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Ibandronic Acid Teva contains
- The active substance is ibandronic acid.
  Each film-coated tablet contains 150 mg ibandronic acid (as 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 (E 171), 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 “I150” 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

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

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