ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ibandronic acid Sandoz 50 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipient with known effect
Each film-coated tablet contains 0.86 mg lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.
White round biconvex tablets

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ibandronic acid Sandoz 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 Sandoz 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
No dose adjustment is necessary (see section 5.2).

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

Method of administration
For oral use.

Ibandronic acid Sandoz 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 Sandoz 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 Sandoz 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 Sandoz.
- 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 Sandoz.

4.3 Contraindications

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

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 Sandoz 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 Sandoz 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 Sandoz 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 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 Sandoz 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 Sandoz. While on treatment, invasive dental procedures should be performed only after careful consideration and be avoided in close proximity to Ibandronic acid Sandoz 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 Sandoz 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.

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.

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

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

This medicinal product contains less than 1mmol (23 mg) sodium 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 Sandoz 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 is administered with H_2-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 should not be used during pregnancy.

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

Fertility
There are no data on the effects of ibandronic acid 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 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 Sandoz 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			
Immune system disorders				Hypersensitivity†, bronchospasm†, angioedema†, Anaphylactic reaction/shock†**	Asthma exacerbation
Metabolism and nutrition disorders	Hypocalcaemia**				

System Organ Class	Common	Uncommon	Rare	Very rare	Not known
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) †	
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 post-marketing 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.

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. 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. 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, Bisphosphonates, 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 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.

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).

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 section 4.2 and section 5.1)
There are no data on the use of Ibandronic acid Sandoz 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

<u>*Tablet core:*</u>
Povidone
Cellulose, microcrystalline
Crospovidone

Maize starch pregelatinised
Glycerol dibehenate
Silica, anhydrous colloidal

Tablet coat:
Lactose monohydrate
Macrogol 4000
Hypromellose
Titanium dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Ibandronic acid Sandoz 50 mg film-coated tablets are supplied in Polyamide/Al/PVC - Aluminium foil blister with 3, 6, 9, 28 or 84 tablets, packaged in a cardboard box.
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

Sandoz GmbH
Biochemiestraße 10
A-6250 Kundl
Austria

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/685/001
EU/1/11/685/002
EU/1/11/685/003
EU/1/11/685/004
EU/1/11/685/005

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26 July 2011
Date of latest renewal: 13 April 2016

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

A. MANUFACTURER(S) 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. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Pharmathen S.A.
6, Dervenakion
EL-15351 Pallini Attiki
Greece

Pharmathen International S.A.
Industrial Park Sapes, Rodopi Prefecture, Block No 5, Rodopi 69300,
Greece

Lek S.A.
ul. Domaniewska 50 C
02-672 Warszawa
Poland

Lek Pharmaceuticals d.d.
Verovškova 57, 1526 Ljubljana
Slovenia

Salutas Pharma GmbH
Otto-von-Guericke-Allee 1, 39179 Barleben
Germany

Salutas Pharma GmbH
Dieselstrasse 5, 70839 Gerlingen
Germany

S.C. Sandoz, S.R.L.
Str. Livezeni nr. 7A, RO-540472 Targu-Mures
Romania

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

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

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)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

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 Sandoz 50 mg film-coated tablets
ibandronic acid

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Contains lactose. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

3 film-coated tablets
6 film-coated tablets
9 film-coated tablets
28 film-coated tablets
84 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Do not suck, chew or crush 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

Store in the original package in order to protect from moisture.

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

Sandoz GmbH
Biochemiestraße 10
A-6250 Kundl
Austria

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/685/001
EU/1/11/685/002
EU/1/11/685/003
EU/1/11/685/004
EU/1/11/685/005

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Ibandronic acid Sandoz 50 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC {number}
SN {number}
NN {number}

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Polyamide/Al/PVC - Aluminium foil blister

1. NAME OF THE MEDICINAL PRODUCT

Ibandronic acid Sandoz 50 mg film-coated tablets
ibandronic acid

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Sandoz GmbH

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Mon
Tue
Wed
Thu
Fri
Sat
Sun

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Ibandronic acid Sandoz 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 Sandoz is and what it is used for

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

Ibandronic acid Sandoz tablets 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 Sandoz 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 Sandoz

Do not take Ibandronic acid Sandoz
- if you are allergic to ibandronic acid or any of the other ingredients of this medicine that are 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 Sandoz.

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 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 don't 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 Sandoz.

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 Sandoz.

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.

Talk to your doctor or pharmacist before taking Ibandronic acid Sandoz
- 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 Sandoz. If you develop these symptoms, stop taking Ibandronic acid Sandoz and tell your doctor straight away (see sections 3 and 4).

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

Other medicines and Ibandronic acid Sandoz
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This is because Ibandronic acid Sandoz can affect the way some other medicines work. Also some other medicines can affect the way Ibandronic acid Sandoz 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 Sandoz can both irritate your stomach and gut
- a type of antibiotic injection called "aminoglycoside" such as gentamicin. This is because aminoglycosides and Ibandronic acid Sandoz 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 Sandoz.

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

Take Ibandronic acid Sandoz at least 6 hours after you 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 Sandoz 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 Sandoz 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 Sandoz contains lactose and sodium
This medicine contains lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

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

3. How to take Ibandronic acid Sandoz

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

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).
- 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
- 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.

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 Sandoz

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.

Store in the original package in order to protect from moisture.
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 Sandoz contains
- The active substance is ibandronic acid. Each film-coated tablet contains 50 mg of ibandronic acid (as ibandronate sodium monohydrate).

The other ingredients are:
- tablet core: povidone, microcrystalline cellulose, crospovidone, maize starch pregelatinised, glycerol dibehenate, colloidal anhydrous silica.
- tablet coat: titanium dioxide, lactose monohydrate, hypromellose, macrogol 4000

What Ibandronic acid Sandoz looks like and contents of the pack
The film-coated tablets are white, round biconvex tablets supplied in Polyamide/Al/PVC - Aluminum foil blister. They are available in packs of 3, 6, 9, 28 and 84 tablets.

Not all pack sizes may be marketed.

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