Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Osbonelle 50 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipients:
Each film-coated tablet contains 54 mg lactose monohydrate.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.
White to off-white, oblong, biconvex film-coated tablets, 9 mm in length and debossed with “I9BE” on one side and on the other side with “50”.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

4.2 Posology and method of administration

Ibandronic acid therapy should only be initiated by physicians experienced in the treatment of cancer.

For oral use.

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

Ibandronic acid 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 tablets. Fasting should be continued for at least 30 minutes after taking the tablet. Plain water may be taken at any time during the course of ibandronic acid treatment.

- The tablets should be swallowed whole with a full glass of plain water (180 to 240 ml) while the patient is standing or sitting in an upright position.

- Patients should not lie down for 60 minutes after taking ibandronic acid.

- Patients should not chew or suck the tablet because of a potential for oropharyngeal ulceration.

- Plain water is the only drink that should be taken with ibandronic acid. Please note that some mineral waters may have a higher concentration of calcium and therefore should not be used.

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

Patients with renal impairment
No dosage adjustment is necessary for patients with mild renal impairment (CLcr ≥50 and<80 mL/min).

For patients with moderate renal impairment (CLcr ≥30 and <50 mL/min) a dosage adjustment to one 50 mg film-coated tablet every second day is recommended (see section 5.2).
For patients with severe renal impairment (CLcr <30 mL/min) the recommended dose is one 50 mg film-coated tablet once weekly. See dosing instructions, above.

Elderly
No dose adjustment is necessary.

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

4.3 Contraindications

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

Ibandronic acid should not be used in children.

4.4 Special warnings and precautions for use

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

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

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 Osbonelle 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 signs or symptoms signaling a possible oesophageal reaction and patients should be instructed to discontinue ibandronic acid and seek medical attention if they develop dysphagia, odynophagia, retrosternal pain, or new or worsening heartburn.

While no increased risk was observed in controlled clinical trials there have been post-marketing reports of gastric and duodenal ulcers with oral bisphosphonate use, some severe and with complications.

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

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.

Ibandronic acid tablets contain lactose and should not be administered to patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption.

Osteonecrosis of the jaw, generally associated with tooth extraction and/or local infection (including osteomyelitis) has been reported in patients with cancer receiving treatment regimens including primarily intravenously administered bisphosphonates. Many of these patients were also receiving chemotherapy and corticosteroids. Osteonecrosis of the jaw has also been reported in patients with osteoporosis receiving oral bisphosphonates.

A dental examination with appropriate preventive dentistry should be considered prior to treatment with bisphosphonates in patients with concomitant risk factors (e.g. cancer, chemotherapy, radiotherapy, corticosteroids, poor oral hygiene).

While on treatment, these patients should avoid invasive dental procedures if possible. For patients who develop osteonecrosis of the jaw while on bisphosphonate therapy, dental surgery may exacerbate the condition. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of osteonecrosis of the jaw. Clinical judgement of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

Drug-Food Interactions
Products containing calcium and other multivalent cations (such as aluminium, magnesium, iron), including milk and food, are likely to interfere with absorption of ibandronic acid 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).

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

Other interaction studies in postmenopausal women have demonstrated the absence of any interaction potential with tamoxifen or hormone replacement therapy (oestrogen).

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

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

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

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

4.6 Fertility, pregnancy and lactation

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

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

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

The safety profile of ibandronic acid is derived from controlled clinical trials in the approved indication and after the oral administration of ibandronic acid at the recommended dose.

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

Adverse reactions are ranked under heading of frequency, the most frequent first, using the following convention: very common (≥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).

Table 1 lists common adverse reactions from the pooled phase III trials. Adverse reactions that are equally frequent in both active and placebo or more frequent in placebo-treated patients are excluded.

Table 1: Adverse Reactions Reported Commonly and Greater than Placebo

Adverse reaction	**Placebo p. o. daily (n=277 patients) No. (%)**	**Ibandronic acid 50 mg p.o. daily (n=286 patients) No. (%)**
Metabolism and Nutrition Disorders		
Hypocalcaemia	14 (5.1)	27 (9.4)
Gastrointestinal Disorders		
Dyspepsia	13 (4.7)	20 (7.0)
Nausea	4 (1.4)	10 (3.5)
Abdominal Pain	2 (0.7)	6 (2.1)
Oesophagitis	2 (0.7)	6 (2.1)
General Disorders		
Asthenia	2 (0.7)	4 (1.4)

Adverse drug reactions occurring at a frequency <1%:

The following list provides information on adverse drug reactions reported in study MF 4414 and MF 4434 occurring more frequently with ibandronic acid 50 mg than with placebo:

Uncommon:

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

Osteonecrosis of the jaw has been reported in patients treated by bisphosphonates. The majority of the reports refer to cancer patients, but such cases have also been reported in patients treated for osteoporosis. Osteonecrosis of the jaw is generally associated with tooth extraction and / or local infection (including osteomyelitis). Diagnosis of cancer, chemotherapy, radiotherapy, corticosteroids and poor oral hygiene are also deemed as risk factors (see section 4.4).

4.9 Overdose

No case of overdose has been reported.

No specific information is available on the treatment of overdosage with ibandronic acid. However, oral overdosage may result in upper gastrointestinal events, such as upset stomach, heartburn, oesophagitis, gastritis or ulcer. Milk or antacids should be given to bind ibandronic acid. Owing to the risk of oesophageal irritation, vomiting should not be induced and the patient should remain fully upright.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmaco-therapeutic group: Bisphosphonates, ATC Code: M05B A06

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

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

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

Bone resorption due to malignant disease is characterized by excessive bone resorption that is not balanced with appropriate bone formation. Ibandronic acid selectively inhibits osteoclast activity, reducing bone resorption and thereby reducing skeletal complications of the malignant disease.

Clinical studies in patients with breast cancer and bone metastases have shown that there is a dose dependent inhibitory effect on bone osteolysis, expressed by markers of bone resorption, and a dose dependent effect on skeletal events.

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

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

The analysis of the SMPR was time-adjusted and considered that one or more events occurring in a single 12 week period could be potentially related. Multiple events were therefore, counted only once in any given 12 week period for the purposes of the analysis. Pooled data from these studies demonstrated a significant advantage for ibandronic acid 50 mg p.o. over placebo in the reduction in SREs measured by the SMPR (p=0.041). There was also a 38% reduction in the risk of developing an SRE for ibandronic acid treated patients when compared with placebo (relative risk 0.62, p=0.003). Efficacy results are summarised in Table 2.

Table 2 Efficacy Results (Breast Cancer Patients with Metastatic Bone Disease)

	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 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

5.2 Pharmacokinetic properties

Absorption
The absorption of ibandronic acid in the upper gastrointestinal tract is rapid after oral administration.
Maximum observed plasma concentrations were reached within 0.5 to 2 hours (median 1 hour) in the fasted state and absolute bioavailability was about 0.6%. The extent of absorption is impaired when taken together with food or beverages (other than plain water). Bioavailability is reduced by about 90% when ibandronic acid is administered with a standard breakfast in comparison with bioavailability seen in fasted subjects. When taken 30 minutes before a meal, the reduction in bioavailability is approximately 30%. There is no meaningful reduction in bioavailability provided ibandronic acid is taken 60 minutes before a meal.

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

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

Metabolism
There is no evidence that ibandronic acid is metabolized in animals or humans.

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

The range of observed apparent half-lives is broad and dependent on dose and assay sensitivity, but the apparent terminal half-life is generally in the range of 10-60 hours. However, early plasma levels fall quickly, reaching 10% of peak values within 3 and 8 hours after intravenous or oral administration respectively.

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

Pharmacokinetics in Special Populations

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

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

Patients with renal impairment
Renal clearance of ibandronic acid in patients with various degrees of renal impairment is linearly related to creatinine clearance (CLcr). No dosage adjustment is necessary for patients with mild or moderate renal impairment (CLcr >30 ml/min). Subjects with severe renal impairment (CLcr ≤ 30 ml/min) receiving oral administration of 10 mg ibandronic acid daily for 21 days, had 2-3 fold higher plasma concentrations than subjects with normal renal function. Total clearance of ibandronic acid was reduced to 44 ml/min in the subjects with severe renal impairment. After intravenous administration of 0.5 mg, total, renal, and non-renal clearances decreased by 67%, 77% and 50%, respectively, in subjects with severe renal impairment. However, there was no reduction in tolerability associated with the increase in exposure. Reduction of the oral dose to one 50 mg tablet once weekly is recommended in patients with severe renal impairment (CLcr <30 ml/min) (see Section 4.2).

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

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

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

5.3 Preclinical safety data

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

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

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Lactose Monohydrate
Crospovidone (E1202)
Cellulose, microcrystalline (E460)
Sylica, Colloidal Anhydrous (E551)
Sodium Stearyl Fumarate

Tablet coating
Poly (Vinyl Alcohol)
Macrogols/PEG 3350
Talc (E553b)
Titanium dioxide (E171)

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

OPA/Al/PVC:Al blisters in carton boxes containing
1, 3, 7, 10, 14, 20, 21, 28, 30, 42, 50, 56, 60, 84, 90, 100, 126, 168 and 210 tablets

PVC/PVDC:Al blisters in carton boxes containing
1, 3, 7, 10, 14, 20, 21, 28, 30, 42, 50, 56, 60, 84, 90, 100, 126, 168 and 210 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Actavis Group PTC ehf
Reykjavikurvegi 76-78
220 Hafnarfjordur
Iceland

8 MARKETING AUTHORISATION NUMBER

PA 1380/117/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21st January 2011

10 DATE OF REVISION OF THE TEXT

June 2011