Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ibandronic acid Vaia 50 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 50 mg of ibandronic acid (as ibandronate sodium monohydrate).
Excipients: Contains 56 mg lactose monohydrate.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.
Ibandronic acid Vaia tablets are white, oblong, biconvex, film-coated tablets, with dimensions of approximately 11.5 x 5.6mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Ibandronic acid Vaia 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 Vaia 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.

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

Patients with 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 dose 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.

Paediatric population
The safety and efficacy of ibandronic acid in children and adolescents below age 18 years have not been established. No data are available.

Method of administration
For oral use.

Ibandronic acid Vaia 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 Vaia 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 Vaia 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 Vaia.

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

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

4.3 Contraindications

- Hypersensitivity to ibandronic acid or to any of the excipients
- 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 Vaia 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 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 Vaia 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 Vaia.

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

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

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

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.

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.

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

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

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 dose 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 substances 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 antineoplastics, diuretics, antibiotics and analgesics without clinically apparent interactions occurring.

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. Ibandronic acid Vaia 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 Vaia should not be used during lactation.

Fertility
There are currently no human data available on fertility. Animal studies revealed some effects (please refer to section 5.3).

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 for the oral administration of ibandronic acid at the recommended dose, and from postmarketing experience.

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, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000); very rare (< 1/10,000).

Table 1 lists adverse drug reactions.

Table 1: Adverse Drug Reactions Reported for Oral Administration of ibandronic acid

System Organ Class	Very common	Common	Uncommon	Rare	Very rare
Blood and lymphatic system disorders			Anaemia		
Metabolism and nutrition disorders		Hypocalcaemia			
Nervous system disorders			Paraesthesia, dysgeusia (taste perversion)		
Eye disorders				Ocular inflammation†**	
Gastrointestinal disorders		Oesophagitis, abdominal pain, dyspepsia, nausea	Haemorrage, duodenal ulcer, gastritis, dysphagia, abdominal pain, dry mouth		
Skin and subcutaneous tissue disorders			Pruritus		
Musculoskeletal and connective tissue disorders				Atypical subtrochanteric and diaphyseal femoral fractures (bisphosphonate class adverse reaction) †	Osteonecrosis of jaw†**
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.

Osteonecrosis of jaw
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).

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.

4.9 Overdose

No specific information is available on the treatment of overdose with ibandronic acid. However, oral overdose 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: Drugs 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 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 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
The safety and efficacy of Ibandronic acid in children and adolescents below age 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 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.

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.

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 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) or severe renal impairment (CLcr <30 mL/min) an adjustment in the dose is recommended (see Section 4.2).

Patients with hepatic impairment
There are no pharmacokinetic data for ibandronic acid in patients who have hepatic impairment. The liver has no significant role in the clearance of ibandronic acid since it is not metabolized but is cleared by renal excretion and by uptake into bone.

Therefore dose 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).

Paediatric population
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 reactions of ibandronic acid in reproductive toxicity studies in the rat were those expected for this class of drugs (bisphosphonates). They include a decreased number of implantation sites, interference with natural delivery (dystocia), an increase in visceral variations (renal pelvis ureter syndrome) and teeth abnormalities in F1 offspring in rats.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Microcrystalline cellulose
Lactose monohydrate
Silicified cellulose, microcrystalline
Crospovidone type A
Copovidone K- value 28
Sodium stearyl fumarate

Tablet coat:
Opadry white 02H28525 consisting of:
Hypromellose 2910/5 cP (E464)
Titanium dioxide (E171)
Propylene glycol
Talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

30 months.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Ibandronic acid Vaia 50 mg film coated tablets are supplied in blisters (OPA/Aluminium/PVC/Aluminium blisters) which are presented as packs containing 28 or 84 tablets.

Pack sizes:

28, 84 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused 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

Vaia S.A.
1, 28 Octovriou str.
Ag. Varvara
12351 Athens
Greece

8 MARKETING AUTHORISATION NUMBER

PA1668/1/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23rd September 2011

10 DATE OF REVISION OF THE TEXT