Safeguarding public health

MHRA

Public Assessment Report

Decentralised Procedure

GEROUSIA 150MG FILM-COATED TABLETS
MIRDEZEL 150MG FILM-COATED TABLETS
ZIVETENO 150MG FILM-COATED TABLETS
QUODIXOR 150MG FILM-COATED TABLETS
BAXOGAR 150MG FILM-COATED TABLETS
(Ibandronic acid)

Procedure No: UK/H/2163, 3375-3378/001/DC

UK Licence No: PL 17277/0074, 0149-50 & 0152-3.

PHARMATHEN SA

LAY SUMMARY

On 14 July 2010, Austria, Belgium, Bulgaria, Czech Republic, Germany, Denmark, Estonia, Spain, Finland, France, Hungary, Ireland, Iceland, Italy, Lithuania, Luxembourg, Latvia, the Netherlands, Norway, Portugal, Romania, Sweden, Slovenia, Slovakia and the UK agreed to grant Marketing Authorisations to Pharmathen SA for the medicinal products Gerousia/Mirdezel/Ziveteno/Quodixor/Baxogar 150mg film-coated tablets (PL 17277/0074, 0149-50, 0152-3; UK/H/2163, 3375-8/001/DC). These licences were granted via the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS). For full details of the list of countries (Concerned Member States) involved for each procedure number please refer to page 4 of this report.

Gerousia/Mirdezel/Zivento/Quodixor/Baxogar 150mg film-coated tablets are prescription-only medicines (POM) used in the treatment of osteoporosis. They contain the active ingredient ibandronic acid.

Ibandronic acid belongs to a group of medicines called bisphosphonates, which may reverse bone loss by stopping more loss of bone and increasing bone mass in most women who take it, even though they won't be able to see or feel a difference. It may help lower the chances of breaking bones (fractures). This reduction in fractures was shown for the spine, but not for the hip.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Gerousia/Mirdezel/Baxogar/Zivento/Quodixor 150mg film-coated tablets outweigh the risks. After a subsequent national phase, Marketing Authorisations were granted in the UK on 17 September 2010 for Gerousia/Mirdezel/Ziveteno/Baxogar 150mg film-coated tablets and 28 September 2010 for Quodixor 150mg film-coated tablets.

TABLE OF CONTENTS

Module 1

Product Name	Gerousia 150mg film-coated tablets Mirdezel 150mg film-coated tablets Ziveteno 150mg film-coated tablets Quodixor 150mg film-coated tablets Baxogar 150mg film-coated tablets
Type of Application	Generic, Article 10.1
Active Substances	Ibandronic acid
Form	Film-coated tablet
Strength	150mg
MA Holder	Pharmathen SA, 6 Dervenakion Street, Pallini, Athens, GR-15351, Greece
Reference Member State (RMS)	UK
Concerned Member States (CMS)	UK/H/2163/001/DC: Austria, Czech Republic, Germany, Spain, France, Hungary, Italy, Portugal and Slovakia UK/H/3375/001/DC: Belgium, Czech Republic, Germany, Spain, France, Italy, Netherlands, Portugal, Romania, and Slovakia UK/H/3376/001/DC: Belgium, Cyprus, Estonia, Iceland, Italy, Lithuania, Luxembourg, Latvia, Netherlands and Slovakia UK/H/3377/001/DC: Austria, Belgium, Bulgaria, Czech Republic, Germany, Denmark, Spain, France, Hungary, Ireland, Italy, Luxembourg, Netherlands, Norway, Poland, Portugal, Romania, Sweden, Slovenia and Slovakia. UK/H/3378/001/DC: Austria, Belgium, Bulgaria, Czech Republic, Germany, Denmark, Estonia, Spain, Finland France, Hungary, Italy, Lithuania, Luxembourg, Latvia, Netherlands, Portugal, Sweden and Slovakia.
Procedure Number	UK/H/2163, 3375-8/001/DC
Timetable	Day 210 – 14 July 2010

Module 2
Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Gerousia 150 mg film-coated tablets
Mirdezel 150 mg film-coated tablets
Ziveteno 150 mg film-coated tablets
Quodixor 150 mg film-coated tablets
Baxogar 150 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipients:
Each film-coated tablet contains a small amount of lactose monohydrate in the film-coating of the tablet. For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.
White, round biconvex tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of osteoporosis in postmenopausal women at increased risk of fracture (see section 5.1).

A reduction in the risk of vertebral fractures has been demonstrated, efficacy on femoral neck fractures has not been established.

4.2 Posology and method of administration

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

Gerousia/Mirdezel/Ziveteno/Quodixor/Baxogar should be taken after an overnight fast (at least 6 hours) and 1 hour before the first food or drink (other than water) of the day (see section 4.5) or any other oral medicinal products or supplementation (including calcium).

In case a dose is missed, patients should be instructed to take one Gerousia/Mirdezel/Ziveteno/Quodixor/Baxogar 150 mg tablet the morning after the tablet is remembered, unless the time to the next scheduled dose is within 7 days. Patients should then return to taking their dose once a month on their originally scheduled date.
If the next scheduled dose is within 7 days, patients should wait until their next dose and then continue taking one tablet once a month as originally scheduled.
Patients should not take two tablets within the same week.

Patients should receive supplemental calcium and / or vitamin D if dietary intake is inadequate (see section 4.4 and section 4.5).

Special populations
Patients with renal impairment
No dosage adjustment is necessary for patients with mild or moderate renal impairment where creatinine clearance is equal or greater than 30 ml/min.
Ibandronic acid is not recommended for patients with a creatinine clearance below 30 ml/min due to limited clinical experience (see section 4.4 and section 5.2).

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

Elderly Population
No dosage adjustment is required (see section 5.2).

Paediatric Population
There is no relevant use of Gerousia/Mirdezel/Ziveteno/Quodixor/Baxogar in children, and Gerousia/Mirdezel/Ziveteno/Quodixor/Baxogar was not studied in paediatric population.

Method of Administration:
For oral use

- Tablets should be swallowed whole with a glass of plain water (180 to 240 ml) while the patient is sitting or standing in an upright position. Patients should not lie down for 1 hour after taking Gerousia/Mirdezel/Ziveteno/Quodixor/Baxogar

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- Plain water is the only drink that should be taken with Gerousia/Mirdezel/Ziveteno/Quodixor/Baxogar Please note that some mineral waters may have a higher concentration of calcium and therefore, should not be used.
- Patients should not chew or suck the tablet, because of a potential for oropharyngeal ulceration.

4.3 Contraindications

- Abnormalities of the oesophagus which delay oesophageal emptying such as stricture or achalasia.
- Inability to stand or sit upright for at least 60 minutes.
- Hypocalcaemia (see section 4.4).
- Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use

Gastrointestinal Disorders
Orally administered bisphosphonates may cause local irritation of the upper gastrointestinal mucosa. Because of these possible irritant effects and a potential for worsening of the underlying disease, caution should be used when Gerousia/Mirdezel/Ziveteno/Quodixor/Baxogar is given to patients with active upper gastrointestinal problems (e.g. known Barrett's oesophagus, dysphagia, other oesophageal diseases, gastritis, duodenitis or ulcers).

Adverse experiences such as oesophagitis, oesophageal ulcers and oesophageal erosions, in some cases severe and requiring hospitalisation, rarely with bleeding or followed by oesophageal stricture or perforation, have been reported in patients receiving treatment with oral biophosphonates. 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 biophosphonates after developing symptoms suggestive of oesophageal irritation. Patients should pay particular attention to and be able to comply with the dosing instructions (see section 4.2).

Physicians should be alert to any signs or symptoms signalling a possible oesophageal reaction and patients should be instructed to discontinue Gerousia/Mirdezel/Ziveteno/Quodixor/Baxogar 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 and bisphosphonates are both associated with gastrointestinal irritation, caution should be taken during concomitant administration.

Hypocalcaemia
Existing hypocalcaemia must be corrected before starting Gerousia/Mirdezel/Ziveteno/Quodixor/Baxogar therapy. Other disturbances of bone and mineral metabolism should also be effectively treated. Adequate intake of calcium and vitamin D is important in all patients.

Renal Impairment
Due to limited clinical experience, ibandronic acid is not recommended for patients with a creatinine clearance below 30 ml/min (see section 5.2).

Osteonecrosis of the Jaw

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

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

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

Galactose intolerance
Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Oral bioavailability of ibandronic acid is generally reduced in the presence of food. In particular, products containing calcium and other multivalent cations (such as aluminium, magnesium, iron), including milk, are likely to interfere with absorption of ibandronic acid, which is consistent with findings in animal studies. Therefore, patients should fast overnight (at least 6 hours) before taking ibandronic and continue fasting for 1 hour following intake of ibandronic acid (see section 4.2).

Calcium supplements, antacids and some oral medicinal products containing multivalent cations (such as aluminium, magnesium, iron) are likely to interfere with the absorption of ibandronic acid. Therefore, patients should not take other oral medicinal products for at least 6 hours before taking ibandronic acid and for 1 hour following intake of ibandronic acid.

Metabolic interactions are not considered likely, since ibandronic acid does not inhibit the major human hepatic P450 isoenzymes and has been shown not to induce the hepatic cytochrome P450 system in rats. Furthermore, plasma protein binding is approximately 85 % - 87 % (determined *in vitro* at therapeutic drug concentrations), and thus there is a low potential for drug-drug interaction due to displacement. Ibandronic acid is eliminated by renal excretion only and does not undergo any biotransformation. The secretory pathway appears not to include known acidic or basic transport systems involved in the excretion of other active substances.

In a two-year study in postmenopausal women with osteoporosis (BM 16549), the incidence of upper gastrointestinal events in patients concomitantly taking aspirin or NSAIDs was similar in patients taking ibandronic acid 2.5 mg daily or 150 mg once monthly after one and two years.

Of over 1500 patients enrolled in study BM 16549 comparing monthly with daily dosing regimens of ibandronic acid, 14 % and 18 % of patients used histamine (H2) blockers or proton pump inhibitors after one and two years, respectively. Among these patients, the incidence of upper gastrointestinal events in the patients treated with ibandronic acid 150 mg once monthly was similar to that in patients treated with ibandronic acid 2.5 mg daily.

In healthy male volunteers and postmenopausal women, intravenous administration of ranitidine caused an increase in ibandronic acid bioavailability of about 20 %, probably as a result of reduced gastric acidity. However, since this increase is within the normal variability of the bioavailability of ibandronic acid, no dosage adjustment is considered necessary when Gerousia/Mirdezel/Ziveteno/Quodixor/Baxogar is administered with H2-antagonists or other active substances which increase gastric pH.

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

No interaction was observed when co-administered with melphalan/prednisolone in patients with multiple myeloma.

4.6 Pregnancy and lactation

Pregnancy

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

Lactation

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

Gerousia/Mirdezel/Ziveteno/Quodixor/Baxogar should not be used during lactation.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The safety of ibandronic acid 2.5 mg daily was evaluated in 1251 patients treated in 4 placebo-controlled clinical studies; with the large majority of patients coming from the pivotal three-year treatment study (MF 4411). The overall safety profile of ibandronic acid 2.5 mg daily in all these studies was similar to that of placebo.

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

The most commonly reported adverse reaction was arthralgia.

Adverse reactions considered by investigators to be causally related to Gerousia/Mirdezel/Ziveteno/Quodixor/Baxogar are listed below by system Organ Class. Frequencies are defined as common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), and rare (≥ 1/10,000 to < 1/1,000). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1: Adverse reactions occurring in postmenopausal women receiving Gerousia/Mirdezel/Ziveteno/Quodixor/Baxogar 150mg once monthly or ibandronic acid 2.5mg daily in the phase III studies BM 16549 and MF 4411.

System Organ Class	Frequency	Adverse reactions
Immune system disorders	Rare	Hypersensitivity reaction
Nervous system disorders	Common	Headache
	Uncommon	Dizziness
Gastrointestinal disorders	Common	Oesophagitis,Gastritis,Gastro oesophageal reflux disease, Dyspepsia Diarrhoea, abdominal pain, nausea
	Uncommon	Oesophagitis including oesophageal ulcerations or strictures and dysphagia, vomiting, flatulence

System Organ Class	Frequency	Adverse reactions
	Rare	Duodenitis
Skin and subcutaneous tissues disorders	Common	Rash
	Rare	Angioedema, Face oedema, Urticaria
Musculoskeletal and connective tissue disorders	Common	Musculoskeletal pain, arthralgia, myalgia. Muscle cramp, Musculoskeletal stiffness
	Uncommon	Back pain
General disorders and administration site conditions	Common	Influenza-like illness*
	Uncommon	Fatigue

MedDRA version 7.1

* Transient, influenza-like symptoms have been reported with ibandronic acid 150 mg once monthly, typically in association with the first dose. Such symptoms were generally of short duration, mild or moderate in intensity, and resolved during continuing treatment without requiring remedial measures. Influenza-like illness includes events reported as acute phase reaction or symptoms including myalgia, arthralgia, fever, chills, fatigue, nausea, loss of appetite, or bone pain.

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

Laboratory test findings
In the pivotal three-year study with ibandronic acid 2.5 mg daily (MF 4411) there was no difference compared with placebo for laboratory abnormalities indicative of hepatic or renal dysfunction, an impaired haematologic system, hypocalcaemia or hypophosphataemia. Similarly, no differences were noted between the groups in study BM 16549 after one and two years.

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

4.9 Overdose

No specific information is available on the treatment of over dosage with ibandronic acid.

However, based on knowledge of this class of compounds, oral over-dosage may result in upper gastrointestinal adverse reactions (such as upset stomach, dyspepsia, oesophagitis, gastritis, or ulcer) or hypocalcaemia. Milk or antacids should be given to bind ibandronic acid, and any adverse reactions treated symptomatically. Owing to the risk of oesophageal irritation, vomiting should not be induced and the patient should remain fully upright.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Bisphosphonates, ATC code: M05B A06

Mechanism of action

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

Pharmacodynamic effects

The pharmacodynamic action of ibandronic acid is inhibition of bone resorption. *In vivo*, ibandronic acid prevents experimentally induced bone destruction caused by cessation of gonadal function, retinoids, tumours or tumour extracts. In young (fast growing) rats, the endogenous bone resorption is also inhibited, leading to increased normal bone mass compared with untreated animals.
Animal models confirm that ibandronic acid is a highly potent inhibitor of osteoclastic activity. In growing rats, there was no evidence of impaired mineralization even at doses greater than 5,000 times the dose required for osteoporosis treatment.
Both daily and intermittent (with prolonged dose-free intervals) long-term administration in rats, dogs and monkeys was associated with formation of new bone of normal quality and maintained or increased mechanical strength even at doses in the toxic range. In humans, the efficacy of both daily and intermittent administration with a dose-free interval of 9-10 weeks of ibandronic acid was confirmed in a clinical trial (MF 4411), in which ibandronic acid demonstrated anti-fracture efficacy.

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

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

Clinical efficacy

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

<u>Ibandronic acid 150 mg once monthly</u>

<u>Bone mineral density (BMD)</u>

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

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

	One year data in study BM 16549		Two year data in study BM 16549	
Mean relative changes from baseline % [95% CI]	Ibandronic acid 2.5 mg daily (N=318)	Ibandronic acid 150 mg once monthly (N=320)	Ibandronic acid 2.5 mg daily (N=294)	Ibandronic acid 150 mg once monthly (N=291)
Lumbar spine L2-L4 BMD	3.9 [3.4, 4.3]	4.9 [4.4, 5.3]	5.0 [4.4, 5.5]	6.6 [6.0, 7.1]
Total hip BMD	2.0 [1.7, 2.3]	3.1 [2.8, 3.4]	2.5 [2.1, 2.9]	4.2 [3.8, 4.5]
Femoral neck BMD	1.7 [1.3, 2.1]	2.2 [1.9, 2.6]	1.9 [1.4, 2.4]	3.1 [2.7, 3.6]
Trochanter BMD	3.2 [2.8, 3.7]	4.6 [4.2, 5.1]	4.0 [3.5, 4.5]	6.2 [5.7, 6.7]

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

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

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

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

Biochemical markers of bone turn-over

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

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

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

Ibandronic acid 2.5 mg daily

In the initial three-year, randomised, double-blind, placebo-controlled, fracture study (MF 4411), a statistically significant and medically relevant decrease in the incidence of new radiographic morphometric and clinical vertebral fractures was demonstrated (table 4). In this study, ibandronic acid was evaluated at oral doses of 2.5 mg daily and 20 mg intermittently as an exploratory regimen. Ibandronic acid was taken 60 minutes before the first food or drink of the day (post-dose fasting period). The study enrolled women aged 55 to 80 years, who were at least 5 years postmenopausal, who had a BMD at lumbar spine of 2 to 5 SD below the premenopausal mean (T-score) in at least one vertebra [L1-L4], and who had one to four prevalent vertebral fractures. All patients received 500 mg calcium and 400 IU vitamin D daily. Efficacy was evaluated in 2,928 patients. Ibandronic acid 2.5 mg administered daily, showed a statistically significant and medically relevant reduction in the incidence of new vertebral fractures. This regimen reduced the occurrence of new radiographic vertebral fractures by 62 % (p=0.0001) over the three year duration of the study. A relative risk reduction of 61 % was observed after 2 years (p=0.0006). No statistically significant difference was attained after 1 year of treatment (p=0.056). The anti-fracture effect was consistent over the duration of the study. There was no indication of a waning of the effect over time.

The incidence of clinical vertebral fractures was also significantly reduced by 49 % (p=0.011). The strong effect on vertebral fractures was furthermore reflected by a statistically significant reduction of height loss compared to placebo (p<0.0001).

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

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

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

Table 4: Results from 3 years fracture study MF 4411 (%, 95 % CI) for patients with lumbar spine BMD T-score below –2.5 at baseline		
	Placebo (N=587)	Ibandronic acid 2.5 mg daily (N=575)
Relative Risk Reduction New morphometric vertebral fractures		59 % (34.5, 74.3)
Incidence of new morphometric vertebral fractures	12.54 % (9.53, 15.55)	5.36 % (3.31, 7.41)
Relative risk reduction of clinical vertebral fracture		50 % (9.49, 71.91)
Incidence of clinical vertebral fracture	6.97 % (4.67, 9.27)	3.57 % (1.89, 5.24)
BMD – mean change relative to baseline lumbar spine at year 3	1.13 % (0.6, 1.7)	7.01 % (6.5, 7.6)
BMD – mean change relative to baseline total hip at year 3	-0.70 % (-1.1, -0.2)	3.59 % (3.1, 4.1)

In the overall patient population of the study MF4411, no reduction was observed for non-vertebral fractures, however daily ibandronate appeared to be effective in a high-risk subpopulation (femoral neck BMD T-score < -3.0), where a non-vertebral fracture risk reduction of 69% was observed.

Daily treatment with 2.5 mg resulted in progressive increases in BMD at vertebral and nonvertebral sites of the skeleton.

Three-year lumbar spine BMD increase compared to placebo was 5.3 % and 6.5 % compared to baseline. Increases at the hip compared to baseline were 2.8 % at the femoral neck, 3.4 % at the total hip, and 5.5 % at the trochanter.

Biochemical markers of bone turnover (such as urinary CTX and serum Osteocalcin) showed the expected pattern of suppression to premenopausal levels and reached maximum suppression within a period of 3-6 months.

A clinically meaningful reduction of 50 % of biochemical markers of bone resorption was observed as early as one month after start of treatment with ibandronic acid 2.5 mg.

Following treatment discontinuation, there is a reversion to the pathological pre-treatment rates of elevated bone resorption associated with postmenopausal osteoporosis.

The histological analysis of bone biopsies after two and three years of treatment of postmenopausal women showed bone of normal quality and no indication of a mineralization defect.

5.2 Pharmacokinetic properties

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

Absorption

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

Distribution

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

Metabolism

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

Elimination

The absorbed fraction of ibandronic acid is removed from the circulation via bone absorption (estimated to be 40 – 50 % in postmenopausal women) and the remainder is eliminated unchanged by the kidney. The unabsorbed fraction of ibandronic acid is eliminated unchanged in the faeces.
The range of observed apparent half-lives is broad, the apparent terminal half-life is generally in the range of 10-72 hours. As the values calculated are largely a function of the duration of study, the dose used, and assay sensitivity, the true terminal half-life is likely to be substantially longer, in common with other bisphosphonates. Early plasma levels fall quickly reaching 10 % of peak values within 3 and 8 hours after intravenous or oral administration respectively.

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

<u>Pharmacokinetics in special clinical situations</u>

Gender

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

Race

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

Patients with renal impairment

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

No dosage adjustment is necessary for patients with mild or moderate renal impairment (CLcr equal or greater than 30 ml/min), as shown in study BM 16549 where the majority of patients had mild to moderate renal impairment.

Subjects with severe renal failure (CLcr less than 30 ml/min) receiving daily oral administration of 10 mg ibandronic acid for 21 days, had 2-3 fold higher plasma concentrations than subjects with normal renal function and total clearance of ibandronic acid was 44 ml/min. After intravenous administration of 0.5 mg, total, renal, and non-renal clearances decreased by 67 %, 77 % and 50 %, respectively, in subjects with severe renal failure but there was no reduction in tolerability associated with the increase in exposure. Due to the limited clinical experience, ibandronic acid is not recommended in patients

with severe renal impairment (see section 4.2 and section 4.4). The pharmacokinetics of ibandronic acid was not assessed in patients with end-stage renal disease managed by other than haemodialysis. The pharmacokinetics of ibandronic acid in these patients is unknown, and ibandronic acid should not be used under these circumstances.

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

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

Paediatric population
There are no data on the use of ibandronic acid in these age groups.

5.3 Preclinical safety data
Toxic effects, e.g signs of renal damage, were observed in dogs only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

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

Reproductive toxicity:
There was no evidence for a direct foetal toxic or teratogenic effect of ibandronic acid in orally treated rats and rabbits and there were no adverse effects on the development in F_1 offspring in rats at an extrapolated exposure of at least 35 times above human exposure. Adverse effects of ibandronic acid in reproductive toxicity studies in the rat were those observed with bisphosphonates as a class. They include a decreased number of implantation sites, interference with natural delivery (dystocia), and an increase in visceral variations (renal pelvis ureter syndrome).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Table core:
Povidone
Cellulose microcrystalline
Maize starch pregelatinised
Crospovidone
Silica, colloidal anhydrous.
Glycerol Dibehenate

Table coat:
Opadry OY-LS-28908 (White II) consisting of:
Hypromellose
Lactose monohydrate
Titanium dioxide (E171)
Macrogol 4000

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

Gerousia/Mirdezel/Ziveteno/Quodixor/Baxogar 150 mg film-coated tablets are supplied in (PA/Aluminium/PVC- Aluminium) foil blisters (alu-alu blister) containing 1 or 3 tablets.
Not all pack sizes are marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Pharmathen SA
6 Dervenakion Street
Pallini
Athens
GR – 15351
Greece

8 MARKETING AUTHORISATION NUMBER(S)

PL 17277/0074
PL 17277/0149
PL 17277/0150
PL 17277/0152
PL 17277/0153

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

17/09/2010 (PL 17277/0074, 0149-150 & 0153)
28/09/2010 (PL 17277/0152 only)

10 DATE OF REVISION OF THE TEXT

17/09/2010 (PL 17277/0074, 0149-150 & 0153)
28/09/2010 (PL 17277/0152 only)

Module 3

The following Mirdezel 150mg Film-Coated Tablets leaflet is included as a representative example leaflet. The leaflets proposed for all the other products are consistent with this leaflet:

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PACKAGE LEAFLET: INFORMATION FOR THE USER

Mirdezel 150 mg Film-coated Tablets

Ibandronic acid

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

In this leaflet:

1. WHAT MIRDEZEL IS AND WHAT IT IS USED FOR

Mirdezel belongs to a group of medicines called ***bisphosphonates*** (used in the treatment of osteoporosis). It contains ibandronic acid. It does not contain hormones.
Mirdezel may reverse bone loss by stopping more loss of bone and increasing bone mass in most women who take it, even though they won't be able to see or feel a difference. Mirdezel may help lower the chances of breaking bones (fractures). This reduction in fractures was shown for the spine but not for the hip.

Mirdezel is prescribed to you to treat osteoporosis because you have an increased risk of fractures. Osteoporosis is a thinning and weakening of the bones, which is common in women after the menopause. At the menopause, a woman's ovaries stop producing the female hormone, oestrogen, which helps to keep her skeleton healthy.

The earlier a woman reaches the menopause, the greater her risk of fractures in osteoporosis. Other things that can increase the risk of fractures include:
- not enough calcium and vitamin D in the diet
- smoking, or drinking too much alcohol
- not enough walking or other weight-bearing exercise
- a family history of osteoporosis

Many people with osteoporosis have no symptoms. If you have no symptoms you may not know if you have the condition. However, osteoporosis makes you more likely to break bones if you fall or hurt yourself. A broken bone after the age of 50 may be a sign of osteoporosis. Osteoporosis can also cause back pain, height loss and a curved back.

Mirdezel prevents loss of bone from osteoporosis, and helps to rebuild bone. Therefore Mirdezel makes bone less likely to break.

A healthy lifestyle will also help you to get the most benefit from your treatment. This includes eating a balanced diet rich in calcium and vitamin D; walking or any other weight-bearing exercise; not smoking; and not drinking too much alcohol.

2. BEFORE YOU TAKE MIRDEZEL

Do not take Mirdezel
- If you are allergic (hypersensitive) to ibandronic acid, or to any of the other ingredients of Mirdezel (see section 6 for a list of the ingredients).
- If you have certain problems with your oesophagus (the tube connecting your mouth with your stomach) such as narrowing or difficulty swallowing.
- If you can't stand or sit upright for at least one hour (60 minutes) at a time.
- ***If you have, or had in the past, low blood calcium.*** Please consult your doctor.

Do not give Mirdezel to children or adolescents.

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

Irritation, inflammation or ulceration of the oesophagus (the tube connecting your mouth with your stomach) often with symptoms of severe pain in the chest, severe pain after swallowing food and/or drink, severe nausea, or vomiting may occur, especially if you do not drink a full glass of plain water and/or if you lie down within an hour of taking Mirdezel. If you develop these symptoms, speak to your doctor straight away.

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. Especially:

- supplements containing calcium, magnesium, iron or aluminium, as they could possibly influence the effects of Mirdezel.
- Aspirin and other non-steroidal anti-inflammatory medicines (NSAIDs) (including ibuprofen, diclofenac sodium and naproxen) may irritate the stomach and intestine. Bisphosphonates (like Mirdezel) may also do so. So be especially careful if you take painkillers or anti-inflammatories while you're taking Mirdezel.

After swallowing your monthly Mirdezel tablet, ***wait for 1 hour before taking any other medication,*** including indigestion tablets or medicine, calcium supplements, or vitamins.

Taking Mirdezel with food and drink
Do not take Mirdezel with food. Mirdezel is less effective if it's taken with food. You can drink plain water but no other drinks (see 3. HOW TO TAKE MIRDEZEL).

Pregnancy and breast-feeding
Do not take Mirdezel if you're pregnant or breast feeding. If you're breast feeding, you may need to stop in order to take Mirdezel.

Driving and using machines
You can drive and use machines as it's very unlikely that Mirdezel will affect your ability to drive and use machines.

Important information about some of the ingredients of Mirdezel
Mirdezel contains an ingredient called lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

3. HOW TO TAKE MIRDEZEL

Always take Mirdezel exactly as your doctor has told you. If you are not sure about anything, ask your doctor or pharmacist.
The usual dose of Mirdezel is one tablet once a month.

Taking your monthly tablet
It's important to follow these instructions carefully. They are designed to help your Mirdezel tablet reach your stomach quickly, so it's less likely to cause irritation.
- ***Take one Mirdezel 150 mg tablet once a month.***
- ***Choose one day of the month*** that will be easy to remember. You can choose either the same date (such as the 1st of each month) or the same day (such as the first Sunday of each month) to take your Mirdezel tablet. Choose the date that best fits your routine.
- Take your Mirdezel tablet ***at least 6 hours after you last had anything*** to eat or drink except plain water.

- Take your Mirdezel tablet
  - ***after you first get up for the day,*** and
  - ***before you have anything else to eat or drink*** (on an empty stomach)

- ***Swallow your tablet with a full glass of plain water*** (at least 180 ml).
  Do not take your tablet with mineral water, fruit juice or any other drinks.

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

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

  - ***do not eat anything***

  - ***do not drink anything*** (except plain water if you need it)
  - ***do not take any other medicines***

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

Do not take your tablet at bedtime or before you get up for the day.

Continuing to take Mirdezel
It's important to keep taking Mirdezel every month, as long as your doctor prescribes it for you. Mirdezel can treat osteoporosis only as long as you keep taking it.

If you take too much Mirdezel
If you've taken more than one tablet by mistake, ***drink a full glass of milk and talk to your doctor straight away.***

Do not make yourself vomit, and do not lie down — this could cause Mirdezel to irritate your oesophagus.

If you forget to take a dose
If you forget to take your tablet on the morning of your chosen day, ***do not take a tablet later in the day.*** Instead, consult your calendar and find out when your next scheduled dose is:

If your next scheduled dose is only 1 to 7 days away...
You should wait until your next scheduled dose is due and take it as normal. Then, continue taking one tablet once a month on the scheduled days you've marked on your calendar.

If your next scheduled dose is more than 7 days away...
You should take one tablet the next morning after the day you remember. Then, continue taking one tablet once a month on the scheduled days you've marked on your calendar.

Never take two Mirdezel tablets within the same week.

4. POSSIBLE SIDE EFFECTS

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

These side effects may occur with certain frequencies, which are defined as follows:
- very common: affects more than 1 user in 10
- common: affects 1 to 10 users in 100
- uncommon: affects 1 to 10 users in 1,000
- rare: affects 1 to 10 users in 10,000
- very rare: affects less than 1 user in 10,000
- not known: frequency cannot be estimated from the available data.

Common side effects are heartburn, indigestion, diarrhoea, stomach ache, and nausea. ***Mirdezel can also irritate the oesophagus, although you can usually avoid this by taking your dose as described in this leaflet. If you develop symptoms such as severe pain in the chest, severe pain after swallowing food or drink, severe nausea, or vomiting, stop taking Mirdezel and tell your doctor straightaway.***
Other common side effects include rash, cramps in the muscles, pain in the muscles and joints, and headache.
It also includes flulike symptoms (aches and pains , feeling of discomfort, fatigue) which are usually mild, are short-lasting and disappear soon after you have taken the first dose. So you should be able to carry on taking Mirdezel. Talk to your doctor if any effects become troublesome or last a long time.

Uncommon side effects are dizziness, back pain and flatulence.

Rare side effects are swelling and itching of the face, lips and mouth.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE MIRDEZEL

Keep out of the reach and sight of children.

Do not use after the expiry date which is stated on the carton after "EXP". The expiry date refers to the last day of that month.

This medicinal product does not require any special storage conditions.

Medicines should not be disposed of via wastewater or household waste. Ask your doctor or pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Mirdezel contains
- The active substance is ibandronic acid. One tablet contains 150 mg of ibandronic acid (as ibandronate sodium monohydrate).
- The other ingredients are:
  tablet core: Povidone, cellulose microcrystalline, maize starch pregelatinised, crospovidone, silica colloidal anhydrous, Glycerol Dibehenate.
  tablet coat: Opadry OY-LS-28908 (white II) consisting of: hypromellose, lactose monohydrate, titanium dioxide (E171), Macrogol 4000.

What Mirdezel looks like and contents of the pack
Mirdezel 150 mg film-coated tablets are white, round biconvex tablets.

Mirdezel 150 mg film-coated tablets are supplied in a cardboard box containing the appropriate number (1 or 3 tablets) of PA/Aluminium/ PVC- Aluminium foil blisters (alu-alu blister) with an instruction leaflet.

Marketing Authorisation Holder and Manufacturer:
Pharmathen S.A, 6 Dervenakion Str., 153 51 Pallini, Attiki, Greece.

This leaflet was last approved in 07/2010 *(to be amended after approval).*

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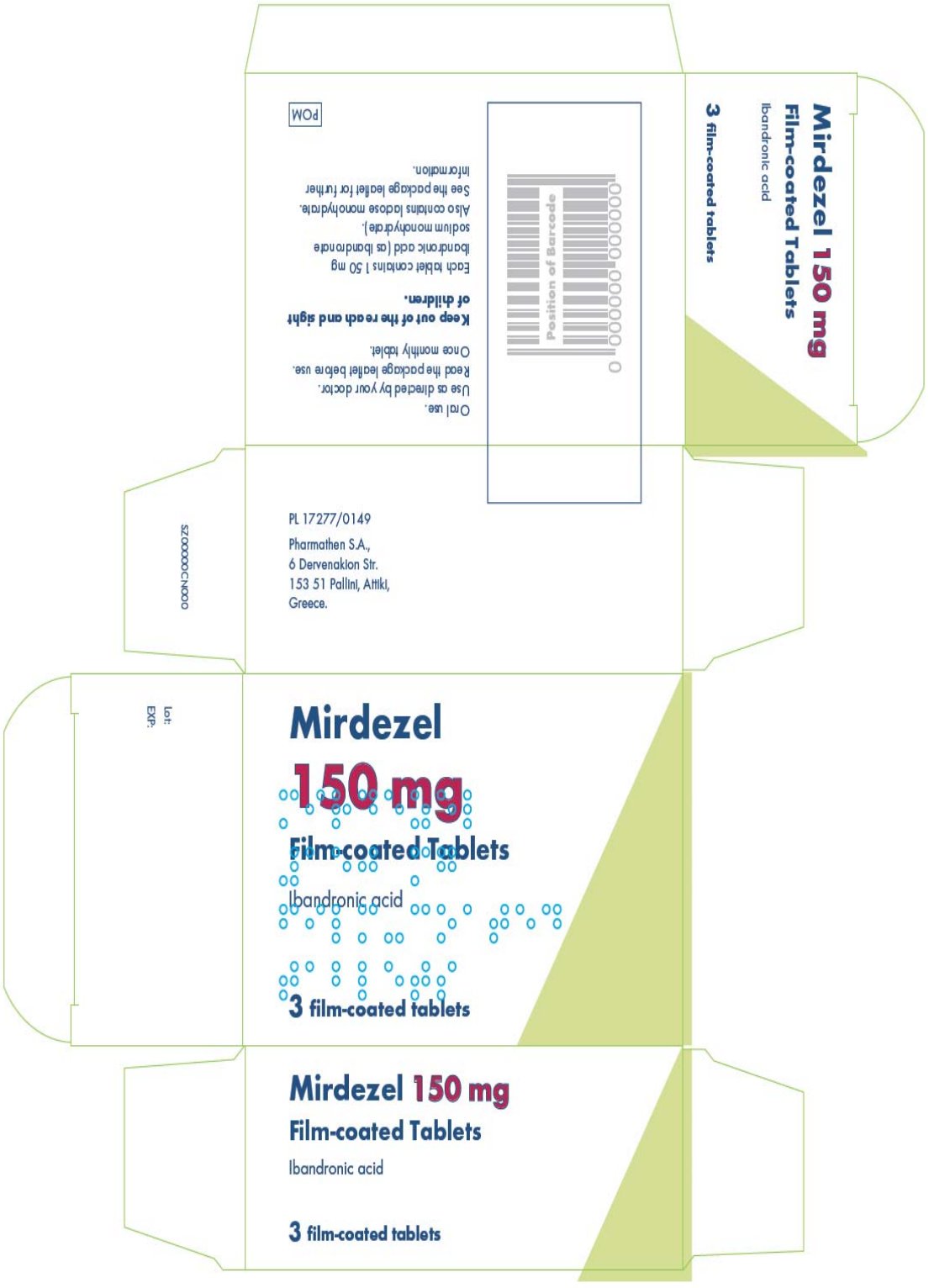
Module 4
Labelling

The following Mirdezel 150mg Film-Coated Tablets labelling (carton and blister) is included as representative example labelling. The labelling proposed for all the other products are consistent with this labelling:

Carton:



Blister:


Mirdezel 150 mg Film-coated Tablets
Ibandronic acid
PL 17277/0149
SZ00000FL000
Pharmathen S.A.
Mirdezel 150 mg Film-coated Tablets
Ibandronic acid
PL 17277/0149
SZ00000FL000
Pharmathen S.A.
Mirdezel 150 mg Film-coated Tablets
Ibandronic acid
PL 17277/0149
SZ00000FL000
Pharmathen S.A.
Mirdezel 150 mg Film-coated Tablets
Ibandronic acid
PL 17277/0149
SZ00000FL000
Pharmathen S.A.
Mirdezel 150 mg Film-coated Tablets
Ibandronic acid
PL 17277/0149
SZ00000FL000
Pharmathen S.A.
Mirdezel 150 mg Film-coated Tablets
Ibandronic acid
PL 17277/0149
SZ00000FL000
Pharmathen S.A.

Module 5
Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the member states considered that the applications for Gerousia/Mirdezel/Ziveteno/Quodixor/Baxogar 150mg film-coated tablets (PL 17277/0074, 0149-50, 0152-3; UK/H/2163, 3375-8/001/DC could be approved. These applications were submitted by the Decentralised Procedure, with the UK as Reference Member State (RMS), and Austria, Belgium, Bulgaria, Czech Republic, Germany, Denmark, Estonia, Spain, Finland, France, Hungary, Ireland, Iceland, Italy, Lithuania, Luxembourg, Latvia, The Netherlands, Norway, Portugal, Romania, Sweden and Slovenia as Concerned Member States (CMS). For full details of CMS involved for each procedure number please refer to page 22 of this report.

Gerousia/Mirdezel/Ziveteno/Quodixor/Baxogar150mg film-coated tablets are prescription-only medicines (POM) for the treatment of osteoporosis in postmenopausal women at increased risk of fracture. A reduction in the risk of vertebral fractures has been demonstrated; efficacy on femoral neck fractures has not been established.

These are applications made according to Article 10.1 of 2001/83/EC, as amended, claiming to be generic medicinal products of Bonviva® 150mg film-coated tablets (Roche Registration Limited, UK). The originator product for these applications is Bondronat 1mg/ml concentrate for infusion, which was granted a licence on 25 June 1996 by the Centralised Procedure to Roche Registrations Limited (EU/1/03/265/003,004).The product used in the bioequivalence study was Bonviva 150mg film-coated tablets, taken from the Greek market. It has been confirmed that this can be considered equivalent to the same product from the UK market.

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

No new non-clinical studies were conducted, which is acceptable given that the applications were for products that are being considered as generic medicinal products of an originator product that have been licensed for over 10 years.

No new clinical studies were conducted, which is acceptable given that the applications were for products that are being considered as generic medicinal products of an originator product that have been licensed for over 10 years. The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these product types at all sites responsible for the manufacture, assembly and batch release of these products.

The RMS and CMS considered that the applications could be approved, with the end of procedure (Day 210) on 14 July 2010. After a subsequent national phase, the licences were granted in the UK on 17 September 2010 (Gerousia/Mirdezel/Zivento/Baxogar 150mg film-coated tablets) and 28 September 2010(Quodixor 150mg film-coated tablets only).

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Gerousia 150mg film-coated tablets Mirdezel 150mg film-coated tablets Ziveteno 150mg film-coated tablets Quodixor 150mg film-coated tablets Baxogar 150mg film-coated tablets
Name(s) of the active substance(s) (INN)	Ibandronic acid
Pharmacotherapeutic classification (ATC code)	Bisphosponates (M05B A06)
Pharmaceutical form and strength(s)	150mg film-coated tablets
Reference numbers for the Mutual Recognition Procedure	UK/H/2163, 3375-8/001/DC
Reference Member State	United Kingdom
Member States concerned	UK/H/2163/001/DC Austria, Czech Republic, Germany, Spain, France, Hungary, Italy, Portugal and Slovakia UK/H/3375/001/DC Belgium, Czech Republic, Germany, Spain, France, Italy, Netherlands, Portugal, Romania, and Slovakia UK/H/3376/001/DC Belgium, Cyprus, Estonia, Iceland, Italy, Lithuania, Luxembourg, Latvia, Netherlands and Slovakia UK/H/3377/001/DC: Austria, Belgium, Bulgaria, Czech Republic, Germany, Denmark, Spain, France, Hungary, Ireland, Italy, Luxembourg, Netherlands, Norway, Poland, Portugal, Romania, Sweden, Slovenia and Slovakia. UK/H/3378/001/DC: Austria, Belgium, Bulgaria, Czech Republic, Germany, Denmark, Estonia, Spain, Finland France, Hungary, Italy, Lithuania, Luxembourg, Latvia, Netherlands, Portugal, Sweden and Slovakia.
Marketing Authorisation Number(s)	PL 17277/0074, 0149-50 and 0152-3
Name and address of the authorisation holder	Pharmathen SA, 6 Dervenakion Street, Pallini, Athens, GR-15351, Greece

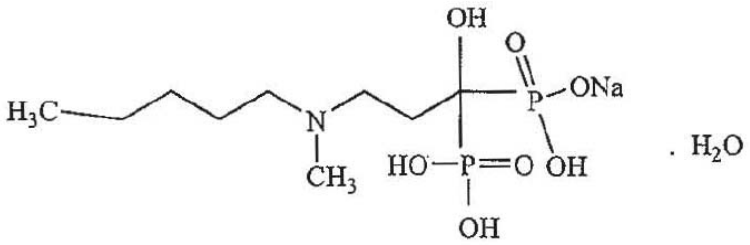
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

S. Active substance

INN: Ibandronate sodium monohydrate

Chemical name: [1-Hydroxy-3-(methylpentylamino) propylidene] bisphosphonic acid sodium salt monohydrate



:

Molecular formula: $C_9H_{22}NO_7P_2Na.H_2O$

Molecular weight: 359

Appearance: a white to almost white crystalline powder, sparingly soluble in water, with no chiral centres and exhibiting polymorphism.

Ibandronate sodium monohydrate was not the subject of a European Pharmacopoeia monograph at the time of assessment.

Synthesis of the drug substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Appropriate proof-of-structure data have been supplied for the active pharmaceutical ingredient. All potential known impurities have been identified and characterised. Satisfactory certificates of analysis have been provided for all working standards. Batch analysis data are provided and comply with the proposed specification.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

P. Medicinal Product

Other Ingredients

Other ingredients consist of the following pharmaceutical excipients povidone, cellulose microcrystalline, maize starch pregelatinised, crospovidone, colloidal anhydrous silica, glycerol dibehenate, hypromellose, lactose monohydrate, titanium dioxide (E171) and macrogol 4000.

All excipients comply with their respective European Pharmacopoeia monograph. Suitable batch analysis data have been provided for each excipient.

None of the excipients contain materials of animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of these products.

Pharmaceutical Development
The objective of the development programme was to formulate robust, stable tablets containing 150mg ibandronic acid that could be considered as generic medicinal products of Bonviva® 150 mg film-coated tablets (Roche Registration Limited).

A satisfactory account of the pharmaceutical development has been provided.

Comparative *in vitro* dissolution and impurity profiles have been provided for the proposed and originator products.

Manufacturing Process
A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specification
The finished product specification proposed is acceptable. Test methods have been described and have been adequately validated. Batch data have been provided and these comply with the release specifications. Certificates of analysis have been provided for all working standards used.

Container-Closure System
The finished product is packaged in polyamide/aluminium/polyvinylchloride blisters, containing 1 or 3 tablets. It has been stated that not all pack sizes may be marketed, however, the marketing authorisation holder has committed to submitting the mock-ups for any pack size to the relevant regulatory authorities for approval before marketing.

Satisfactory specifications and certificates of analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

Stability of the Product
Stability studies were performed in accordance with current guidelines on batches of all strengths of finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 2 years, with no special storage conditions.

Bioequivalence/bioavailability
Satisfactory certificates of analysis have been provided for the test and reference batches used in the bioequivalence study.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels
The SmPC, PIL and labels are pharmaceutically acceptable.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

MAA Forms
The MAA forms are pharmaceutically satisfactory.

Expert Report
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion
There are no objections to the approval of these applications from a pharmaceutical viewpoint.

III.2 NON-CLINICAL ASPECTS
As the pharmacodynamic, pharmacokinetic and toxicological properties of ibandronic acid are well-known, no new non-clinical studies are required and none have been provided.

The applicant's non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the products' pharmacology and toxicology.

A suitable justification has been provided for non-submission of an environmental risk assessment.

There are no objections to the approval of these products from a non-clinical viewpoint.

III.3 CLINICAL ASPECTS
Pharmacokinetics
In support of these applications, the marketing authorisation holder has submitted the following bioequivalence study:

A randomised, single-dose, two–period, two-sequence, crossover, single-centre study to compare the pharmacokinetics of the test product Ibandronate 150mg tablets (Pharmathen SA) versus the reference product Bonviva® 150 mg tablets (Roche Registration Limited, Greece) in healthy adult volunteers under fasted conditions.

All volunteers received the allocated drug after an overnight fast. Blood samples were taken for the measurement of pharmacokinetic parameters at pre- and up to 72 hours post dose. The washout period between treatment periods was at least 4 weeks.

The pharmacokinetic results for ibandronic acid presented below:

Treatment	AUC_{0-t} ng/ml/h	$AUC_{0-\infty}$ ng/ml/h	C_{max} ng/ml
Test (mean)	253.67	267.88	60.04
Reference (mean)	230.46	244.09	62.42
***Ratio (90% CI)**	106.45 (92.23-122.87%)	106.18 (91.79-122.83%)	98.22 (83.71-155.24%)

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration

**ln-transformed values*

The 90% confidence intervals for AUC and C_{max} for test versus reference product are within predefined acceptance criteria specified in the Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98). Thus, the data support the claim that the test product is bioequivalent to the reference product. As the Greek and UK versions of Bonviva 150mg tablets can be considered to be identical, bioequivalence has been shown between the test product and the UK reference product (Bonviva 150mg tablets).

Pharmacodynamics
No new pharmacodynamic data were submitted and none were required for these applications.

Efficacy
No new efficacy data were submitted and none were required for these applications.

Safety
With the exception of the data generated during the bioequivalence study, no new safety data were submitted and none were required for these applications. During the bioequivalence study gastrointestinal side effects were observed following administration of the test product and reference product in both treatment periods. The gastrointestinal side-effects experienced are recognised adverse effects of the active substance ibandronate and are all reported as 'common' in the reference product SmPC. There were no withdrawals due to adverse events and no serious adverse events were recorded during the study.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels
The SmPC, PIL and labels are medically acceptable. The SmPC is consistent with that for the originator product. The PIL is consistent with the SmPC and in-line with current guidelines. The labelling is in-line with current guidelines.

Clinical Expert Report
The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Pharmacovigilance System and Risk Management Plan
The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

A suitable justification has been provided for not submitting a Risk Management Plan for these products.

Conclusion
There are no objections to the approval of these applications from a clinical viewpoint.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Gerousia/Mirdezel/Zivento/Quodixor/Baxogar 150mg film-coated tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit-risk balance.

NON-CLINICAL
No new non-clinical data were submitted and none are required for applications of this type. The pharmacodynamic, pharmacokinetic and toxicological properties of ibandronic acid are well-known.

EFFICACY
A pharmacokinetic study was submitted, showing that this product can be considered to be a generic medicinal product of the originator product Bonviva® 150 mg tablets (Roche Registration Limited, UK).

No other clinical data have been submitted with these applications and none are required.

SAFETY
During the bioequivalence study, gastrointestinal side effects were observed following administration of the test product and reference product in both treatment periods .The gastrointestinal side-effects experienced are recognised adverse effects of the active substance ibandronate and are all reported as 'common' in the reference product SmPC. There were no withdrawals due to adverse events and no serious adverse events were recorded during the study.

No new or unexpected safety concerns arise from these applications

PRODUCT LITERATURE
The SmPCs, PIL and labelling are satisfactory and consistent with that for the reference product, where appropriate.

BENEFIT-RISK ASSESSMENT
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant's product and the originator product are interchangeable. Extensive clinical experience with ibandronic acid is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is, therefore, considered to be positive.

Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome