SCHEDULING STATUS
S4

1.NAME OF THE MEDICINE
BONDRONAT® 50, film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains 50 mg ibandronic acid, (as ibandronic sodium monohydrate).

Contains sugar: Lactose monohydrate 92,75 mg per tablet

For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM
Film-coated tablets.
White to off-white, oblong shaped, film-coated tablet, engraved L2 on one side and IT on the other side.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
BONDRONAT 50 is indicated in patients with breast cancer and bone metastases for the prevention of skeletal complications requiring radiotherapy.

4.2 Posology and method of administration
Posology
The recommended dose is one 50 mg film-coated tablet daily.

Special populations
Special Dosage instructions
Patients confined to bed
Patients with inability to stand or sit upright for 60 minutes have not been studied for the oral formulation. See section 4.3.

Patients with hepatic impairment
No dosage adjustment is expected to be necessary.

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

For patients with moderate renal impairment (CLcr ≥ 30 and < 50 mℓ/min) a dosage adjustment to one 50 mg film-coated tablet every second day is recommended.

For patients with severe renal impairment (CLcr < 3 0 mℓ/min) the recommended dose is one 50 mg film-coated tablet once weekly. See *Pharmacokinetics in special populations.*

Elderly
No dose adjustment is necessary.

Children and adolescents
Safety and efficacy have not been established in patients less than 18 years old (see section 4.3).

Method of administration
For oral use.

BONDRONAT 50 should be taken after an overnight fast (at least 6 hours) and 30 - 60 minutes before the first food or drink of the day. Medicinal products and supplements (including calcium) should similarly be avoided prior to taking BONDRONAT 50 tablets. Fasting should be continued for 30 - 60 minutes after taking the tablet. Plain water may be taken at any time during the course of BONDRONAT 50 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 BONDRONAT 50.
- Patients should not chew or suck the tablet because of a potential for oropharyngeal ulceration.
- Plain water is the only drink that should be taken with BONDRONAT 50. Please note that some mineral waters may have a higher concentration of calcium and therefore should not be used.

4.3 Contraindications
BONDRONAT 50 is contraindicated in patients with:

- Known hypersensitivity to ibandronic acid, or other bisphosphonates or to any of the excipients listed in section 6.1.
- Hypocalcaemia, see section 4.4.
- Abnormalities of the oesophagus which delay oesophageal emptying such as stricture or achalasia, see section 4.4.
- Inability to stand or sit upright for at least 60 minutes, see sections 4.2 and 4.4.
- BONDRONAT 50 should not be used during pregnancy and lactation due to a lack of clinical experience, see section 4.6.
- BONDRONAT 50 should not be used in children, due to lack of clinical experience, see section 4.2.

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 BONDRONAT 50 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 BONDRONAT 50 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 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.

Medical practitioners should be alert to any signs or symptoms signalling a possible oesophageal reaction and patients should be instructed to discontinue BONDRONAT 50 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 BONDRONAT 50 use, some severe and with complications.

Acetylsalicylic acid and NSAIDs
Since Acetylsalicylic acid and NSAIDs are associated with gastrointestinal irritation, caution should be taken during concomitant oral medication with BONDRONAT 50.

Osteonecrosis of the jaw
Osteonecrosis of the jaw (ONJ) has been reported very rarely in the post marketing setting in patients receiving BONDRONAT 50 for oncology indications (see section 4.8).
The start of treatment or of a new course of treatment should be delayed in patients with unhealed open soft tissue lesions in the mouth.

A dental examination with preventive dentistry and an individual benefit-risk assessment is recommended prior to treatment with BONDRONAT 50 in patients with concomitant risk factors.

The following risk factors should be considered when evaluating a patient's risk of developing ONJ:

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

All patients should be encouraged to maintain good oral hygiene, undergo routine dental check-ups, and immediately report any oral symptoms such as dental mobility, pain or swelling, or non-healing of sores or discharge during treatment with BONDRONAT 50. While on treatment, invasive dental procedures should be performed only after careful consideration and be avoided in close proximity to BONDRONAT 50 administration.

The management plan of the patients who develop ONJ should be set up in close collaboration between the treating physician and a dentist or oral surgeon with expertise in ONJ. Temporary interruption of BONDRONAT 50 treatment should be considered until the condition resolves and contributing risk factors are mitigated where possible.

Osteonecrosis of the external auditory canal
Osteonecrosis of the external auditory canal has been reported with bisphosphonates (including BONDRONAT 50), mainly in association with long-term therapy. Possible risk factors for osteonecrosis of the external auditory canal include steroid use and chemotherapy and/or local risk factors such as infection or trauma. Other risk factors may include repetitive minor trauma (e.g. habitual cotton bud use). The possibility of osteonecrosis of the external auditory canal should be considered in patients receiving bisphosphonates who present with ear symptoms including chronic ear infections.

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

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

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

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

Renal function
Clinical studies have rarely shown any evidence of deterioration in renal function with long term BONDRONAT 50 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 BONDRONAT 50.

Sugars
BONDRONAT 50 tablets contain lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take BONDRONAT 50.

4.5 Interaction with other medicines and other forms of interaction
Medicine - 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 BONDRONAT 50 tablets. Therefore, with such products, including food, intake must be delayed 30 - 60 minutes following oral administration.
Bioavailability was reduced by approximately 75 % when BONDRONAT 50 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 - 60 minutes after the dose has been taken. See section 4.2.

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

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

H2-antagonists or other medicinal products that increase gastric pH
In healthy male volunteers and postmenopausal women, *IV* ranitidine caused an increase in ibandronic acid bioavailability of about 20 % (which is within the normal variability of the bioavailability of ibandronic acid), probably as a result of reduced gastric acidity. However, no dosage adjustment is required when BONDRONAT 50 is administered with H_2-antagonists or other medicines that increase gastric pH.

Interactions with other medicinal products
In relation to disposition, no 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.

Aminoglycosides
Caution is advised when BONDRONAT 50 50 mg tablets are administered with aminoglycosides, since both medicines can lower serum calcium levels for prolonged periods. Attention should also be paid to the possible existence of simultaneous hypomagnesaemia.

In clinical studies, BONDRONAT 50 has been administered concomitantly with commonly used anticancer medicines, diuretics, antibiotics and analgesics without clinically apparent interactions occurring.

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

4.6 Fertility, pregnancy and lactation
BONDRONAT 50 should not be used during pregnancy and lactation (see section 4.3).

Pregnancy
BONDRONAT 50 should not be used during pregnancy.
There are no adequate data from the use of ibandronic acid in pregnant women. Studies in rats have shown some reproductive toxicity. The potential risk for humans is unknown. Ibandronic acid crosses the placenta.

Breastfeeding
It is not known whether ibandronic acid is excreted in human milk. Studies in lactating rats have demonstrated the presence of ibandronic acid in the milk following intravenous administration. Consequently, caution should be exercised when prescribing BONDRONAT 50 to breastfeeding women. BONDRONAT 50 should not be used during lactation.

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

4.7 Effects on ability to drive and use machines

On the basis of the pharmacodynamic and pharmacokinetic profile and reported adverse reactions, it is expected that BONDRONAT 50 has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

a) Summary of the safety profile

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

b) Tabulated list of adverse reactions

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

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

Table 1: Adverse Drug Reactions Reported for Oral Administration of BONDRONAT 50

System Organ Class	**Frequency**	**Adverse reaction**
Blood and lymphatic system disorders	Uncommon	Anaemia
Immune system disorders	Very rare	Hypersensitivity†, bronchospasm†, angioedema†, Anaphylactic reaction/shock†**
	Not Known	Asthma exacerbation
Metabolism and nutrition disorders	Common	Hypocalcaemia**
Nervous system disorders	Uncommon	Paraesthesia, dysgeusia (taste perversion)
Eye disorders	Rare	Ocular Inflammation (such as uveitis, episcleritis and scleritis)†**
Gastrointestinal disorders	Common	Oesophagitis, abdominal pain, dyspepsia, nausea
	Uncommon	Abdominal pain, dry mouth, diarrhoea, duodenal ulcer, constipation, haemorrhage, dysphagia, gastritis, anorexia
Skin and subcutaneous tissues disorders	Uncommon	Pruritus
	Very rare	Stevens-Johnson Syndrome†, Erythema multiforme†, Dermatitis bullous†
Musculoskeletal and,	Rare	Atypical subtrochanteric

connective tissue disorders		and diaphyseal femoral fractures†
	Very rare	Osteonecrosis of jaw†**, Osteonecrosis of the external auditory canal (bisphosphonate class adverse reaction) †
	Not known	Atypical fractures of long bones other than the femur
Renal and urinary disorders	Uncommon	Azotaemia (uraemia), increased creatinine
General disorders and administration site conditions	Common	Asthenia
	Uncommon	Chest pain, influenza-like illness, malaise, pain
Investigations	Uncommon	Increased blood parathyroid hormone

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

c) Description of selected adverse reactions

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

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

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

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

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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

Reporting can also be done directly to Adcock Ingram Limited at Adcock.aereports@adcock.com.

4.9 Overdose
No specific information is available on the treatment of overdosage with BONDRONAT 50. However, oral overdosage may result in upper gastrointestinal events, such as upset stomach, heartburn, oesophagitis, gastritis or ulcer. Milk or antacids should be given to bind BONDRONAT 50. 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
Category and class: A3.2 Connective tissue medicines. Non-hormonal preparations.
Pharmacotherapeutic group: Medicinal products for treatment of bone diseases, bisphosphonates, ATC code: M05BA06

Ibandronic acid is a bisphosphonate. 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.
At doses that were considerably higher than the pharmacologically effective doses, ibandronic acid did not have any effect in animal studies on bone mineralisation.

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 breakfast the reduction in bioavailability is 42 %, compared to one hour before breakfast. Absorption is about 16 % less when taken one hour before breakfast compared to 2 hours before breakfast.
Bioavailability was reduced by approximately 75 % when BONDRONAT 50 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 30 - 60 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 the absorbed dose reaching the bone is estimated to be 40 - 50 % of the circulating dose. Protein binding in human plasma is low (approximately 87 % bound at therapeutic concentrations), and thus interaction due to displacement is unlikely.

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 (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 varies widely, but the apparent terminal half-life is

generally in the range of 10 - 60 hours. However, early plasma levels fall quickly, reaching 10 % of peak values within 3 and 8 hours after intravenous or oral administration respectively. Total clearance of ibandronic acid is low with average values in the range 84 - 160 mℓ/min. Renal clearance (about 60 mℓ/min in healthy postmenopausal females) accounts for 50 - 60 % of total clearance and is related to creatinine clearance. The difference between the apparent total and renal clearances is considered to reflect the uptake by bone.

Pharmacokinetics in Special Populations

Gender

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

Race

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

Patients with renal impairment

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

Patients with severe renal impairment (CLcr $\leq$ 30 mℓ/min) receiving oral administration of 10 mg ibandronic acid daily for 21 days, had 2 - 3-fold higher plasma concentrations than patients with normal renal function (CLcr ≥ 80 mℓ/min). Total clearance of ibandronic acid was reduced to 44 mℓ/min in patients with severe renal impairment compared with 129 mℓ/min in patients with normal renal function. For patients with mild renal impairment (CLcr ≥ 50 and < 80 mℓ/min) no dosage adjustment is necessary. 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, *Special dosage instructions*.

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 metabolised but cleared by renal excretion and by uptake into bone. Therefore, dosage adjustment is not necessary in patients with hepatic impairment. Further, as protein binding of ibandronic acid is low at therapeutic concentrations (85 %), 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.

Children and adolescents

There are no data on the use of BONDRONAT 50 in patients less than 18 years old.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Colloidal anhydrous silica
Crospovidone
Lactose monohydrate
Microcrystalline cellulose
Povidone k25
Stearic acid 95

Tablet coat:
Hypromellose
Macrogol 6 000
Talc
Titanium dioxide

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
5 years

6.4 Special precautions for storage
Store at or below 30 °C
Keep in the original package as the tablets are sensitive to moisture.

6.5 Nature and contents of container
28 and 84 film-coated tablets packed in transparent PVC/aluminium or aluminium/aluminium blister strips.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling
No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION
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