**SCHEDULING STATUS**
**S4**

## 1. NAME OF THE MEDICINE
BONIVA® 150 mg, film-coated tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains 150 mg ibandronic acid (as ibandronic sodium monohydrate).

Contains sugar: Lactose monohydrate 162,75 mg

For list of excipients, see section 6.1

## 3. PHARMACEUTICAL FORM
Film-coated tablets

White to off-white film-coated tablets, of oblong shape, marked “BNVA” on one side and “150” on the other side.

## 4. CLINICAL PARTICULARS
### 4.1 Therapeutic indications
BONIVA 150 mg is indicated for the treatment of osteoporosis in postmenopausal women, in order to reduce the risk of vertebral fractures.

### 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.

BONIVA 150 mg 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 product or supplementation (including calcium).

In case a dose is missed, patients should be instructed to take one BONIVA 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**
***Renal impairment***
No dosage adjustment is necessary for patients with mild or moderate renal impairment where creatinine clearance is equal to or greater than 30 mL/min. BONIVA 150 mg is not recommended for patients with a creatinine clearance below 30 mL/min due to limited clinical experience. See section 4.4 and section 4.5.

***Hepatic impairment***
No dosage adjustment is required, see section 5.2.

***Elderly***
No dosage adjustment is required, see section 5.2.

**Children and adolescents**
BONIVA 150 mg has not been tested in these age groups and should not be given to them.

**Method of administration**
For oral use.

Tablets should be swallowed whole with a glass of plain water (180 – 240 mL) while the patient is sitting or standing in an upright position. Patients should not lie down for 1 hour after taking BONIVA 150 mg.

Plain water is the only drink that should be taken with BONIVA 150 mg. 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**
- Hypersensitivity to ibandronic acid or to any of the excipient listed in section 6.1.
- Hypocalcaemia, see section 4.4.
- Severe renal impairment (creatinine clearance < 30 mL/min).
- Abnormalities of the oesophagus which delay oesophageal emptying such as stricture or achalasia.
- Inability to stand or sit upright for at least 60 minutes.

**4.4 Special warnings and precautions for use**
**Hypocalcaemia**
Existing hypocalcaemia must be corrected before starting BONIVA 150 mg therapy.

Other disturbances of bone and mineral metabolism should also be effectively treated before starting BONIVA 150 mg therapy. All patients must receive adequate supplemental calcium and vitamin D.

**Gastrointestinal irritation**
Orally administered bisphosphonates have been associated with dysphagia, oesophagitis and oesophageal or gastric ulcers. Therefore patients, especially those with a history of prolonged oesophageal transit time, should pay particular attention to and be able to comply with the dosing instructions. See section 4.2.

Physicians should be alert to signs or symptoms signalling a possible oesophageal reaction during therapy, and patients should be instructed to discontinue BONIVA 150 mg and seek medical attention if they develop symptoms of oesophageal irritation such as new or worsening dysphagia, pain on swallowing, retrosternal pain or heartburn.

Since NSAIDs and bisphosphonates are both associated with gastrointestinal irritation, caution should be taken during concomitant administration.

**Osteonecrosis of the jaw**
Osteonecrosis of the jaw (ONJ) has been reported in patients treated with bisphosphonates including BONIVA 150 mg. Most cases have been in cancer patients undergoing dental procedures, but some have occurred in patients with postmenopausal osteoporosis or other diagnoses. Known risk factors for ONJ include a diagnosis of cancer, concomitant therapies (e.g., chemotherapy, radiotherapy, corticosteroids), and co-morbid disorders (e.g., anaemia, coagulopathy, infection, pre-existing dental disease). Most reported cases have been in patients treated with bisphosphonates intravenously but some have been in patients treated orally. For patients who develop ONJ 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 ONJ. Clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

**Osteonecrosis of the external auditory canal**
Osteonecrosis of the external auditory canal has been reported with bisphosphonates, mainly in association with long-term therapy. Possible risk factors for osteonecrosis of the external auditory canal include steroid use and chemotherapy and/or local risk factors such as infection or trauma. The possibility of osteonecrosis of the external auditory canal should be considered in patients receiving bisphosphonates who present with ear symptoms including chronic ear infections.

**Atypical fractures of the femur**
Atypical subtrochanteric and diaphyseal femoral fractures have been reported with bisphosphonate therapy, primarily in patients receiving long-term treatment for osteoporosis. These transverse or short oblique fractures can occur anywhere along the femur from just below the lesser trochanter to just above the supracondylar flare.

These fractures occur after minimal or no trauma and some patients experience thigh or groin pain, often associated with imaging features of stress fractures, weeks to months before presenting with a completed femoral fracture. Fractures are often bilateral; therefore, the contralateral femur should be examined in bisphosphonate treated patients who have sustained a femoral shaft fracture. Poor healing of these fractures has also been reported. Discontinuation of bisphosphonate therapy in patients suspected to have an atypical femur fracture should be considered pending evaluation of the patient, based on an individual benefit risk assessment.

During bisphosphonate treatment patients should be advised to report any thigh, hip or groin pain and any patient presenting with such symptoms should be evaluated for an incomplete femur fracture (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 impairment**
Due to limited clinical experience, BONIVA 150 mg is not recommended for patients with a creatinine clearance below 30 mL/min. See section 4.2, 4.3 and 5.2.

**Excipients with known effect**
BONIVA 150 mg contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this BONIVA 150 mg.

**4.5 Interaction with other medicines and other forms of interaction**
**Food interactions**
Oral bioavailability of BONIVA 150 mg 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 BONIVA 150 mg, which is consistent with findings in animal studies. Therefore, patients should fast overnight (at least 6 hours) before taking BONIVA 150 mg and continue fasting for 1 hour following intake of BONIVA 150 mg.

**Medicine interactions**
Metabolic interactions are not considered likely, since BONIVA 150 mg 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 medicine concentrations), and thus there is a low potential for medicine-medicine interaction due to displacement. BONIVA 150 mg 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.

***Calcium supplements, antacids and some oral medicinal products containing multivalent cations***
Calcium supplements, antacids and some oral medicinal products containing multivalent cations (such as aluminium, magnesium, iron) are likely to interfere with the absorption of BONIVA 150 mg. Therefore, patients should not take other oral medicinal products for at least 6 hours before taking BONIVA 150 mg and for 1 hour following intake of BONIVA 150 mg.

***Tamoxifen or hormone replacement therapy (estrogen)***
Pharmacokinetic interaction studies in postmenopausal women have demonstrated the absence of any interaction potential with tamoxifen or hormone replacement therapy (estrogen). No interaction was observed when co-administered with melphalan/ prednisolone in patients with multiple myeloma.

***H2-antagonists or proton pump inhibitors***
In healthy male volunteers and postmenopausal women, intravenous administration of ranitidine caused an increase in BONIVA 150 mg 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 BONIVA 150 mg, no dosage adjustment is considered necessary when BONIVA 150 mg is administered with H2-antagonists or other active substances which increase gastric pH.

***Acetylsalicylic acid and NSAIDs***
Since 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**
BONIVA 150 mg should not be used during pregnancy and lactation.

**Pregnancy**
There are no adequate data from the use of BONIVA 150 mg in pregnant women. Studies in rats have shown some reproductive toxicity. The potential risk for humans is unknown.

**Breastfeeding**
It is not known whether BONIVA 150 mg is excreted in human milk. Studies in lactating rats have demonstrated the presence of low levels of BONIVA 150 mg in the milk following intravenous administration.

**Fertility**
There are no data on the effects of ibandronic acid from humans. In reproductive studies in rats by the oral route, BONIVA 150 mg decreased fertility. In studies in rats using the intravenous route, BONIVA 150 mg decreased fertility at high daily doses (see section 5.3).

**4.7 Effects on ability to drive and use machines**
On the basis of the pharmacodynamic and pharmacokinetic profile and reported adverse reactions, it is expected that BONIVA 150 mg 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 for the jaw and ocular inflammation (see paragraph “Description of selected adverse reactions” and section 4.4).

The most frequently reported adverse reactions are arthralgia and influenza-like symptoms. These symptoms are typically in association with the first dose, generally of short duration, mild or moderate in intensity, and usually resolve during continuing treatment without requiring remedial measures (please see paragraph “Influenza like illness”).

**b. Tabulated list of adverse reactions**
In table 1 a complete list of known adverse reactions is presented.

The safety of oral treatment with 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 fracture study (MF 4411).

In a two-year study in postmenopausal women with osteoporosis (BM16549) the overall proportion of patients who experienced a side effect, i.e. adverse event with a possible or probable relationship to trial medication, was 22,7 % for BONIVA 150 mg once monthly. The majority of side effects were mild to moderate in intensity. Most cases did not lead to cessation of therapy.

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 reactions occurring in postmenopausal women receiving BONIVA 150 mg once monthly or ibandronic acid 2.5 mg daily in the phase III studies BM16549 and MF4411 and in post-marketing experience.

| **System Organ Class** | **Frequency** | **Adverse reaction** |
|---|---|---|
| Immune system disorders | Uncommon | Asthma exacerbation |
| | Rare | Hypersensitivity reaction |
| | Very rare | Anaphylactic reaction/shock*† |
| Metabolism and Nutrition disorders | Uncommon | Hypocalcaemia† |
| Nervous system disorders | Common | Headache |
| | Uncommon | Dizziness |
| Eye disorders | Rare | Ocular inflammation*† |
| Gastrointestinal disorders | Common | Oesophagitis,<br>Gastritis,<br>Gastro-oesophageal reflux disease,<br>Dyspepsia,<br>Diarrhoea,<br>Abdominal pain,<br>Nausea |
| | Uncommon | Oesophageal ulcerations or strictures and dysphagia,<br>Vomiting,<br>Flatulence |
| | Rare | Duodenitis |
| Skin and subcutaneous tissues disorders | Common | Rash |
| | Rare | Angioedema,<br>Face oedema,<br>Urticaria |
| | Very rare | Stevens-Johnson Syndrome†,<br>Erythema Multiforme†,<br>Dermatitis Bullous† |
| Musculoskeletal and, connective tissue disorders | Common | Arthralgia,<br>Myalgia,<br>Musculoskeletal pain,<br>Muscle cramp,<br>Musculoskeletal stiffness |
| | Uncommon | Back pain |
| | Rare | Atypical subtrochanteric and diaphyseal femoral fractures† |
| | Very rare | Osteonecrosis of jaw*†<br>Osteonecrosis of the external auditory canal (bisphosphonate class adverse reaction)† |
| | Not known | Atypical fractures of long bones other than the femur |
| General disorders and Administration site conditions | Common | Influenza like illness* |
| | Uncommon | Fatigue |

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

**c. Description of selected adverse reactions**

***Gastrointestinal adverse reactions***

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.

***Influenza-like illness***

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. Such symptoms were generally of short duration, mild or moderate in intensity, and resolved during continuing treatment without requiring remedial measures.

***Osteonecrosis of jaw***

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

***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.

**4.9 Overdose**

No specific information is available on the treatment of over dosage with BONIVA 150 mg. However, based on the 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 BONIVA 150 mg 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

Category and class: A3.2 Connective tissue medicines. Non-hormonal preparations
Pharmacotherapeutic group: Medicinal products for treatment of bone diseases, bisphosphonates, ATC code: M05-BA06

**Mechanism of action**

Ibandronic acid is a 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 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 mineralisation 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 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.

### 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 medicine concentrations), and thus there is a low potential for 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.

**Pharmacokinetics in special populations**
***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.

***Renal impairment***
Renal clearance of ibandronic acid in patients with various degrees of renal impairment is linearly related to creatinine clearance (CLcr). No dosage adjustment is necessary for patients with mild or moderate renal impairment (CLcr equal or greater than 30 mL/min), as shown in study BM16549 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 ibandronic acid, 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, 4.3 and 4.4. The pharmacokinetics of ibandronic acid was not assessed in patients with end-stage renal disease managed other than by haemodialysis. Therefore, the pharmacokinetics of ibandronic acid in these patients

is unknown. Due to the limited data available, ibandronic acid should not be used in patients with end-stage renal disease.

***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***
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 above).

***Children and adolescents***
There are no data on the use of ibandronic acid in these age groups.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients
*Tablet core:*
Colloidal anhydrous silica
Crospovidone
Lactose monohydrate
Microcrystalline cellulose
Povidone
Stearic acid
*Film-coating:*
Hypromellose
Macrogol 6 000
Talc
Titanium dioxide

### 6.2 Incompatibilities
Not applicable.

### 6.3 Shelf life
Aluminium-aluminium blisters: 3 years
PVC/PVDC (duplex) blisters: 5 years

### 6.4 Special precautions for storage
Store at or below 30 °C.
Keep in original pack until required for use.

### 6.5 Nature and contents of container
1 or 3 tablets packed in aluminium-aluminium or PVC/PVDC (duplex) -aluminium blisters.

Not all pack sizes and/or pack types may be marketed.

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

**7. HOLDER OF CERTIFICATE OF REGISTRATION**
Adcock Ingram Limited
1 New Road,
Erand Gardens,
Midrand, 1685
Customer Care: 0860 ADCOCK / 232625

**8. REGISTRATION NUMBER(S)**
41/3.2/0527

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
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**10. DATE OF REVISION OF THE TEXT**
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