SCHEDULING STATUS
S4

1. NAME OF THE MEDICINE
BONIVA® 3 mg/3 mL, Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
One pre-filled syringe contains 3 mg/3 mL ibandronic acid (as ibandronate monosodium salt, monohydrate).

Sugar free.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Injection

Clear, colourless solution in a pre-filled syringe.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
BONIVA 3 mg/3 mL 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 of BONIVA 3 mg/3 mL is 3 mg, administered as an intravenous injection over 15 – 30 seconds, every three months. Strict adherence to the intravenous route is required, see section 4.4.

Patients must receive supplemental calcium and vitamin D. See section sections 4.4 and 6.2.

If a dose is missed, the injection should be administered as soon as convenient. Thereafter, injections should be scheduled every 3 months from the date of the last injection.

Special populations
Renal impairment
No dosage adjustment is necessary for patients with mild or moderate renal impairment where serum creatinine is equal or below 200 µmol/L (2,3 mg/dL) or where creatinine clearance (measured or estimated) is equal or greater than 30 mℓ/min.

BONIVA 3 mg/3 mL is not recommended for use in patients who have a serum creatinine above 200 µmol/L (2,3 mg/dL) or who have a creatinine clearance (measured or estimated) below 30 mL/min, because of limited clinical data available from studies including such patients. See sections 4.3, 4.4 and 5.2.

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 3 mg/3 mL has not been tested in these age groups and should not be given to them.

Method of administration
For intravenous use.

4.3 Contraindications
- Hypersensitivity to ibandronic acid or to any of the excipients listed in section 6.1.
- Hypocalcaemia, see section 4.4.
- Severe renal impairment (creatinine clearance < 30 mL/min).

4.4 Special warnings and precautions for use
Administration failures
Strict adherence to the intravenous route of administration is required. Care must be taken not to administer BONIVA 3 mg/3 mL via intra-arterial or paravenous administration as this could lead to tissue damage.

Hypocalcaemia
BONIVA 3 mg/3 mL, administered intravenously, may cause a transient decrease in serum calcium values. Hypocalcaemia must be corrected before starting BONIVA 3 mg/3 mL therapy. Other disturbances of bone and mineral metabolism should also be effectively treated before starting BONIVA 3 mg/3 mL therapy.

All patients must receive adequate supplemental calcium and vitamin D.

Anaphylactic reaction/shock
Cases of anaphylactic reaction/shock, including fatal events, have been reported in patients treated with BONIVA 3 mg/3 mL.

Appropriate medical support and monitoring measures should be readily available when BONIVA 3 mg/3 mL is administered. If anaphylactic or other severe hypersensitivity/allergic reactions occur, immediately discontinue the injection and initiate appropriate treatment.

Renal impairment
Patients with concomitant diseases, or who use medicinal products which have potential for undesirable effects on the kidney, should be reviewed regularly in line with good medical practice during treatment.

Due to limited clinical experience, BONIVA 3 mg/3 mL is not recommended for patients with a serum creatinine above 200 µmol/L (2,3 mg/dL) or with a creatinine clearance below 30 mL/min. See sections 4.2, 4.3 and 5.2.

Patients with cardiac impairment
Overhydration should be avoided in patients at risk of cardiac failure.

Osteonecrosis of the jaw
Osteonecrosis of the jaw (ONJ) has been reported in patients treated with bisphosphonates including BONIVA 3 mg/3 mL. 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 (eg, 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).

Excipients with known effect
BONIVA 3 mg/3 mL is essentially sodium free.

4.5 Interaction with other medicines and other forms of interaction
Metabolic interactions are not considered likely, since BONIVA 3 mg/3 mL 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 BONIVA 3 mg/3 mL concentrations), and thus there is a low potential for medicine-medicine interaction due to displacement. BONIVA 3 mg/3 mL 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.

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.

4.6 Fertility, pregnancy and lactation
BONIVA 3 mg/3 mL should not be used during pregnancy and lactation.

Pregnancy
There are no adequate data from the use of BONIVA 3 mg/3 mL 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 3 mg/3 mL is excreted in human milk. Studies in lactating rats have demonstrated the presence of low levels of BONIVA in the milk following intravenous administration.

Fertility
There are no data on the effects of BONIVA 3 mg/3 mL from humans. In reproductive studies in rats by the oral route, BONIVA 3 mg/3 mL decreased fertility. In studies in rats using the intravenous route, BONIVA 3 mg/3 mL 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 BONIVA 3 mg/3 mL has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects
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”).

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

In the pivotal two-year study in postmenopausal women with osteoporosis (BM 16550), the overall proportion of patients who experienced an adverse reaction was 26,0 % and 28,6 % for BONIVA 3 mg /3 mL every 3 months after one year and two years, respectively. The majority of adverse reactions were mild to moderate in intensity. Most cases of adverse reactions 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 3 mg/3 mL every 3 months or ibandronic acid 2,5 mg daily in the phase III studies BM16550 and MF 4411, and in post-marketing experience.

System Organ Class	**Frequency**	**Adverse reaction**
Immune system disorders	Uncommon	Asthma exacerbation
	Rare	Hypersensitivity reactions
	Very rare	Anaphylactic reaction/shock*†
Metabolism and nutrition disorders	Uncommon	Hypocalcaemia†
Nervous system disorders	Common	Headache
Eye disorders	Rare	Ocular inflammation*†
Vascular disorders	Uncommon	Phlebitis/thrombophlebitis
Gastrointestinal disorders	Common	Gastritis, Dyspepsia, Diarrhoea, Abdominal pain, Nausea, Constipation
Skin and subcutaneous tissues disorders	Common	Rash
	Rare	Angioedema, Facial swelling/oedema, Urticaria
	Very rare	Stevens-Johnson Syndrome†, Erythema multiforme†, Dermatitis bullous†
Musculoskeletal and connective tissue disorders	Common	Arthralgia, Myalgia, Musculoskeletal pain, Back pain
	Uncommon	Bone pain
	Rare	Atypical subtrochanteric 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
General disorders and administration site conditions	Common	Influenza like illness*, Fatigue
	Uncommon	Injection site reactions, Asthenia

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

Description of selected adverse reactions

Influenza-like illness

Transient, influenza-like symptoms have been reported in patients receiving intravenous injection of BONIVA 3 mg/3 mL every 3 months, typically in association with the first dose. Influenza-like illness includes events reported as acute phase reaction or symptoms, including myalgia, arthralgia, fever, chills, fatigue, nausea, loss of appetite, and 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 the 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, consistent 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.

Laboratory test findings

In the pivotal two-year study with BONIVA 3 mg/3 mL every 3 months (BM16550) there was no difference compared with placebo for laboratory abnormalities indicative of hepatic or renal dysfunction, impaired haematologic system, hypocalcaemia or hypophosphataemia.

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 overdosage with BONIVA 3 mg/3 mL. Based on knowledge of this class of compounds, intravenous overdosage may result in hypocalcaemia, hypophosphataemia, and hypomagnesaemia. Clinically relevant reductions in serum levels of calcium, phosphorus, and magnesium should be corrected by intravenous administration of calcium gluconate, potassium or sodium phosphate, and magnesium sulphate, respectively.

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

Mechanism of action

Ibandronic acid is a bisphosphonate belonging to the nitrogen-containing group of bisphosphonates, which acts selectively on bone tissue and specifically inhibits 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 bone destruction experimentally induced 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)).

Both daily, intermittent (with a dose-free interval of 9 – 10 weeks per quarter) oral doses as well as intravenous doses of ibandronic acid in postmenopausal women produced biochemical changes indicative of dose-dependent inhibition of bone resorption.

Ibandronic acid intravenous injection decreased levels of serum C-telopeptide of the alpha chain of Type I collagen (CTX) within 3 – 7 days of starting treatment and decreased levels of osteocalcin within 3 months.

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 with doses of oral ibandronic acid 2,5 mg daily and intermittent intravenous doses of up to 1 mg every 3 months showed bone of normal quality and no indication of a mineralisation defect. An expected decrease in bone turnover, normal quality of bone and absence of defects in mineralisation were also seen after two years of treatment with ibandronic acid 3 mg injection.

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.

Plasma concentrations of ibandronic acid increase in a dose-proportional manner after intravenous administration of 0,5 mg to 6 mg.

Absorption

Not applicable.

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 ibandronic acid 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

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 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 the 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

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 is limited 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 above 30 mL/min). Subjects with severe renal impairment (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 sections 4.2, 4.3 and 4.4. The pharmacokinetics of ibandronic acid in patients with end-stage renal disease was only assessed in a small number of patients managed by haemodialysis. Therefore, the pharmacokinetics of ibandronic acid in the patients not undergoing haemodialysis is unknown. Due to the limited data available, ibandronic acid should not be used in all 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, renal function 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
Glacial acetic acid
Sodium acetate
Sodium chloride
Water for injection

6.2 Incompatibilities
BONIVA 3 mg/3 mL must not be mixed with calcium-containing solutions or other intravenously administered medicinal products.

6.3 Shelf life
2 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 4 pre-filled syringe(s) made of colourless glass and has a grey rubber plunger stopper and grey tip cap packed together with an injection stainless-steel needle(s), in an outer carton.

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
Adcock Ingram Limited
1 New Road,
Erand Gardens,
Midrand, 1685
Customer Care: 0860 ADCOCK / 232625

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