SCHEDULING STATUS:

S4

1. NAME OF THE MEDICINE

BONRIX 2 mg/2 ml (concentrate solution for dilution for IV infusion)

BONRIX 6 mg/6 ml (concentrate solution for dilution for IV infusion)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

BONRIX 2 mg/2 ml: Each vial contains 2 mg ibandronic acid per 2 ml

BONRIX 6 mg/6 ml: Each vial contains 6 mg ibandronic acid per 6 ml

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate solution for dilution for IV infusion

BONRIX 2 mg/2 ml injection: clear, colourless, sterile solution, free from visible particles.

BONRIX 6 mg/6 ml injection: clear, colourless, sterile solution, free from visible particles.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS:

BONRIX is indicated in:

- The treatment of tumour-induced hypercalcaemia with, or without metastases.
- Patients with breast cancer and bone metastases for the prevention of skeletal complications requiring radiotherapy.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

Posology

Treatment of Metastatic Bone Disease

The recommended dose for metastatic bone disease is 6 mg I.V given every 3 – 4 weeks. The dose should be infused over at least 15 minutes. For infusion, the contents of the vial should be added to 100 ml isotonic sodium chloride solution (or 100 ml of 5 % dextrose solution). A shorter (i.e. 15 min) infusion time should only be used for patients with normal renal function or mild renal impairment. There are no data available characterising the use of a shorter infusion time in patients with creatinine clearance below 50 ml/min. Refer to

the section further below, Patients with Renal Impairment, for recommendations on dosing and administration in this patient group.

Treatment of Tumour-induced Hypercalcaemia

Adults and elderly: Consideration should be given to the severity of hypercalcaemia as well as the tumour type.

In general, patients with osteolytic bone metastases require lower doses than patients with the humoral type of hypercalcaemia.

Recommended single dose: Prior to treatment with **BONRIX** injection solution, the patient should be adequately rehydrated with 0,9 % sodium chloride.

Warning: Overhydration should be avoided in patients at risk of cardiac failure/pulmonary oedema. Repeated treatment is possible in case of recurrent hypercalcaemia or insufficient efficacy. However, until adequate clinical experience has been gained, a cumulative dose of 6 mg should not be exceeded. **BONRIX** injection solution should be administered as an intravenous infusion.

The contents of the vials are to be added to 500 ml isotonic sodium chloride solution (or 500 ml of 5 % dextrose solution) and infused over 2 hours.

	Albumin-corrected serum calcium* after adequate rehydration	**Dose**
Severe hypercalcaemia	≥ 3,5 mmol/l (≥ 12 mg/dl)	2 – 4 mg
Moderate hypercalcaemia	< 3,5 mmol/l (< 12 mg/dl)	1 – 2 mg

The highest dose used in clinical trials (for hypercalcaemia) was 6 mg, but this dose does not add any further benefit in terms of efficacy.

*Note: Albumin-corrected serum calcium concentrations are calculated as follows:

Albumin-corrected serum calcium (mmol/l) = serum calcium (mmol/l) – [0,02 x albumin (g/L)] + 0,8.

or

Albumin-corrected serum calcium (mg/dl) = serum calcium (mg/dl + 0,8 x [4 – albumin (g/dl)]

To convert the albumin-corrected serum calcium in mmol/l value to mg/dl, multiply by 4.

In most cases a raised serum calcium level can be reduced to the normal range within 7 days. Median time to relapse (re-increase of serum albumin corrected serum calcium above 3 mmol/l) was 18 – 19 days for the 2 mg and 4 mg doses, and 26 days for the 6 mg dose.

Special populations:

Patients with hepatic impairment: No dosage adjustment is expected to be necessary. (See section 4.4).

Patients with renal impairment: For the prevention of skeletal events in patients with breast cancer and bone metastases the following recommendations should be followed:

Creatinine Clearance (ml/min)	**Dosage / infusion time [1]**	**Infusion Volume [2]**
≥ 50	6 mg / 15 minutes	100 ml
30 < CLcr < 50	6 mg / 1 hour	500 ml
< 30	2 mg / 1 hour	500 ml

[1] Administration every 3 to 4 weeks

[2] 0,9 % sodium chloride solution or 5 % glucose solution

A 15 minute infusion time has not been studied in cancer patients with CLcr < 50 ml/min.

Elderly: No dosage adjustment is necessary.

Paediatric population

Safety and efficacy have not been established in patients less than 18 years old.

Method of administration

- **BONRIX** should only be administered intravenously (IV).
- The concentrate solution for dilution for IV infusion is for single use only.
- Only clear solution without particles should be used.
- Unused solution should be discarded.

4.3 CONTRAINDICATIONS:

- **BONRIX** injection solution must not be used in patients with known hypersensitivity to ibandronate, or any of the excipients of **BONRIX** as listed in section 6.1, or in patients with known hypersensitivity to other bisphosphonates.

- **BONRIX** injection solution should not be used during pregnancy and lactation (see section 4.6 ~~**PREGNANCY AND LACTATION**~~).
- Hypocalcaemia.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

The inadvertent intra-arterial administration as well as perivenous administration is not recommended. This can lead to tissue damage. Ensure that **BONRIX** is only administered intravenously.

Patients under 18 years of age

- **BONRIX** injection solution should not be used in children and adolescents younger than 18 years due to lack of clinical experience.

Patients with disturbances of bone and mineral metabolism

- Hypocalcaemia should be corrected and other disturbances of bone and mineral metabolism should be effectively treated before starting **BONRIX** 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.

Anaphylactic reaction/shock

- Cases of anaphylactic reaction/shock, including fatal events, have been reported in patients treated with intravenous ibandronic acid.
- Appropriate medical support and monitoring measures should be readily available when **BONRIX** intravenous injection is administered. If anaphylactic or other severe hypersensitivity/allergic reactions occur, immediately discontinue the injection and initiate appropriate treatment.

Patients with known hypersensitivity to other bisphosphonates

- Caution is to be taken in patients with known hypersensitivity to other bisphosphonates.

Patients with renal impairment

- Clinical studies have not shown any evidence of deterioration in renal function with long term **BONRIX** therapy. Nevertheless, according to clinical assessment of the individual patient, it is recommended

that the renal function, serum calcium, phosphate, and magnesium should be monitored in patients treated with **BONRIX** (see section 4.2).

Patients with hepatic impairment

- As no clinical data are available, dosage recommendations cannot be given for patients with severe hepatic insufficiency (see section 4.2).

Patients with cardiac impairment

- Overhydration should be avoided in patients at risk of cardiac failure.

Osteonecrosis of the jaw (ONJ)

- 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.
- 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, including **BONRIX**. 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, such as **BONRIX**.
- A dental examination with appropriate preventive dentistry should be considered prior to treatment with bisphosphonates, such as **BONRIX** in patients with concomitant risk factors.
- The following risk factors should be considered:
    - Potency of the medicine that inhibits 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: chemotherapy, radiotherapy to head and neck, corticosteroids, angiogenesis inhibitors
    - 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 **BONRIX**. While on treatment, these patients should avoid invasive dental procedures if possible. For patients who develop osteonecrosis of the jaw while on

bisphosphonate therapy, such as BONRIX, dental surgery may exacerbate the condition. Clinical judgement of the treating medical practitioner should guide the management plan of each patient.

Osteonecrosis of the external auditory canal

- Osteonecrosis of the external auditory canal has been reported with bisphosphonates such as **BONRIX**, 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 such as **BONRIX** who present with ear symptoms including chronic ear infections.

Atypical fractures of the femur

- Atypical, low energy fractures of the subtrochanteric and proximal femoral shaft have been reported with long-term use (usually longer than 3 years) in bisphosphonate-treated patients. Some were stress fractures (also reported as insufficiency fractures) occurring in the absence of apparent trauma. Some patients experienced prodromal pain in the affected area, often associated with imaging features of stress fracture, weeks to months before a fracture occurred. Approximately one third of these fractures were bilateral; therefore the contralateral femur should be examined in patients who have sustained a femoral shaft stress fracture and receive appropriate orthopaedic care. Bisphosphonate treatment should be stopped in patients with stress fractures and they should receive appropriate orthopaedic care.
- 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 **BONRIX** 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 **BONRIX** 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.

Excipients with known effect

BONRIX contains less than 1 mmol sodium (23 mg) per vial, i.e., essentially sodium free.

4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

BONRIX should not be mixed with calcium containing solutions.

When co-administered with melphalan/prednisolone in patients with multiple myeloma no interaction was observed. Other interaction studies in postmenopausal women have demonstrated the absence of any interaction potential with tamoxifen or hormone replacement therapy (oestrogen). In 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 appears not to include known acidic or basic transport systems involved in the excretion of other medicines. In addition, 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. Plasma protein binding is low at therapeutic concentrations and ibandronic acid is therefore unlikely to displace other active substances.

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

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

Interaction studies have only been performed in adults.

4.6 FERTILITY, PREGNANCY AND LACTATION

BONRIX injection solution should not be used during pregnancy and lactation due to a lack of clinical experience. (See section 4.3).

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

On the basis of the pharmacodynamic and pharmacokinetic profile and reported adverse reactions, **BONRIX** causes headaches and dizziness and can affect the ability to drive and use machines.

4.8 UNDESIRABLE EFFECTS

Adequate intake of calcium and vitamin D is important in all patients. Patients should receive supplemental calcium or vitamin D if dietary intake is inadequate. Hypocalcaemia may occur and serum calcium level of patients should be corrected accordingly.

Frequently, decreased renal calcium excretion is accompanied by a fall in serum phosphate levels not requiring therapeutic measures. The serum calcium level may fall to hypocalcaemic values.

Tabulated list of adverse reactions

System organ class	**Frequency**	**Adverse reaction**
Infections and infestations	Frequent	Infection
	Less frequent	Cystitis, vaginitis, oral candidiasis
Neoplasms benign and malignant (including cysts and polyps)	Less frequent	Benign skin neoplasm
Blood and lymphatic system disorders	Less frequent	Anaemia, blood dyscrasia
Immune system disorders	Less frequent	Hypersensitivity, bronchospasm, angioedema, anaphylactic reaction/shock
	Frequency unknown	Asthma exacerbation
Endocrine disorders	Frequent	Parathyroid disorder
Metabolism and nutrition disorders	Frequent	Hypocalcaemia
	Less frequent	Hypophosphataemia
Psychiatric disorders	Less frequent	Sleep disorder, anxiety, affection lability
Nervous system disorders	Frequent	Headache, dizziness, dysgeusia (taste perversion)
	Less frequent	Cerebrovascular disorder, nerve root lesion, amnesia, migraine, neuralgia, hypertonia, hyperaesthesia, circumoral paraesthesia, parosmia
Eye disorders	Frequent	Cataract

	Less frequent	Ocular inflammation
Ear and labyrinth disorders	Less frequent	Deafness
Cardiac disorders	Frequent	Bundle branch block
	Less frequent	Myocardial ischaemia, cardiovascular disorder, palpitations
Vascular disorders	Less frequent	Hypertension, lymphoedema, varicose veins
Respiratory, thoracic and mediastinal disorders	Frequent	Pharyngitis
	Less frequent	Bronchospasm, lung oedema, stridor
Gastro-intestinal disorders	Frequent	Diarrhoea, vomiting, dyspepsia, gastrointestinal pain, tooth disorder
	Less frequent	Gastroenteritis, gastritis, mouth ulceration, dysphagia, cheilitis
Hepato-biliary disorders	Less frequent	Cholelithiasis
Skin and subcutaneous tissue disorders	Less frequent	Angioneurotic oedema, skin disorder, ecchymosis, rash, alopecia, Stevens-Johnson syndrome, erythema multiforme, dermatitis bullous
Musculoskeletal, connective tissue and bone disorders	Frequent	Bone pain, osteoarthritis, myalgia, arthralgia, joint disorder
	Less frequent	Atypical subtrochanteric and diaphyseal femoral fractures, osteonecrosis of jaw, osteonecrosis of the external auditory canal (bisphosphonate class adverse reaction)
Renal and urinary disorders	Less frequent	Urinary retention, renal cyst
Reproductive system and breast disorders	Less frequent	Pelvic pain
General disorders and administration site conditions	Frequent	Pyrexia (fever), influenza-like illness, peripheral oedema, asthenia, thirst
	Less frequent	Chills/ rigors, hypothermia, injection site pain

Investigations	Frequent	Increased Gamma-GT, increased creatinine
	Less frequent	Blood alkaline phosphatase increase, weight decrease
Injury, poisoning and procedural complications	Less frequent	Injury

Description of selected adverse reactions

Administration of other bisphosphonates has been associated with broncho-constriction in acetylsalicylic acid-sensitive asthmatic patients.

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.

Influenza-like illness

A flu-like syndrome consisting of fever, chills, bone and/or muscle ache-like pain can occur. In most cases no specific treatment is required and the symptoms subsided after a couple of hours/days.

Osteonecrosis of jaw

Cases of osteonecrosis of the jaw have been reported, predominantly in cancer patients treated with medicines that inhibit bone resorption, such as ibandronic acid (see section 4.4.)

Ocular inflammation

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

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.

Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 OVERDOSE

Symptoms may be an exacerbation of side-effects. Since both the kidney and the liver were found to be target organs for toxicity, kidney and liver function should be monitored. Clinically relevant hypocalcaemia should be corrected by i.v. administration of calcium gluconate. Standard haemodialysis procedures result in significant clearance of ibandronic acid.

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacological classification: A 3.2 Connective tissue medicines, Non-hormonal preparations

Pharmacotherapeutic group: Medicinal products for treatment of bone diseases, bisphosphonate, ATC Code: M05BA06.

Ibandronic acid is a bisphosphonate belonging to the nitrogen-containing group of bisphosphonates, which act on bone tissue and inhibit osteoclast activity. It does not interfere with osteoclast recruitment. The action of ibandronic acid on bone tissue is based on the high affinity of this compound for hydroxyapatite, which represents the mineral matrix of the bone.

Ibandronic acid reduces bone resorption, with no direct effect on bone formation. 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. The endogenous bone resorption is also inhibited, leading to increased bone mass compared with untreated animals.

In vitro, ibandronic acid pre-treatment of bone slices inhibited tumour cell attachment and spreading as well as tumour cell invasion. When added with tumour cells to untreated bone slices, ibandronic acid showed additive effects with cytotoxic medicines such as toxoids.

5.2 PHARMACOKINETIC PROPERTIES

Absorption: After infusion of 2, 4 and 6 mg ibandronic acid over 2 hours, pharmacokinetic parameters are dose proportional.

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 low (approximately 85 % bound at therapeutic 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 systemically available fraction of ibandronic acid is removed from the circulation via bone adsorption (40 – 50 %) and the remainder is eliminated unchanged by the kidney.

The range of observed apparent half-lives is broad and dependent on dose and assay sensitivity, but the apparent terminal plasma half-life is generally in the range of 10 – 60 hours. However, early plasma levels fall quickly, reaching 10 % of peak values within 3 hours after intravenous administration.

No systemic accumulation was observed when ibandronic acid was administered intravenously once every 4 weeks for 48 weeks to patients with metastatic bone disease.
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.

Special populations:

Patients with renal impairment: Exposure to ibandronic acid in patients with various degrees of renal impairment is related to creatinine clearance (CLcr). In a clinical pharmacology trial, after a single dose, intravenous administration of 6 mg (15 minutes infusion), mean AUC_{0-24} increased by 14 % and 86 %, respectively, in subjects with mild (mean estimated CLcr = 68,1 ml/min) and moderate (mean estimated CLcr = 41,2 ml/min) renal impairment compared to healthy volunteers (mean estimated CLcr = 120 ml/min). Mean C_{max} was not increased in patients with mild renal impairment and increased by 12 % in patients with moderate renal impairment. There is no evidence of a reduction in tolerability associated with an increase in exposure. However, an adjustment in the dose or infusion time, based on the creatinine clearance, is recommended in patients being treated for the prevention of skeletal events with breast cancer and bone metastases and who have renal impairment. See section 4.2.

Approximately 37 % of ibandronate was cleared from the body during a standard 4-hour haemodialysis procedure.

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. See section: "*Patients with renal impairment*", mentioned above.

Children: There are no data on the use of ibandronic acid in patients less than 18 years old

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Sodium chloride

Sodium acetate trihydrate

Glacial acetic acid

Water for injection

6.2 INCOMPATIBILITIES

BONRIX should only be diluted with 0,9 % sodium chloride or 5 % dextrose solution (see section 4.2)

BONRIX concentrate solution for dilution for IV infusion should not be mixed with calcium containing solutions.

6.3 SHELF LIFE

24 months

<u>After dilution:</u>

Mixtures are stable for 24 hours at 2 – 8 °C.

From a microbiological point of view, the intravenous infusion solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8 °C, unless reconstitution has taken place in controlled and validated aseptic conditions.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store at or below 25 °C.

Do not freeze.

For storage conditions of the diluted medicine, see section 6.3.

6.5 NATURE AND CONTENTS OF CONTAINER

BONRIX 2 mg/ 2ml is packaged in a 2 ml, clear, colourless glass vial (type I) with 20 mm grey rubber stopper and 20 mm aluminium seal with a lavender flip-off cap, which is further packed in an outer carton containing 1 vial.

BONRIX 6 mg/ 6ml is packaged in a 6 ml, clear, colourless glass vial (type I) with 20 mm grey rubber stopper and 20 mm aluminium seal with a pink flip-off cap, which is further packed in an outer carton containing 1 vial.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

The concentrate solution for dilution for IV infusion is for single use only.

Only clear solution without particles should be used.

Unused solution should be discarded.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Accord Healthcare (Pty) Ltd

Building 2, Tuscany Office Park

6 Coombe Place, Rivonia,

Gauteng,

South Africa.

8. REGISTRATION NUMBER:

BONRIX 2 mg/ 2 ml: 49/3.2/0583

BONRIX 6 mg/ 6 ml: 49/3.2/0584

9. DATE OF FIRST AUTHORISATION

11 June 2018

10. DATE OF REVISION OF THE TEXT

26 August 2022