SCHEDULING STATUS

S3

1 NAME OF THE MEDICINE

RISEDRONATE 35 BIOTECH, Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each RISEDRONATE 35 BIOTECH contains 35 mg monosodium risedronate hemipentahydrate equivalent to 35 mg risedronate sodium as the active pharmaceutical ingredient.

Excipient with known effect:

Contains sugar. Each tablet contains 120,0 mg lactose monohydrate.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablets

Orange, oval, biconvex, film-coated tablet, encoded 35 on one side, approximately 11,6 X 5,8 mm in size.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of osteoporosis in postmenopausal women in combination with calcium 500 to1 000 mg per day. Additional administration of vitamin D should be considered when deficiency might be expected.

4.2 Posology and method of administration

Posology

The recommended dose is one 35 mg tablet orally, once a week.

The tablet should be taken on the same day each week.

Special populations

Elderly

No dosage adjustment is necessary since bioavailability and disposition are similar in elderly (> 60 years of age) and younger subjects.

Renal impairment

No dosage adjustment is necessary in patients with creatinine clearance ≥30 ml/min RISEDRONATE 35 BIOTECH is contraindicated in patients with severe renal impairment (creatinine clearance <30 ml/min), (see section 4.3).

Paediatric population

Safety and efficacy of RISEDRONATE 35 BIOTECH have not been established in children and growing adolescents.

Method of administration

For oral administration.

Food, drinks (other than plain water) and other products containing polyvalent cations (such as

aluminium, calcium, iron or magnesium) decrease the absorption of RISEDRONATE 35 BIOTECH and should not be taken at the same time.

Therefore, RISEDRONATE 35 BIOTECH should be taken either, at least 30 minutes before the first food, or other medicine, or drink (other than plain water) of the day or, at least 2 hours away from food or drink at any other time of the day and at least 30 minutes before going to bed.

Patients should be instructed that if a dose is missed, one RISEDRONATE 35 BIOTECH tablet should be taken on the day that the tablet is remembered. Patients should then return to taking one tablet once a week on the day the tablet is normally taken. Two tablets should not be taken on the same day.

The tablets must be swallowed whole and not sucked or chewed.

Patients should take RISEDRONATE 35 BIOTECH while in an upright position (standing or sitting) with a glass of plain water (≥ 120 ml) to aid delivery to the stomach. Patients should not lie down for 30 minutes after taking the tablet (see section 4.4).

4.3 Contraindications

- Known hypersensitivity to risedronate sodium or to any of the excipients of RISEDRONATE 35 BIOTECH listed in section 6.1.
- Hypocalcaemia (see sections 4.4 and 4.8).
- Advanced renal impairment: creatinine clearance < 30 ml/min (see section 4.4).
- Pregnancy and lactation (see section 4.6).

4.4 Special warnings and precautions for use

Efficacy of bisphosphonates including RISEDRONATE 35 BIOTECH in the treatment of osteoporosis is related to the presence of low bone mineral density and/or prevalent fracture.

High age or clinical risk factors for fracture alone are not sufficient reasons to initiate treatment of osteoporosis with a bisphosphonate such as RISEDRONATE 35 BIOTECH.

The evidence to support efficacy of bisphosphonates including RISEDRONATE 35 BIOTECH in the very elderly (>80 years) is limited.

RISEDRONATE 35 BIOTECH may cause upper gastrointestinal disorders such as dysphagia, oesophagitis, oesophageal ulcer and gastric ulcer, and should be used with caution in patients with a history of upper gastrointestinal disorders.

Caution should be taken:

- in patients who have a history of oesophageal disorders which delay oesophageal transit or emptying e.g., stricture or achalasia
- in patients who are unable to stay in the upright position for at least 30 minutes after taking the tablet
- if RISEDRONATE 35 BIOTECH is given to patients with active or recent oesophageal or upper gastrointestinal problems (including known Barrett's oesophagus).

Prescribers should therefore emphasise the importance of the dosing instructions (see section 4.2) in patients who have a history of these disorders and be alert to any signs and symptoms oesophageal reaction.

These patients should be instructed to seek medical attention timeously if they develop any symptoms of oesophageal irritation such as dysphagia, pain on swallowing, retrosternal pain or new or worsened

heartburn (see section 4.8).

In order to facilitate delivery to the stomach and minimise the possibility of gastrointestinal adverse effects, patients should take RISEDRONATE 35 BIOTECH whole with a full glass of plain water while in an upright position (standing or sitting) and should avoid lying down for 30 minutes after taking this medication. Caution should therefore also be exercised in patients who are unable to stand or sit upright for at least 30 minutes.

Absorption of RISEDRONATE 35 BIOTECH is decreased by food, drinks (other than plain water) and other products containing aluminium, calcium, iron or magnesium, including antacids and mineral supplements and some osmotic laxatives and should not be taken at the same time.
Therefore, to achieve the proven benefits of RISEDRONATE 35 BIOTECH, patients should take the tablet either, at least 30 minutes before the first food, medicine or drink (other than plain water) of the day or, at least 2 hours away from food or drink at any other time of the day.

Hypocalcaemia and other disturbances of bone and mineral metabolism should be effectively treated before starting RISEDRONATE 35 BIOTECH therapy. Asymptomatic decreases in serum calcium and phosphorus levels have been observed. Adequate intake of calcium and vitamin D is important. Patients should receive supplemental calcium and vitamin D if dietary intake is inadequate.

The patient should be informed to pay particular attention to the dosing instructions as the clinical benefits may be compromised by failure to take RISEDRONATE 35 BIOTECH according to the instructions.

RISEDRONATE 35 BIOTECH is contraindicated in patients with severe renal impairment (creatinine clearance less than 30 ml/min) (see section 4.3).

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 or months before a facture occurred. Approximately one third of these fractures were bilateral; therefor the contralateral femur should be examined in patients who have sustained a femoral shaft stress fracture and receive appropriate orthopaedic care. Poor healing of these fractures have been reported.

RISEDRONATE 35 BIOTECH treatment should be stopped in patients with stress fractures and they should receive appropriate orthopaedic care.

During therapy with RISEDRONATE 35 BIOTECH, 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.

Osteonecrosis of the jaw has been reported by patients with osteoporosis receiving oral bisphosphonates such as RISEDRONATE 35 BIOTECH.

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

While on treatment, these patients should avoid invasive dental procedures if possible. Patients who develop osteonecrosis of the jaw while on bisphosphonate the dental surgery may exacerbate the condition. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of RISEDRONATE 35 BIOTECH treatment reduces the risk of osteonecrosis of the jaw. Clinical judgement of the treating medical practitioner should guide the management plan of each patient based on individual benefit/risk assessment.

Osteonecrosis of the external auditory canal has been reported with bisphosphonates such as RISEDRONATE 35 BIOTECH, 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 RISEDRONATE 35 BIOTECH who present with ear symptoms including chronic ear infections.

Excipients

Contains lactose. Patients with the rare hereditary problems of galactose intolerance, total lactase deficiency or, glucose-galactose malabsorption should not take RISEDRONATE 35 BIOTECH.

4.5 Interaction with other medicines and other forms of interaction

Absorption of RISEDRONATE 35 BIOTECH is decreased by food, drinks (other than plain water) and other products containing aluminium, calcium, iron or magnesium, including antacids and mineral

supplements and some osmotic laxatives (see section 4.4).

The use of RISEDRONATE 35 BIOTECH with aspirin and NSAIDs may result in an increased incidence of gastrointestinal irritation.

There may be additive hypo-calcaemic effects with aminoglycosides.

Risedronate sodium as contained in RISEDRONATE 35 BIOTECH is not systemically metabolised, does not induce cytochrome P450 enzymes, and has low protein binding.

RISEDRONATE 35 BIOTECH may be used concomitantly with hormone replacement therapy.

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of this preparation in pregnant women has not been established, therefore the use of RISEDRONATE 35 BIOTECH is contraindicated (see section 4.3

Breastfeeding

The safety of this preparation in lactating women has not been established, therefore the use of RISEDRONATE 35 BIOTECH is contraindicated (see section 4.3).

4.7 Effects on ability to drive and use machines

RISEDRONATE 35 BIOTECH has no or negligible influence on the ability to drive or use machinery.

4.8 Undesirable effects

a) Tabulated summary of adverse reactions

Blood and lymphatic system disorders	
Less frequent:	Anaemia, thrombocytopenia, leucopenia

Frequency unknown:	Eosinophilia, neutropenia
Immune system disorders	
Less frequent:	Hypersensitivity reactions
Frequency unknown:	Anaphylactic reaction, skin reactions including angioedema
Metabolism and nutrition disorders	
Less frequent:	Hypocalcaemia, hypophosphatemia
Nervous system disorders	
Frequent:	Headache
Psychiatric disorders	
Frequency unknown:	Insomnia, somnolence
Eye disorders	
Frequent:	Dry eyes, sore eye, conjunctivitis
Less frequent:	Uveitis, iritis, sclerites, episcleritis, non-specific conjunctivitis, abnormal vision, blurred vision
Gastrointestinal disorders	
Frequent:	Dyspepsia, nausea, vomiting, abdominal pain, constipation, diarrhoea, gastrointestinal disorders
Less frequent:	Oesophagitis, oesophageal ulcers or erosions, gastritis, dysphagia, duodenitis, glossitis, oesophageal stricture, peptic ulceration
Frequency unknown:	Flatulence, gastric haemorrhage, eructation, odynophagia
Hepato-biliary disorders	
Less frequent:	Abnormal liver function tests
Frequency unknown:	Serious hepatic disorders

Skin and subcutaneous tissue disorders	
Less frequent:	Generalised rash and bullous skin reactions, urticaria, angioedema, Stevens-Johnson syndrome, toxic epidermal necrolysis and leukocytoclastic vasculitis, hair loss
Frequency unknown:	Hyperhidrosis
Musculoskeletal, connective tissue and bone disorders	
Frequent:	Musculoskeletal pain, arthralgia, bone pain, osteonecrosis of the jaw, atypical femoral fractures, myalgia
Less frequent:	Atypical subtrochanteric and diaphyseal femoral fractures (bisphosphonate class adverse reaction), osteonecrosis of the ear canal
Reproductive system and breast disorders	
Frequency unknown:	Decreased libido
General disorders and administration site conditions	
Frequent:	Pain
Less frequent:	Fever, chills, fatigue, malaise
Frequency unknown:	Acute mountain sickness
Investigations	
Less frequent:	Oesophageal cancer

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 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

Decreases in serum calcium would be expected to occur with substantial overdose in some patients.

Milk or antacids containing magnesium, calcium or aluminium should be given to bind RISEDRONATE 35 BIOTECH and minimise absorption.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 3.2 Connective tissue medicines, non-hormonal preparation.

Pharmacotherapeutic group: Drugs affecting bone structure and mineralization, Bisphosphonates, ATC code: M05BA07

Risedronate sodium is a pyridinyl bisphosphonate that binds to bone hydroxyapatite and inhibits osteoclast-mediated bone resorption, while bone formation is preserved.

5.2 Pharmacokinetic properties

Absorption

Risedronate sodium is relatively rapidly absorbed after oral administration. Absorption is reduced by food, especially by products containing calcium or other polyvalent cations.

The mean bioavailability is 0,63 % in the fasting state, and is reduced by 30 % when given 1 hour before breakfast, and by 55 % when given half an hour before breakfast.

Distribution

Human plasma protein binding of the medicine is about 24 %.

Biotransformation

There is no evidence of systemic metabolism of risedronate sodium.

Elimination

Approximately half of the absorbed dose is excreted in the urine within 24 hours; and 85 % of an intravenous dose is recovered in the urine over 28 days the remainder is sequestered to bone for a prolonged period. Mean renal clearance is 105 ml/min and mean total clearance is 122 ml/min, with the difference primarily reflecting non-renal clearance or clearance due to absorption to bone. The renal clearance is not concentration dependent and there is a linear relationship between renal clearance and creatinine clearance.

Risedronate exhibits multi-exponential elimination. The plasma t½ for the first and second exponential phases is 9.0 and 13 hours, respectively. The longer terminal t½ reported is thought to represent dissociation of risedronate from the surface of bone. Following a 5 mg oral dose given once daily to healthy men.

Unabsorbed risedronate sodium is eliminated unchanged in the faeces.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Crospovidone

Lactose monohydrate

Magnesium stearate

Microcrystalline cellulose (PH 200)

Opadry orange consisting of:

Ferric oxide, yellow (E172)

Ferric oxide, red (E172)

Hypromellose

Macrogol

Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

12 months

6.4 Special precautions for storage

Store at or below 25 °C in the original packing until intended for use.

6.5 Nature and contents of container

White, HDPE containers with white tamper-evident screw caps containing 4 tablets or transparent PVC/

Al foil blister packs containing 4 tablets.

The blister strips are packed in the outer cardboard carton box.

6.6 Special precautions for disposal and other handling

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Biotech Laboratories (Pty) Ltd.

Ground Floor Block K West

400 16th Street,

Randjespark

Midrand, 1685

8 REGISTRATION NUMBER

43/3.2/1158

9 DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION

Date of registration: 20 June 2013

10 DATE OF REVISION OF THE TEXT

01 August 2024