FINAL PROFESSIONAL INFORMATION

SCHEDULING STATUS: S3

PROPRIETARY NAME AND DOSAGE FORM:

BONTELVIA 35 mg (film-coated tablet)

COMPOSITION:

Each film-coated tablet contains risedronate sodium 35 mg. Contains lactose.

Excipients: crospovidone, magnesium stearate and microcrystalline cellulose.

The coating ingredients contain: colloidal silicon dioxide, hydroxy propyl cellulose, hypermellose, iron oxide red (C.I. No: 77491), iron oxide yellow (C.I. No: 77492), polyethylene glycol and titanium dioxide (C.I. No: 77891).

PHARMACOLOGICAL CLASSIFICATION:

A 3.2 Connective Tissue medicines, Non hormonal preparations.

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

Risedronate sodium is a pyridinyl bisphosphonate that binds to bone hydroxyapatite and inhibits osteoclast-mediated bone resorption, while bone formation is preserved. In preclinical studies risedronate sodium demonstrated potent anti-osteoclast and antiresorptive activity, dose dependently. The activity of risedronate sodium was confirmed by bone marker measurements.

Pharmacokinetic properties:

Absorption: Absorption after an oral dose is relatively rapid (t_{max} ~1 hour) and occurs through out the upper gastrointestinal tract. Absorption is independent of dose over the range studied (single dose study, 2,5 to 30 mg; multiple dose studies, 2,5 to 5 mg daily and up to 50 mg dosed weekly). Mean oral bioavailability of the tablet is 0,63 % and is decreased significantly when risedronate sodium is administered with food.

Distribution:

Preclinical studies in rats and dogs dosed intravenously with single doses of [^{14}C]- risedronate sodium indicate that approximately 60 % of the dose is distributed to bone. The remainder of the dose is excreted in the urine.The mean steady state volume of distribution is 6,3 l/kg in humans. Human plasma protein binding is about 24 %.

Metabolism: There is no evidence of systemic metabolism of risedronate sodium.

Elimination:

Approximately half of the absorbed dose is excreted in urine within 24 hours, and 85 % of an intravenous dose is recovered in the urine over 28 days. 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 adsorption to bone. The renal clearance is not concentration dependent, and there is a linear relationship between renal clearance and creatinine clearance.
Unabsorbed risedronate sodium is eliminated unchanged in faeces. Once risedronate sodium is absorbed, the serum concentration-time profile is multiphasic with an initial half life of about 1,5 hours and a terminal exponential half-life of 480 hours.

Special populations:

Elderly and patients with renal impairment (See dosage and directions for use).

INDICATIONS:

Treatment of osteoporosis in postmenopausal women in combination with calcium 500 to 1000 mg per day. Additional administration of vitamin D should be considered when deficiency might be expected.

Treatment of primary osteoporosis in males.

CONTRA – INDICATIONS:

Known hypersensitivity to risedronate and any other ingredients of **BONTELVIA 35 mg**.

Hypocalcaemia (see WARNINGS AND SPECIAL PRECAUTIONS).

Advanced renal impairment: creatinine clearance < 30 ml/min.

Pregnancy and lactation.

WARNINGS AND SPECIAL PRECAUTIONS:

Efficacy of bisphosphonates including **BONTELVIA 35 mg** 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 **BONTELVIA 35 mg**.

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

Bisphosphonates, including **BONTELVIA 35 mg**, have been associated with oesophagitis, gastritis, oesophageal ulcerations and gastroduodenal ulcerations. Thus, caution should be used:

- 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 **BONTELVIA 35 mg** is given to patients with active or recent oesophageal or upper gastrointestinal problems (including known Barrett's oesophagus).

Medical practitioners should emphasise to patients the importance of paying attention to the dosing instructions and be alert to any signs and symptoms of possible oesophageal reaction. The patients should be instructed to seek timely medical attention if they develop symptoms of oesophageal irritation such as dysphagia, pain on swallowing, retrosternal pain or

new/worsened heartburn.

In order to facilitate delivery to the stomach and minimise the possibility of gastrointestinal adverse effects, patients should take **BONTELVIA 35 mg** while in an upright position (sitting or standing) with a full glass of plain water and should avoid lying down for 30 minutes after taking **BONTELVIA 35 mg**.

Foods, drinks (other than plain water) and medicinal products containing polyvalent cations (such as calcium, magnesium, iron and aluminium) interfere with the absorption of **BONTELVIA 35 mg** and should not be taken at the same time. Therefore to achieve the benefits of **BONTELVIA 35 mg**, 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 time of the day.

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

BONTELVIA 35 mg is contraindicated in patients with severe renal impairment (creatinine clearance less than 30 ml/min) (see CONTRA-INDICATIONS).

Osteonecrosis of the jaw, frequently associated with tooth extraction and/or local infection (including osteomyelitis) has been reported. Osteonecrosis of the jaw has also been reported in patients with osteoporosis receiving oral bisphosphonates such as **BONTELVIA 35 mg**.

A dental examination with appropriate preventive dentistry should be considered prior to treatment with **BONTELVIA 35 mg** 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. For patients who develop osteonecrosis of the jaw while on **BONTELVIA 35 mg** therapy, dental surgery may exacerbate the condition. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate (such as in **BONTELVIA 35 mg**) treatment reduces the risk of osteonecrosis of the jaw. Clinical judgment 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 including **BONTELVIA 35 mg**, 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 **BONTELVIA 35 mg** who present with ear symptoms including chronic ear infections.

Atypical fractures of the femur:

Atypical subtrochanteric and diaphyseal femoral fractures have been reported with **BONTELVIA 35 mg**, 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 **BONTELVIA 35 mg**-treated patients who have sustained a femoral shaft fracture. Poor healing of these fractures has also been reported. Discontinuation of **BONTELVIA 35 mg** 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 **BONTELVIA 35 mg** 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.

Effect on the ability to drive and use machines:

BONTELVIA 35 mg has no or negligible influence on the ability to drive and use machines.

Lactose warning:

BONTELVIA 35 mg contains lactose. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take **BONTELVIA 35 mg**.

BONTELVIA 35 mg contains lactose which may have an effect on the glycaemic control of patients with diabetes mellitus.

INTERACTIONS:

BONTELVIA 35 mg has been used with aspirin and NSAIDs.

BONTELVIA 35 mg may be used concomitantly with hormone replacement therapy.

Concomitant ingestion of medicines containing polyvalent cations (e.g. calcium, magnesium, iron and aluminium) will interfere with the absorption of **BONTELVIA 35 mg**.

BONTELVIA 35 mg is not systemically metabolised, does not induce cytochrome P450 enzymes and has low protein binding.

PREGNANCY AND LACTATION:

BONTELVIA 35 mg is contraindicated in pregnant and breastfeeding women (see CONTRA-INDICATIONS).

DOSAGE AND DIRECTIONS FOR USE:

The recommended dose is one 35 mg tablet orally once a week. The tablet should be taken on the same day each week. Foods, drinks (other than plain water) and medicinal products containing polyvalent cations (such as calcium, magnesium, iron and aluminum) may interfere with absorption of **BONTELVIA 35 mg** and should not be taken as same time. Therefore **BONTELVIA 35 mg** 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 **BONTELVIA 35 mg** 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 tablet must be swallowed whole and not sucked or chewed. Patients should take **BONTELVIA 35 mg** while in an upright (standing or sitting) position 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 Warnings and Special Precautions).

Elderly:

No dosage adjustment is necessary since bioavailability, and disposition were similar in elderly (>60 years of age) compared to younger patients.

Renal impairment:

No dosage adjustment is necessary in patients with creatinine clearance ≥ 30 ml/min. There is no clinical data in patients with severe renal impairment. (Creatinine clearance less than 30 ml/min) (see CONTRA-INDICATIONS).

Children:

Safety and efficacy of **BONTELVIA 35 mg** have not been established in children and growing adolescents.

SIDE EFFECTS

Immune system disorders:

Frequency not known: anaphylactic reaction, hypersensitivity and skin reactions including angioedema.

Eye disorders:

Less frequent: iritis.

Frequency not known: uveitis.

Gastrointestinal disorders:

Frequent: dyspepsia, nausea, constipation, diarrhoea, gastrointestinal disorders.

Less frequent: oesophagitis, oesophageal ulcer, gastritis, dysphagia, duodenitis, oesophageal stricture, abdominal pain, glossitis.

Frequency not known: flatulence, gastric haemorrhage, eructation, odynophagia.

Psychiatric disorders:

Frequency not known: insomnia, somnolence.

Nervous system disorders:

Frequent: headache.

Hepato-biliary disorders:

Less frequent: abnormal liver function tests.

Frequency not known: serious hepatic disorders.

Musculoskeletal and connective tissues disorders:

Frequent: musculoskeletal pain, arthralgia, bone pain.

Less frequent: osteonecrosis of the external auditory canal.

Frequency not known: osteonecrosis of the jaw, atypical subtrochanteric and diaphyseal femoral fractures.

Skin and subcutaneous disorders:

Frequency not known: generalised rash and bullous skin reactions, some severe including Stevens-Johnson syndrome toxic epidermal necrolysis, hyperhidrosis, hair loss, leukocytoclastic vasculitis.

Blood and lymphatic system disorders:

Frequency not known: eosinophilia, neutropenia.

Reproductive system and breast disorders:

Frequency not known: decreased libido.

General disorders:

Frequent: pain.

Frequency not known: fatigue, acute mountain sickness, pyrexia.

Investigations:

Frequency not known: Decreases in serum calcium and phosphate levels.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Decreases in serum calcium following overdose may be expected in some patients. Signs and symptoms of hypocalcaemia may also occur in some of these patients.

Milk or antacids containing magnesium, calcium or aluminium should be given to bind risedronate and reduce absorption of **BONTELVIA 35 mg**.

IDENTIFICATION:

Orange colour, circular, biconvex, film-coated tablet debossed with “CL 92” on one side and plain on other side.

PRESENTATION:

BONTELVIA 35 mg

1) Blister Pack:

Tablets are packed in Triplex 250/25/90 clear PVC/PE/PVdC as the forming material and 25 μ aluminium foil with 6-8 gsm heat seal lacquer as the lidding material. Each blister contains 4 tablets packed in a pre-printed unit carton.

Pack size: 4’s – Each carton contains 1 blister of 4 tablets each.

2) HDPE Container Pack:

Tablets are packed in white, round 40 ml HDPE container with 33 mm neck finish closed with 33 mm white closure with wad having induction sealing liner. Each container contains 30 tablets packed in a pre-printed unit carton.

Pack size: 30's - One HDPE container contains 30 tablets.

STORAGE INSTRUCTIONS:

Store at or below 25 °C. Protect from light.

Keep the blisters in the carton until required for use.

Keep HDPE containers well closed.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:

46/3.2/0904

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

Macleods Pharmaceuticals SA (Pty) Ltd

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