PROPOSED PROFESSIONAL INFORMATION

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

ACTAMAX 35 mg film coated tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains risedronate sodium hemipentahydrate equivalent to 35 mg risedronate sodium.

Contains sugar (lactose monohydrate 2 mg per tablet)

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Film coated tablet.

White, round, biconvex film coated tablets, embossed with “35” on one side, 11,2 ± 0,1 mm in diameter and 5,0 mm ± 0,2 mm in thickness.

4. CLINICAL PARTICULARS

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4.1 Therapeutic indications

ACTAMAX 35 mg is indicated in the treatment of osteoporosis in postmenopausal women, in combination with calcium 500 – 1000 mg per day. Additional administration of vitamin D should be considered, when vitamin D deficiency is expected.

Treatment of primary osteoporosis in males.

4.2 Posology and method of administration

Posology

Adults:

Take one 35 mg tablet orally, once a week on the same day each week.

Special populations

Elderly

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

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 < 30 ml/min) (see section 4.3).

Paediatric population

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

Method of administration

ACTAMAX 35 mg must be taken at least 30 minutes before the first food, liquid or any other medicine of the day other than water, at least two hours before or after food or liquid at any other time of the day and at least 30 minutes before going to bed. ACTAMAX 35 mg should not be taken at bedtime or before getting up in the morning. The tablets must be swallowed whole and not sucked or chewed.

Food, beverages and medicines containing calcium, magnesium, iron and aluminium may interfere with the absorption of ACTAMAX 35 mg and should not be taken at the same time.

Patients should take ACTAMAX 35 mg while in an upright 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 section 4.4).

Missed dose

One ACTAMAX 35 mg tablet should be taken on the day that the tablet is remembered if a dose is missed. 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.

4.3 Contraindications

- Hypersensitivity to risedronate or to any of the ingredients of ACTAMAX 35 mg.
- 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 ACTAMAX 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 ACTAMAX 35 mg.

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

- ACTAMAX 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 ACTAMAX 35 mg is given to patients with active or recent oesophageal or upper gastrointestinal problems (including known Barrett's oesophagus).
- Prescribers should emphasize the importance of the dosing instructions in patients who have a history of these disorders 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 (see section 4.8).

- ACTAMAX 35 mg should be taken while in an upright position (standing or sitting) with a full glass of water. Patients should not lie down for 30 minutes after taking ACTAMAX 35 mg and should not take ACTAMAX at bedtime, or before getting up for the day, in order to minimise the possibility of gastrointestinal adverse effects (see section 4.2).
- Foods, drinks and medicines containing calcium, magnesium, iron and aluminium may interfere with the absorption of ACTAMAX and should not be taken at the same time (see section 4.5). Therefore, to achieve the benefits of ACTAMAX 35 mg, the tablets should be taken at least 30 minutes before the first food, drink or any other medicine of the day, other than water. Failing this, ACTAMAX 35 mg should be taken two hours either before or after the intake of food or liquid.
- Hypocalcaemia and other disturbances of bone and mineral metabolism should be effectively treated before ACTAMAX 35 mg therapy is initiated. 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 clinical benefits may be compromised by failure to take ACTAMAX 35 mg according to instructions.
- ACTAMAX 35 mg is contraindicated in patients with severe renal impairment (creatinine clearance less than 30 ml/min) (see section 4.3).

- 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 ACTAMAX 35 mg.
- A dental examination with appropriate preventive dentistry should be considered prior to treatment with ACTAMAX 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 developed osteonecrosis of the jaw while on ACTAMAX 35 mg therapy, dental surgery may exacerbate the condition. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of ACTAMAX 35 mg 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 ACTAMAX 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 ACTAMAX 35 mg 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 patient's 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. Poor healing of these fractures has been reported.

- ACTAMAX 35 mg treatment should be stopped in patients with stress fractures and they should receive appropriate orthopaedic care.
- During therapy with ACTAMAX 35 mg, 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.

Information on excipients of ACTAMAX

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

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

4.5 Interaction with other medicines and other forms of interaction

- Concomitant use of medicines containing calcium, magnesium, iron and aluminium, including antacids, mineral supplements and some osmotic laxatives may interfere with the absorption of ACTAMAX 35 mg (see section 4.4).
- ACTAMAX 35 mg and concurrent use with aspirin and NSAID medicine may increase gastrointestinal irritation.
- ACTAMAX 35 mg may be used concomitantly with Hormone Replacement Therapy.
- There may be additive hypocalcaemic effects with aminoglycosides.
- ACTAMAX 35 mg is not systemically metabolised, does not induce cytochrome P450 enzymes and has low protein binding.

4.6 Fertility, pregnancy and lactation

The safety of ACTAMAX 35 mg in pregnancy and breastfeeding has not been established and use of ACTAMAX 35 mg is contraindicated (see section 4.3).

4.7 Effects on ability to drive and use machines

ACTAMAX 35 mg has no or negligible influence on the ability to drive and use machinery.

4.8 Undesirable effects

a) Tabulated summary of adverse reactions

System Organ Class	**Frequency**	**Side effects**
Blood and lymphatic system disorders	Less frequent Frequency unknown	Anaemia, thrombocytopenia, leukopenia Eosinophilia, neutropenia

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Immune system disorders	Frequent Frequency unknown	Hypersensitivity reactions Anaphylactic reaction, skin reactions including angioedema
Metabolism and nutrition disorders	Less frequent	Hypocalcaemia, hypophosphatemia
Psychiatric disorders	Frequency unknown	Insomnia, somnolence
Nervous system disorders	Frequent	Headache
Eye disorders	Frequent Less frequent	Dry eye, sore eye, conjunctivitis Iritis, scleritis, episcleritis, uveitis, non-specific conjunctivitis, abnormal vision, blurred vision
Gastrointestinal disorders	Frequent Less frequent Frequency unknown	Dyspepsia, nausea, vomiting, abdominal pain, constipation, diarrhoea, gastrointestinal disorders Oesophagitis, oesophageal ulcer, gastritis, dysphagia, duodenitis, glossitis, oesophageal stricture, peptic ulceration Flatulence, gastric haemorrhage, eructation, odynophagia
Hepato-biliary disorders	Frequent Frequency unknown	Abnormal liver function tests Serious hepatic disorders
Skin and subcutaneous tissue disorders	Less frequent Frequency unknown	Generalised rash and bullous skin reactions, urticaria, angioedema, Stevens-Johnson syndrome, toxic epidermal necrolysis and leukocytoclastic vasculitis, hair loss Hyperhidrosis

Musculoskeletal, connective tissue and bone disorders	Frequent Less frequent	Musculoskeletal pain, arthralgia, bone pain, atypical femoral fractures, myalgia Atypical subtrochanteric and diaphyseal femoral fractures (bisphosphonate class adverse reaction), osteonecrosis of the jaw and ear canal
Reproductive system and breast disorders	Frequency unknown	Decreased libido
General disorders and administrative site conditions	Frequent Less frequent Frequency unknown	Pain Fever, chills, fatigue, malaise Acute mountain sickness, pyrexia
Investigations	Less frequent Frequency unknown	Oesophageal cancer Decreases in serum calcium and phosphate levels

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

4.9 Overdose

Signs and symptoms

Although overdose with risedronate has not been reported, decreases in serum calcium would be expected to occur with substantial overdose.

Signs and symptoms of hypocalcaemia may also occur in some of these patients.

Management of overdose

Standard procedures for treatment of hypocalcaemia are to be followed. Milk or antacids containing magnesium, calcium or aluminium should be given to bind ACTAMAX 35 mg and reduce absorption of risedronate. In cases of substantial overdose, gastric lavage may be considered to remove unabsorbed medicine.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs affecting bone structure and mineralization, Bisphosphonates

ATC code: M05BA07

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

Risedronate sodium is an aminobisphosphonate, of the pyridinyl type. Risedronate binds to bone hydroxyapatite and at cellular level, inhibits osteoclast-mediated bone resorption, while bone formation is preserved. Preclinical studies indicated that risedronate reduces bone turnover (activation frequency, i.e. the number of sites at which bone is remodelled) and bone resorption at modelling sites.

5.2 Pharmacokinetic properties

Absorption

Risedronate is relatively rapidly (t_{max} ≈ 1 hour) and dose independently absorbed throughout the upper gastrointestinal tract. The mean oral bioavailability of risedronate is 0,63 % and is significantly decreased when administered with food. The bioavailability of risedronate was similar in men and women.

Distribution

Preclinical studies indicate that approximately 60 % of the dose of risedronate was distributed to bone with the remainder of the dose being excreted in the urine. The mean steady state volume of distribution is 6,3 L/kg of body weight in humans. Risedronate has a low human plasma protein binding of about 24 %.

Biotransformation

There is no evidence that risedronate is metabolised systemically.

Elimination

The unabsorbed risedronate is faecally eliminated unchanged. Renal risedronate is eliminated unchanged, with approximately 50 % of the absorbed dose excreted in urine within 24 hours and 85 % 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 absorption to bone. The renal clearance is not concentration dependent and there is a linear relationship between renal clearance and creatinine clearance. The initial half–life of risedronate is about 1,5 hours and the terminal exponential half-life 480 hours.

Pharmacokinetics in special patient groups

Elderly and patients with renal impairment (see section 4.2).

5.3 Preclinical safety data

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Crospovidone

Magnesium stearate

Microcrystalline cellulose

Pregelatinised starch

Film coating (Opadry white):

Hypromellose

Lactose monohydrate

Macrogol/PEG 4000

Titanium dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

60 months

6.4 Special precautions for storage

Store at or below 25 °C.

Do not remove from the outer carton until required for use.

6.5 Nature and contents of container

Tablets are packed in white opaque PVC/PE/PVDC and silver aluminium blister strips of 1 x 4 tablets each inside a printed outer carton.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

Pharma Dynamics (Pty) Ltd

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8. REGISTRATION NUMBER

A42/3.2/0455

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