SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Risedronate sodium 5 mg film-coated tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 5 mg risedronate sodium (equivalent to 4.64 mg risedronic acid).

Excipients with known effect:
Each film-coated tablet contains 21.6 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

SUMMARY OF PRODUCT CHARACTERISTICS

3 PHARMACEUTICAL FORM

Film-coated tablets.
Light-yellow coloured, round, film-coated tablets of 4.6 mm diameter, debossed with "5" on one side and plain on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of postmenopausal osteoporosis, to reduce the risk of vertebral fractures. Treatment of established postmenopausal osteoporosis, to reduce the risk of hip fractures. Prevention of osteoporosis in postmenopausal women with increased risk of osteoporosis (see section 5.1).

To maintain or increase bone mass in postmenopausal women undergoing long-term (more than 3 months), systemic corticosteroid treatment at doses ≥ 7.5mg/day prednisone or equivalent.

4.2 Posology and method of administration

Posology

The recommended daily dose in adults is one 5 mg tablet orally.

Special populations
Elderly: No dosage adjustment is necessary since bioavailability, distribution and elimination were similar in elderly (>60 years of age) compared to younger subjects.

Renal Impairment: No dosage adjustment is required for those patients with mild to moderate renal impairment. The use of risedronate sodium is contraindicated in patients with severe renal impairment (creatinine clearance lower than 30 ml/min) (see sections 4.3 and 5.2).

Paediatric population: Risedronate sodium is not recommended for use in children below age 18 due to insufficient data on safety and efficacy (also see section 5.1).

Method of administration
The absorption of Risedronate sodium 5 mg is affected by food, thus to ensure adequate absorption patients should take Risedronate sodium 5 mg:

- Before breakfast: At least 30 minutes before the first food, other medicinal product or drink (other than plain water) of the day.

In the particular instance that before breakfast dosing is not practical, Risedronate sodium 5 mg can be taken between meals or in the evening at the same time every day, with strict adherence to the following instructions, to ensure Risedronate sodium 5 mg is taken on an empty stomach:

- Between meals: Risedronate sodium 5 mg should be taken at least 2 hours before and at least 2 hours after any food, medicinal product or drink (other than plain water).
- In the evening: Risedronate sodium 5 mg should be taken at least 2 hours after the last food, medicinal product or drink (other than plain water) of the day. Risedronate sodium 5 mg should be taken at least 30 minutes before going to bed.

If an occasional dose is missed, Risedronate sodium 5 mg can be taken before breakfast, between meals, or in the evening according to the instructions above.

The tablets must be swallowed whole and not sucked or chewed. To aid delivery of the tablet to the stomach Risedronate sodium 5 mg is to be taken while in an upright position with a glass of plain water (≥120 ml). Patients should not lie down for 30 minutes after taking the tablet (see section 4.4).

Supplemental calcium and vitamin D should be considered if the dietary intake is inadequate.

The optimal duration of bisphosphonate treatment for osteoporosis has not been established. The need for continued treatment should be re-evaluated periodically based on the benefits and potential risks of risedronate on an individual patient basis, particularly after 5 or more years of use.

4.3 Contraindications

Hypersensitivity to risedronate sodium or to any of the excipients listed in section 6.1.

Hypocalcaemia (see section 4.4).

Pregnancy and lactation.

Severe renal impairment (creatinine clearance <30ml/min).

4.4 Special warnings and precautions for use

Foods, drinks (other than plain water) and medicinal products containing polyvalent cations (such as calcium, magnesium, iron and aluminium) interfere with the absorption of bisphosphonates and should not be taken at the same time as Risedronate sodium 5 mg (see section 4.5) In order to achieve the intended efficacy, strict adherence to dosing recommendations is necessary (see section 4.2).
Efficacy of bisphosphonates in the treatment of postmenopausal osteoporosis is related to the presence of low bone mineral density (BMD T-score at hip or lumbar spine ≤-2.5 SD) and/or prevalent fracture.
High age or clinical risk factors for fracture alone are not reasons to initiate treatment of osteoporosis with a bisphosphonate.
The evidence to support efficacy of bisphosphonates including Risedronate sodium 5 mg in very elderly women (>80 years) is limited (see section 5.1).

Bisphosphonates 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 risedronate is given to patients with active or recent oesophageal or upper gastrointestinal problems (including known Barrett's oesophagus).

Prescribers should emphasise to patients the importance of paying attention to the dosing instructions and be alert to any signs or 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.

Hypocalcaemia should be treated before starting Risedronate sodium 5 mg therapy. Other disturbances of bone and mineral metabolism (e.g. parathyroid dysfunction, hypovitaminosis D) should be treated at the time of starting Risedronate sodium 5 mg therapy.

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. 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.

A dental examination with appropriate preventive 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. For patients who develop osteonecrosis of the jaw 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 osteonecrosis of the jaw.

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 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.

This medicine contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

No formal interaction studies have been performed, however no clinically relevant interactions with other medicinal products were found during clinical trials.

In the Risedronate sodium 5 mg Phase III osteoporosis studies, acetyl salicylic acid or NSAID use was reported by 33% and 45% of patients respectively.

If considered appropriate risedronate sodium may be used concomitantly with oestrogen supplementation.

Concomitant ingestion of medications containing polyvalent cations (e.g. calcium, magnesium, iron and aluminium) will interfere with the absorption of risedronate sodium (see section 4.4).

Risedronate sodium is not systemically metabolised, does not induce cytochrome P450 enzymes, and has low protein binding.

4.6 Fertility, pregnancy and lactation

There are no adequate data from the use of risedronate sodium in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Studies in animal indicate that a small amount of risedronate sodium pass into breast milk.

Risedronate sodium 5 mg must not be used during pregnancy or by breast-feeding women.

4.7 Effects on ability to drive and use machines

No effects on ability to drive and use machines have been observed.

4.8 Undesirable effects

Risedronate sodium has been studied in phase III clinical trials involving more than 15,000 patients.
The majority of undesirable effects observed in clinical trials were mild to moderate in severity and usually did not require cessation of therapy.

Adverse experiences reported in phase III clinical trials in postmenopausal women with osteoporosis treated for up to 36 months with risedronate 5mg/day (n=5020) or placebo (n=5048) and considered possibly or probably related to risedronate are listed below using the following convention (incidences versus placebo are shown in brackets): very common (≥1/10); common (≥1/100; <1/10); uncommon (≥1/1,000; <1/100); rare (≥1/10,000; <1/1,000); very rare (<1/10,000).

Nervous system disorders:
Common: headache (1.8% vs. 1.4%)

Eye disorders:
Uncommon: iritis*

Gastrointestinal disorders:
Common: constipation (5.0% vs. 4.8%), dyspepsia (4.5% vs. 4.1%), nausea (4.3% vs. 4.0%), abdominal pain (3.5% vs. 3.3%), diarrhoea (3.0% vs. 2.7%)

Uncommon: gastritis (0.9% vs. 0.7%), oesophagitis (0.9% vs. 0.9%), dysphagia (0.4% vs. 0.2%), duodenitis (0.2% vs. 0.1%), oesophageal ulcer (0.2% vs. 0.2%)
Rare: glossitis (<0.1% vs. 0.1%), oesophageal stricture (<0.1% vs. 0.0%)

Musculoskeletal and connective tissues disorders:
Common: musculoskeletal pain (2.1% vs. 1.9%)
Very rare: Osteonecrosis of the external auditory canal (bisphosphonate class adverse reaction).

Investigations:
Rare: abnormal liver function tests*

* No relevant incidences from Phase III osteoporosis studies; frequency based on adverse event/laboratory/rechallenge findings in earlier clinical trials.

Laboratory findings: Early, transient, asymptomatic and mild decreases in serum calcium and phosphate levels have been observed in some patients.

The following additional adverse reactions have been reported during post-marketing use (frequency unknown):

Eye disorders:
iritis, uveitis

Musculoskeletal and connective tissues disorders:
osteonecrosis of the jaw

Skin and subcutaneous tissue disorders:
hypersensitivity and skin reactions, including angioedema, generalised rash, urticaria and bullous skin reactions, some severe including isolated reports of Stevens-Johnson syndrome, toxic epidermal necrolysis and leukocytoclastic vasculitis.
hair loss.

Immune system disorders:
anaphylactic reaction

Hepatobiliary disorders:
serious hepatic disorders. In most of the reported cases the patients were also treated with other products known to cause hepatic disorders.

During post-marketing experience the following reactions have been reported (frequency rare):
Atypical subtrochanteric and diaphyseal femoral fractures (bisphosphonate class adverse reaction).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

No specific information is available on the treatment of overdose with risedronate sodium.

Decreases in serum calcium following substantial overdose may be expected. 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 risedronate sodium. In cases of substantial overdose, gastric lavage may be considered to remove unabsorbed risedronate sodium.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmaco-therapeutic group: Bisphosphonates

ATC Code: M05BA07.

Mechanism of action
Risedronate sodium is a pyridinyl bisphosphonate that binds to bone hydroxyapatite and inhibits osteoclast-mediated bone resorption. The bone turnover is reduced while the osteoblast activity and bone mineralisation is preserved.

Pharmacodynamic effects
In preclinical studies risedronate sodium demonstrated potent anti-osteoclast and anti-resorptive activity, and dose dependently increased bone mass and biomechanical skeletal strength. The activity of risedronate sodium was confirmed by measuring biochemical markers for bone turnover during pharmacodynamic and clinical studies. Decreases in biochemical markers of bone turnover were observed within 1 month and reached a maximum in 3-6 months.

Clinical efficacy and safety
Treatment and Prevention of Postmenopausal Osteoporosis*:*
A number of risk factors are associated with postmenopausal osteoporosis including low bone mass, low bone mineral density, early menopause, a history of smoking and a family history of osteoporosis. The clinical consequence of osteoporosis is fractures. The risk of fractures is increased with the number of risk factors.

The clinical programme studied the effect of risedronate sodium on the risk of hip and vertebral fractures and contained early and late postmenopausal women with and without fracture. Daily doses of 2.5 mg and 5 mg were studied and all groups, including the control groups, received calcium and vitamin D (if baseline levels were

low). The absolute and relative risk of new vertebral and hip fractures were estimated by use of a time-to-first event analysis.

- Two placebo-controlled trials (n=3,661) enrolled postmenopausal women under 85 years with vertebral fractures at baseline. Risedronate sodium 5 mg daily given for 3 years reduced the risk of new vertebral fractures relative to the control group. In women with respectively at least 2 or at least 1 vertebral fractures, the relative risk reduction was 49% and 41% respectively (incidence of new vertebral fractures with risedronate sodium 18.1% and 11.3%, with placebo 29.0% and 16.3%, respectively). The effect of treatment was seen as early as the end of the first year of treatment. Benefits were also demonstrated in women with multiple fractures at baseline. Risedronate sodium 5 mg daily also reduced the yearly height loss compared to the control group.

- Two further placebo controlled trials enrolled postmenopausal women above 70 years with or without vertebral fractures at baseline. Women 70-79 years were enrolled with femoral neck BMD T-score <-3 SD (manufacturer's range, i.e. -2.5 SD using NHANES III (National Health and Nutrition Examination Survey)) and at least one additional risk factor. Women ≥80 years could be enrolled on the basis of at least one non-skeletal risk factor for hip fracture or low bone mineral density at the femoral neck. Statistical significance of the efficacy of risedronate sodium versus placebo is only reached when the two treatment groups 2.5 mg and 5 mg are pooled. The following results are only based on *a-posteriori* analysis of subgroups defined by clinical practise and current definitions of osteoporosis:

    - In the subgroup of patients with femoral neck BMD T-score ≤-2.5SD (NHANES III) and at least one vertebral fracture at baseline, risedronate sodium given for 3 years reduced the risk of hip fractures by 46% relative to the control group (incidence of hip fractures in combined risedronate sodium 2.5 and 5 mg groups 3.8%, placebo 7.4%);

    - Data suggest that a more limited protection than this may be observed in the very elderly (≥80 years). This may be due to the increasing importance of non-skeletal factors for hip fracture with increasing age.

In these trials, data analysed as a secondary endpoint indicated a decrease in the risk of new vertebral fractures in patients with low femoral neck BMD without vertebral fracture and in patients with low femoral neck BMD with or without vertebral fracture.

- Risedronate sodium 5 mg daily given for 3 years increased bone mineral density (BMD) relative to control at the lumbar spine, femoral neck, trochanter and wrist and prevented bone loss at the mid-shaft radius.
- In a one-year follow-up off therapy after three years treatment with risedronate sodium 5 mg daily there was rapid reversibility of the suppressing effect of risedronate sodium on bone turnover rate.
- In postmenopausal women taking oestrogen, risedronate sodium 5 mg daily increased bone mineral density (BMD) at the femoral neck and mid-shaft radius only, compared to oestrogen alone.
- Bone biopsy samples from postmenopausal women treated with risedronate sodium 5 mg daily for 2 to 3 years, showed an expected moderate decrease in bone turnover. Bone formed during risedronate sodium treatment was of normal lamellar structure and bone mineralisation. These data together with the

decreased incidence of osteoporosis related fractures at vertebral sites in women with osteoporosis appear to indicate no detrimental effect on bone quality.

- Endoscopic findings from a number of patients with a number of moderate to severe gastrointestinal complaints in both risedronate sodium and control patients indicated no evidence of treatment related gastric, duodenal or oesophageal ulcers in either group, although duodenitis was uncommonly observed in the risedronate sodium group.
- In a trial comparing before-breakfast dosing and dosing at other times of the day in women with postmenopausal osteoporosis, lumbar spine BMD gains were statistically higher with before-breakfast dosing.
- In osteopenic postmenopausal women, risedronate sodium has shown superiority to placebo in increasing lumbar spine BMD at 12 and 24 months.

Corticosteroid Induced Osteoporosis: The clinical programme included patients initiating corticosteroid therapy (≧ 7.5 mg/day prednisone or equivalent) within the previous 3 months or patients who had been taking corticosteroids for more than 6 months. Results of these studies demonstrate that:

- Risedronate sodium 5 mg daily given for one year maintains or increases bone mineral density (BMD) relative to control at the lumbar spine, femoral neck, and trochanter.
- Risedronate sodium 5 mg daily reduced the incidence of vertebral fractures, monitored for safety, relative to control at 1 year in pooled studies.
- histological examination of bone biopsies from patients taking corticosteroids and risedronate sodium 5 mg daily did not show signs of disturbed mineralisation process.

Paediatric population: The safety and efficacy of risedronate sodium has been investigated in a 3 year study (a randomized, double-blind, placebo-controlled, multicenter, parallel group study of one-year duration followed by 2 years of open-label treatment) in paediatric patients aged 4 to less than 16 years with mild to moderate osteogenesis imperfecta. In this study, patients weighing 10-30 kg received risedronate 2.5 mg daily and patients weighing more than 30 kg received risedronate 5 mg daily.
After completion of its one-year randomized, double-blind, placebo controlled phase, a statistically significant increase in lumbar spine BMD in the risedronate group versus placebo group was demonstrated; however an increased number of patients with at least 1 new morphometric (identified by x-ray) vertebral fracture was found in the risedronate group compared to placebo. During the one year double blind period, the percentage of patients who reported clinical fractures was 30.9% in the risedronate group and 49.0% in the placebo group.

In the open label period when all patients received risedronate (month 12 to month 36), clinical fractures were reported by 65.3% of patients initially randomized to the placebo group and by 52.9% of patients initially randomized to the risedronate group. Overall, results do not support the use of risedronate sodium in paediatric patients with mild to moderate osteogenesis imperfecta.

5.2 Pharmacokinetic properties

Absorption: Absorption after an oral dose is relatively rapid (tmax ~1 hour) and is independent of dose over the range studied (2.5 to 30 mg). Mean oral bioavailability of the tablet is 0.63% and is decreased when risedronate sodium is administered with food. Bioavailability was similar in men and women.

Distribution: The mean steady state volume of distribution is 6.3 l/kg in humans. Plasma protein binding is about 24%.

Biotransformation: 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 after 28 days. Mean renal clearance is 105 ml/min and mean total clearance is 122 ml/min, with the difference probably attributed to 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. After oral administration the concentration-time profile shows three elimination phases with a terminal half-life of 480 hours.

Special populations:
Elderly: no dosage adjustment is necessary.

Acetyl salicylic acid/NSAID users: Among regular acetyl salicylic acid or NSAID users (3 or more days per week) the incidence of upper gastrointestinal adverse events in Risedronate sodium treated patients was similar to that in control patients.

5.3 Preclinical safety data

In toxicological studies in rat and dog dose dependent liver toxic effects of risedronate sodium were seen, primarily as enzyme increases with histological changes in rat. The clinical relevance of these observations is unknown. Testicular toxicity occurred in rat and dog at exposures considered in excess of the human therapeutic exposure. Dose related incidences of upper airway irritation were frequently noted in rodents. Similar effects have been seen with other bisphosphonates. Lower respiratory tract effects were also seen in longer term studies in rodents, although the clinical significance of these findings is unclear. In reproduction toxicity studies at exposures close to clinical exposure ossification changes were seen in sternum and/or skull of foetuses from treated rats and hypocalcemia and mortality in pregnant females allowed to deliver. There was no evidence of teratogenesis at 3.2mg/kg/day in rat and 10mg/kg/day in rabbit, although data are only available on a small number of rabbits.

Maternal toxicity prevented testing of higher doses. Studies on genotoxicity and carcinogenesis did not show any particular risks for humans.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core: Lactose monohydrate
Microcrystalline cellulose
Crospovidone
Magnesium stearate.

Film coating: Hypromellose
Titanium Dioxide
Macrogol
Hydroxypropyl Cellulose
Iron oxide yellow
Colloidal Anhydrous Silica

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

OPA-Al-PVC/aluminium foil blisters of 10 or 14 tablets in a cardboard carton.

14 , 20 (2 x 10), 28 (2 x 14), 30 (3 x 10), 84 (6 x 14) or 98 (7 x 14) tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Waymade Healthcare Plc trading as Sovereign Medical

Sovereign House

Miles Gray Road

Basildon

Essex, SS14 3FR

United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

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