Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Riseseus 30 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film−coated tablet contains 30 mg risedronate sodium (amorphous), equivalent to 27.84 mg risedronic acid.

Excipient:
Each film−coated tablet contains 131.3 mg lactose monohydrate.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film−coated tablet.

White 8.5 mm round, biconvex, film−coated tablet.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of Paget's disease of the bone.

4.2 Posology and method of administration

The recommended daily dose in adults is one 30 mg tablet orally for 2 months. If re-treatment is considered necessary (at least two months post-treatment), a new treatment with the same dose and duration of therapy could be given. The absorption of Riseseus 30 mg Film-coated Tablets is affected by food, thus to ensure adequate absorption patients should take Riseseus 30 mg Film-coated Tablets:

– 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, Riseseus 30 mg Film-coated Tablets can be taken between meals or in the evening at the same time everyday, with strict adherence to the following instructions, to ensure Riseseus 30 mg Film-coated Tablets is taken on an empty stomach:

- Between meals: Riseseus 30 mg Film-coated Tablets 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: Riseseus 30 mg Film-coated Tablets should be taken at least 2 hours after the last food, medicinal product or drink (other than plain water) of the day Riseseus 30 mg Film-coated Tablets should be taken at least 30 minutes before going to bed.

If an occasional dose is missed, Riseseus 30 mg Film-coated Tabletscan be taken before breakfast, between meals, or in the evening according to the instructions above.

The tablet must be swallowed whole and not sucked or chewed. To aid delivery of the tablet to the stomach Riseseus 30 mg Film-coated Tablets are 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).

Physicians should consider the administration of supplemental calcium and vitamin D if the dietary intake is inadequate, especially as bone turnover is significantly elevated in Paget's disease.

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 in not recommended for use in children below age 18 due to insufficient data on safety and efficacy (see also section 5.1

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients.
- Hypocalcaemia (see section 4.4).
- Pregnancy and lactation.
- Severe renal impairment (creatinine clearance < 30 ml/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 (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 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.

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.

The evidence to support efficacy of bisphosphonates including risedronate sodium in the very elderly (> 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 sodium is given to patients with active or recent oesophageal or upper gastrointestinal problems.

Prescribers 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.

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

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.

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 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 sodium 5 mg/day (n=5020) or placebo (n=5048) and considered possibly or probably related to risedronate sodium are listed below using the following convention (incidences versus placebo are shown in brackets):
Very common (≥1/10)
Common (≥1/100 to <1/10),
Uncommon (≥1/1,000 to <1/100),
Rare (≥1/10,000 to <1/1,000),
Very rare (<1/10,000),
Not known (cannot be estimated from the available data).

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%)

Investigations
Rare: Abnormal liver function tests*
Early, transient, asymptomatic and mild decreases in serum calcium and phosphate levels have been observed in some patients.

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

In a one-year, double-blind, multicentre study comparing risedronate sodium 5 mg daily (n= 480) and risedronate sodium 35 mg weekly (n=485) in postmenopausal women with osteoporosis, the overall safety and tolerability profiles were similar. The following additional adverse experiences considered possibly or probably drug related by investigators have been reported (incidence greater in risedronate 35 mg than in risedronate sodium 5 mg group): gastrointestinal disorder (1.6% vs. 1.0%) and pain (1.2% vs. 0.8%).

In a 2−year study in men with osteoporosis, the overall safety and tolerability were similar between the treatment and the placebo groups. Adverse experiences were consistent with those previously observed in women.

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

Immune system disorders
Not known: Anaphylactic reaction.

Eye disorders
Not known: Iritis, uveitis.

Hepatobiliary disorders
Not known: Serious hepatic disorders. In most of the reported cases the patients were also treated with other products known to cause hepatic disorders.

Skin and subcutaneous tissue disorders
Not known: Hypersensitivity and skin reactions, including angioedema, generalised rash, urticaria, bullous skin reactions and leukocytoclastic vasculitis, some severe including isolated reports of Stevens Johnson syndrome and toxic epidermal necrolysis.
Hair loss.

Muskuloskeletal and connective tissues disorders
Not known: Osteonecrosis of the jaw.

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

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

Pharmacotherapeutic group: Bisphosphonates, ATC code: M05 BA07

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.

Paget's disease of the bone: In the clinical programme Riseseus 30 mg Film-coated Tablets was studied in patients with Paget's disease. After treatment with Riseseus 30 mg/day for 2 months the following was seen:

- serum alkaline phosphatase normalised in 77% of patients compared to 11% in the control group (etidronate 400 mg/day for 6 months). Significant reductions were observed in urinary hydroxyproline/creatinine and urinary deoxypyridinoline/creatinine
- radiographs taken at baseline and after 6 months demonstrated a decrease in the extent of osteolytic lesions in both the appendicular and axial skeleton. No new fractures were observed.

The observed response was similar in pagetic patients regardless of whether they had previously received other treatments for Paget's disease, or the severity of the disease.

53% of patients followed for 18 months after initiation of a single 2 month course of Riseseus 30 mg Film-coated Tablets remained in biochemical remission.

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.

Paediatric population: The safety and efficacy of risedronate sodium is being investigated in an on-going study of paediatric patients aged 4 to less than 16 years with osteogenesis imperfecta. 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 at least 1 new morphometric (identified by x-ray) vertebral fracture was found in the risedronate group compared to placebo. Overall, results do not support the use of risedronate sodium in paediatric patients with osteogenesis imperfecta.

5.2 Pharmacokinetic properties

Absorption: Absorption after an oral dose is relatively rapid (t_{max} ~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%.

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 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.

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 3.2 mg/kg/day in rat and 10 mg/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:
Magnesium stearate
Crospovidone
Lactose monohydrate
Microcrystalline cellulose

Film-coating:
Hypromellose (E464)
Colloidal anhydrous silica
Hydroxypropylcellulose (E463)
Macrogol 400
Macrogol 8000
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Al/PVC blister packs and tablet containers (HDPE) closed with sealed plastic cap (LDPE) with desiccant.

Blisters: 7, 14, 28, 56 and 84 film−coated tablets
Tablet containers: 30 and 100 film−coated tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Caduceus Pharma Limited
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94 Wigmore Street
London W1U 3RF
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA 1399/4/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 1st April 2011

10 DATE OF REVISION OF THE TEXT

January 2012