Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Actonel Once a Week 35mg film coated tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 35 mg risedronate sodium which is equivalent to 32.5 mg risedronic acid.
Excipients include lactose
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Product imported from the UK and Italy:
Oval light-orange film-coated tablet with 'RSN' on one side and '35 mg' on the other.

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 (see section 5.1).
Treatment of osteoporosis in men at high risk of fractures (see section 5.1).

4.2 Posology and method of administration

Posology
The recommended dose in adults is one 35 mg tablet orally once a week. The tablet should be taken on the same day each week.

Method of administration
The absorption of risedronate sodium is affected by food, thus to ensure adequate absorption patients should take Actonel Once a Week 35 mg:

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

Patients should be instructed that if a dose is missed, one Actonel Once a Week 35 mg 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 tablet must be swallowed whole and not sucked or chewed. To aid delivery of the tablet to the stomach Actonel Once a Week 35 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.

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. This has also been shown in the very elderly, 75 years old and above postmenopausal population.

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).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
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 Actonel Once a Week 35 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 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.
The evidence to support efficacy of bisphosphonates including risedronate 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 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 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 Actonel Once a Week 35 mg therapy. Other disturbances of bone and mineral metabolism (i.e. parathyroid dysfunction, hypovitaminosis D) should be treated at the time of starting Actonel Once a Week 35 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 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.

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

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 studies.

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.

In the risedronate sodium Phase III osteoporosis studies with daily dosing, acetyl salicylic acid or NSAID use was reported by 33% and 45% of patients respectively. In the Phase III once a week study in postmenopausal women, acetyl salicylic acid or NSAID use was reported by 57% and 40% of patients respectively. 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.
If considered appropriate risedronate sodium may be used concomitantly with oestrogen supplementation (for women only).

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 animals indicate that a small amount of risedronate sodium passes 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

Actonel Once A Week 35 mg has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

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

Adverse experiences reported in phase III clinical studies in postmenopausal women with osteoporosis treated for up to 36 months with risedronate sodium 5mg/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; <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%)

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 studies.

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.

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

Muskuloskeletal 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).

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: 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. In studies of postmenopausal women, decreases in biochemical markers of bone turnover were observed within 1 month and reached a maximum in 3-6 months. Decreases in biochemical markers of bone turnover were similar with Actonel Once a Week 35 mg and Optinate 5 mg daily at 12 months.

In a study in men with osteoporosis, decreases in biochemical markers of bone turnover were observed at the earliest time point of 3 months and continued to be observed at 24 months.

Clinical efficacy and safety
Treatment 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.

Based on effects on mean change in lumbar spine BMD, Actonel Once a Week 35 mg (n=485) was shown to be equivalent to Optinate 5 mg daily (n=480) in a one-year, double-blind, multicentre study of postmenopausal women with osteoporosis

The clinical programme for risedronate sodium administered once daily 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 was estimated by use of a time-to-first event analysis.

- Two placebo-controlled studies (n=3661) 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 studies 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 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 *α-posteriori* analysis of subgroups defined by clinical practise and current definitions of osteoporosis:

- In the subgroup of patients with femoral neck BMD T-score ≤-2.5 SD (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 mg 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 studies, 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 maintained bone density 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.

- 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.

Treatment of Osteoporosis in Men
Risedronate sodium 35 mg once a week demonstrated efficacy in men with osteoporosis (age range 36 to 84 years) in a 2-year, double-blind, placebo-controlled study in 284 patients (risedronate sodium 35 mg n=191). All patients received supplemental calcium and vitamin D.
Increases in BMD were observed as early as 6 months following initiation of risedronate sodium treatment. Risedronate sodium 35 mg once a week produced mean increases in BMD at the lumbar spine, femoral neck, trochanter and total hip compared to placebo after 2 years of treatment. Antifracture efficacy was not demonstrated in this study.
The bone effect (BMD increase and BTM decrease) of risedronate sodium is similar in males and females.

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 (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 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 (see section 4.5).

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:
Dri-Klear
Hypromellose
macrogol 400
Hyprolose
macrogol 8000
silicon dioxide
Chroma-Tone White DDB-7536W
titanium dioxide (E171)
hypromellose
ferric oxide yellow (E172)
ferric oxide red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The shelf life expiry date of this product shall be the date shown on the container and outer package of the product on the market in the country of origin.

6.4 Special precautions for storage

No special precautions for storage.

6.5 Nature and contents of container

Clear PVC/aluminium foil blister in a cardboard carton. Pack size 4

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 PARALLEL PRODUCT AUTHORISATION HOLDER

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8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA 1151/21/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of Last Renewal: 16th February 2012

10 DATE OF REVISION OF THE TEXT

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