Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Actonel Plus Ca & D Tablet 35mg and 500mg/400 IU film-coated tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Actonel Plus Ca & D Tablet is composed of Actonel 35 mg tablets (light-orange tablets) and calcium/vitamin D3 tablets (white tablets).

Light-orange tablets
Each film-coated tablet contains 35 mg risedronate sodium (equivalent to 32.5 mg risedronic acid).

White tablets
Each film-coated tablet contains 1250 mg calcium carbonate equivalent to 500 mg calcium and 10 micrograms (400 IU) colecalciferol (vitamin D_3).

Excipients:
Each light-orange tablet contains lactose.

Each white tablet contains sucrose.
For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Risedronate sodium tablet:
Oval, light-orange, film-coated tablet with RSN on one side and 35 mg on the other.

Calcium/vitamin D_3 tablet:
Capsule-shaped, white, film-coated tablet with "CA+D_3" on one side and blank 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).
Actonel Plus Ca & D Tablet is only intended for use in assessed patients for whom the amount of calcium and vitamin D_3 included is considered to provide adequate supplementation.

4.2 Posology and method of administration

A weekly unit of Actonel Plus Ca & D Tablet, consists of 1 Actonel 35 mg film-coated tablet and 12 calcium/vitamin D_3 tablets packaged in a blister card.

The recommended dose in adults is 1 Actonel 35 mg tablet on the first day followed on the next day by 1 calcium/vitamin D_3 tablet twice daily for 6 days. This 7-day sequence is then repeated each week starting with the Actonel 35 mg tablet.

Actonel 35 mg (light-orange tablets):

The Actonel 35 mg tablet should be taken orally on the same day each week.

The absorption of risedronate sodium is affected by food, thus to ensure adequate absorption, patients should take the tablet:

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

The tablet must be swallowed whole and not sucked or chewed. To aid delivery of the tablet to the stomach the Actonel 35 mg tablet 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).

Calcium/vitamin D_3 (white tablets):

Two calcium/vitamin D_3 tablets should be taken each day, one in the morning and one in the evening, for 6 days per week starting on the day after the Actonel 35 mg tablet is taken. The absorption of calcium can be affected by foods containing high amounts of oxalic acid and phytic acid (see section 4.5), patients should take the tablet at least 2 hours after eating such foods.

The tablet must be swallowed whole and not sucked or chewed. The tablet should be taken with a glass of plain water (≥120 ml).

In case the Actonel 35 mg tablet dose is missed, patients should be instructed that the Actonel 35 mg tablet should be taken on the next day in the morning according to the dosing instructions. In this particular instance, patients should then take their calcium/vitamin D_3 tablet on the following day. Patients should be instructed that they should never take the Actonel 35mg tablet and the calcium/Vitamin D3 tablet on the same day.

If the calcium/vitamin D_3 tablet is missed, the patient should be instructed to continue taking the calcium/vitamin D_3 tablet each morning and one tablet each evening, beginning on the day the missed dose is remembered. Patients should be instructed that they should not take three calcium/vitamin D_3 tablets on the same day. Any remaining tablets in the blister pack at the end of the weekly cycle should be discarded.

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.

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 in postmenopausal population.

Renal Impairment: No dosage adjustment is required for those patients with mild to moderate renal impairment. The use of risedronate sodium and calcium/vitamin D_3 is contraindicated in patients with severe renal impairment (creatinine clearance lower than 30ml/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 risedronate sodium, calcium carbonate, colecalciferol or to any of the excipients.
Hypocalcaemia (see section 4.4)
Hypercalcaemia.
Hypercalciuria
Diseases and/or conditions (such as prolonged immobilization) associated with hypercalcaemia and/or hypercalciuria
Nephrolithiasis
Pregnancy and lactation.
Severe renal impairment (creatinine clearance <30ml/min).
Hypervitaminosis D

4.4 Special warnings and precautions for use

Risedronate sodium:

Foods, drinks (other than plain water) and medicinal products containing polyvalent cations (such as calcium, magnesium, iron and aluminium) may interfere with the absorption of risedronate sodium and should not be taken at the same time (see section 4.5). Therefore the risedronate sodium tablet (light-orange tablet) should be taken at least 30 minutes before the first food, other medicinal product or drink of the day (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 $\leq$-2.5 standard deviations (SD)] 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 sodium 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.

Prescribers should emphasise to patients the importance of paying attention to the dosing instructionsand 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 Actonel Plus Ca & D Tablet therapy. Other disturbances of bone and mineral metabolism (i.e. parathyroid dysfunction, hypovitaminosis D) should be treated at the time of starting Actonel Plus Ca & D Tablet 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.

In patients with mild to moderate renal impairment or a history of absorptive or renal hypercalciuria, nephrocalcinosis, kidney stone formation, or hypophosphataemia, renal function, serum and urinary calcium and phosphate should be monitored regularly.

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.

Calcium carbonate/vitamin D3:

Vitamin D3 should be used with caution in patients with impairment of renal function and the effect on calcium and phosphate levels should be monitored. The risk of soft tissue calcification should be taken into account. In patients with severe renal insufficiency, vitamin D in the form of colecalciferol is not metabolised normally and another form of vitamin D should be used (see section 4.3)

During long-term treatment, serum and urinary calcium levels should be followed. Renal function should be monitored through measurement of serum creatinine. Monitoring is especially important in elderly patients on concomitant treatme with cardiac glycosides or diuretics (see section 4.5) and in patients with a high tendency to calculus formation. Treatme must be reduced or suspended if urinary calcium exceeds 7.5 mmol/24 hour (300 mg/24 hour). In case of hypercalcaemi signs of impaired renal function, treatment with calcium/vitamin D3 tablets should be discontinued.

The dose of vitamin D3 in the tablets should be considered when prescribing other drugs containing vitamin D. Additior doses of calcium or vitamin D should be taken under close medical supervision. In such cases it is necessary to monitor serum calcium levels and urinary calcium excretion frequently.

Calcium/vitamin D3 tablets should be used with caution in patients suffering from sarcoidosis because of the risk of increased metabolism of vitamin D to its active metabolite. In these patients, serum calcium levels and urinary calcium excretion must be monitored.

Calcium/vitamin D3 tablets should be used with caution in immobilised patients with osteoporosis due to the increased risk of hypercalcaemia. The calcium/vitamin D3 treatment might be discontinued in prolonged immobilization and should only be resumed once the patient becomes mobile again.

This medicinal product contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Risedronate sodium:

No formal interaction studies have been performed with risedronate sodium, however no clinically relevant interactions with other medicinal products were found during clinical trials. In the risedronate sodium Phase III osteoporosis studies with daily dosing, acetyl salicylic acid or non-steroidal anti-inflammatory drug (NSAID) use was reported by 33% and 45% of patients respectively. In the Phase III once a week study, 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.

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.

Calcium carbonate/vitamin D_3:

Thiazide diuretics reduce the urinary excretion of calcium. Due to increased risk of hypercalcemia serum calcium should be regularly monitored during concomitant use of thiazide diuretics.

Systemic corticosteroids reduce calcium absorption. During concomitant use, it may be necessary to increase the dose of calcium.

Calcium carbonate may interfere with the absorption of concomitant administered tetracycline preparations. For this reason, tetracycline preparations should be administered at least two hours before or four to six hours after oral intake of calcium carbonate/vitamin D_3.

Hypercalcaemia may increase the toxicity of digitalis and other cardiac glycosides (risk of dysrhythmia) during treatment with calcium combined with vitamin D_3. Such patients should be monitored with regard to electrocardiogram (ECG) and serum calcium levels.

If sodium fluoride is used concomitantly, this preparation should be administered at least three hours before intake of calcium carbonate/vitamin D_3 since gastrointestinal absorption may be reduced.

Oxalic acid (found in spinach and rhubarb) and phytic acid (found in whole cereals) may inhibit calcium absorption through formation of insoluble compounds with calcium ions. The patient should not take calcium products within two hours of eating foods with high concentration of oxalic acid and phytic acid.

Simultaneous treatment with ion exchange resins such as cholestyramine or laxatives such as paraffin oil may redu gastrointestinal absorption of vitamin D.

4.6 Fertility, pregnancy and lactation

This medicinal product is contraindicated during pregnancy and lactation (see section 4.3).

Risedronate sodium:

There are no adequate data from use of risedronate sodium in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk to 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.

Calcium carbonate/vitamin D_3:

During pregnancy the daily intake should not exceed 1500 mg calcium and 600 IU colecalciferol (15µg vitamin D_3). There are no indications that vitamin D at therapeutic doses is teratogenic in humans. Studies in animals have shown reproductive toxicity with high doses of vitamin D. In pregnant women, overdoses of calcium and vitamin D should be avoided as permanent hypercalcaemia has been related to adverse effects on the developing foetus. Calcium and vitamin D_3 pass into breast milk. Calcium 1000 mg/vitamin D_3 800 IU daily dose must not be used during pregnancy and lactation.

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:

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 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 trials.

In a one-year, double-blind, multicentre study comparing risedronate 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%).

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 and 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)

Calcium carbonate/vitamin D_3

Adverse reactions are listed below, by system organ class and frequency following convention: 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).

Metabolism and nutrition disorders

Uncommon: Hypercalcaemia and hypercalciuria.

Gastrointestinal disorders

Rare: Constipation, flatulence, nausea, abdominal pain and diarrhoea.

Skin and subcutaneous disorders

Rare: Pruritus, rash and urticaria.

4.9 Overdose

Risedronate sodium:

No specific information is available on the treatment of acute 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 sodium and reduce absorption of risedronate sodium. In cases of substantial overdose, gastric lavage may be considered to remove unabsorbed risedronate sodium.

Calcium carbonate/vitamin D_3:

Overdose can lead to hypervitaminosis, hypercalciuria and hypercalcaemia. Symptoms of hypercalcaemia may include anorexia, thirst, nausea, vomiting, constipation, abdominal pain, muscle weakness, fatigue, mental disturbances, polydipsia, polyuria, bone pain, nephrocalcinosis, renal calculi and in severe cases, cardiac arrhythmias. Extreme hypercalcaemia may result in coma and death. Persistently high calcium levels may lead to irreversible renal damage and soft tissue calcification.

Treatment of hypercalcaemia: The treatment with calcium must be discontinued. Treatment with thiazide diuretics, lithium, vitamin A, vitamin D_3 and cardiac glycosides must also be discontinued. Emptying of the stomach in patients with impaired consciousness. Rehydration, and, according to severity, isolated or combined treatment with loop diuretics, bisphosphonates, calcitonin and corticosteroids. Serum electrolytes, renal function and diuresis must be monitored. In severe cases, ECG and central venous pressure should be followed.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmaco-therapeutic group:
Bisphosphonates combinations, ATC Code: M05BB.
Vitamin D and analogues: ATC Code: A11CC05

Risedronate sodium:

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. In preclinical studies risedronate sodium demonstrated potent anti-osteoclast and antiresorptive 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. Decreases in biochemical markers of bone turnover were similar with risedronate sodium 35 mg weekly and risedronate sodium 5 mg daily at 12 months.

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 bone mineral density (BMD), risedronate sodium 35 mg weekly (n=485) was shown to be equivalent to risedronate sodium 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 were estimated by use of a time-to-first event analysis.

- Two placebo-controlled trials (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 trials enrolled postmenopausal women above 70 years of age 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) and at least one additional risk factor. Women $\geq$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 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.

Calcium carbonate/vitamin D_3:

In case of calcium deficiency, oral intake of calcium supplementation supports the remineralisation of the skeleton. Vitamin D_3 increases the intestinal absorption of calcium.

Administration of calcium and vitamin D_3 counteracts the increase in parathyroid hormone (PTH) which is caused by calcium deficiency which causes increased bone resorption.

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

Risedronate sodium:

Absorption: risedronate sodium absorption after an oral dose is relatively rapid (t_{max} ~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 of risedronate sodium 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 risedronate sodium 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.

Calcium carbonate:

Absorption: Calcium carbonate is converted to calcium chloride by gastric acid. Calcium is absorbed to the extent of about 15-25% from the gastro-intestinal tract
Distribution and metabolism: 99% of calcium in the body is concentrated in the hard structure of bones and teeth. The remaining 1% is present in the intra- and extracellular fluids. About 50% of the total blood calcium content is physiologically active ionised form with approximately 10% being complexed to citrate, phosphate or other anions, the remaining 40% being bound to proteins, principally albumin.
Elimination: Calcium is eliminated through faeces, urine and sweat. Renal excretion depends on glomerular filtration and calcium tubular reabsorption.

Vitamin D_3:

Absorption: Vitamin D is well absorbed in the small intestine.
Distribution and metabolism: Cholecalciferol and its metabolites circulate in the blood bound to a specific globulin. Cholecalciferol is converted in the liver by hydroxylation to the active form 25-hydroxycolecalciferol. It is then further converted in the kidneys to 1,25 hydroxycolecalciferol. 1,25 hydroxycolecalciferol is the metabolite responsible for increasing calcium absorption. Vitamin D which is not metabolised is stored in adipose and muscle tissues.
Elimination: Vitamin D is excreted in faeces and urine.

5.3 Preclinical safety data

Risedronate sodium:
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 risk for humans.

Calcium carbonate/vitamin D_3:
At doses far higher than the human therapeutic range, teratogenicity has been observed in animal studies (see section 4.6). There is no further information of relevance to the safety assessment in addition to what is stated in other parts of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Light-orange tablet:

Tablet core: Lactose monohydrate
Cellulose microcrystalline
Crospovidone A
Magnesium stearate.

Film coating: Hypromellose
Macrogol
Hyprolose
Silicon dioxide
Titanium dioxide (E171)
Iron oxide yellow (E172)
Iron oxide red (E172).

White tablets:

Tablet core: Maltodextrin
Cellulose powder
Liquid paraffin
Silicon dioxide
Butylhydroxytoluene (E321)
Triglycerides medium-chain
Maize starch modified
Sodium aluminium silicate
Gelatin
Sucrose.

Film coating: Titanium dioxide (E171)
Hypromellose
Polysorbate 80
Triacetin
Carnauba wax.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

Each weekly unit contains:
Aluminium/Aluminium foil blister containing one risedronate sodium (light-orange) film-coated tablet and twelve Calcium/vitamin D_3 (white) film-coated tablets.

Pack sizes:
1 weekly unit: 1x(1 risedronate sodium film-coated tablet and 12 Calcium/vitamin D_3 film-coated tablets)
2 weekly units: 2x(1 risedronate sodium film-coated tablet and 12 Calcium/vitamin D_3 film-coated tablets)
4 weekly units: 4x(1 risedronate sodium film-coated tablet and 12 Calcium/vitamin D_3 film-coated tablets)
12 weekly units: 12x(1 risedronate sodium film-coated tablet and 12 Calcium/vitamin D_3 film-coated tablets)
16 weekly units: 16x(1 risedronate sodium film-coated tablet and 12 Calcium/vitamin D_3 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

Warner Chilcott UK Limited
Old Belfast Road
Millbrook
Larne
County Antrim
BT40 2SH
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA1635/3/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 4th July 2008.

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September 2011