Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Optinate Plus Ca & D 35 mg film-coated tablets + 1000 mg/880 IU Effervescent Granules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 35 mg risedronate sodium, (equivalent to 32.5 mg risedronic acid).
Each sachet of effervescent granules contains 1000mg calcium (as 2500 mg calcium carbonate) and 22 micrograms (880 IU) colecalciferol (vitamin D3).

Excipients:
Each film-coated tablet contains 126.0 mg of lactose monohydrate (equivalent to 119.7 mg lactose).
Each sachet of effervescent granules contains potassium (163 mg), sucrose (3.6 mg), soya-bean oil (0.7 mg) and sorbitol (100 mg).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

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

Effervescent granules
White effervescent granules.

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).
Optinate Plus Ca & D is only intended for use in assessed patients for whom the amount of calcium and vitamin D_3included is considered to provide adequate supplementation.

4.2 Posology and method of administration

A weekly unit of Optinate Plus Ca & D consists of 1 Optinate 35 mg film-coated tablet and 6 calcium/vitamin D 3 sachets in a box.

Posology
The recommended dose in adults is 1 Optinate 35 mg tablet on the first day followed on the next day by 1 calcium/vitamin D 3 sachet daily for 6 days. This 7-day sequence is then repeated each week starting with Optinate 35 mg tablet.

Method of administration
Optinate 35 mg (light-orange tablet):
The Optinate 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 Optinate 35 mg 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 Optinate 35 mg tablet is to be taken while in an upright position with a glass of plain water ($\geq$120 ml).Patients should not lie down for 30 minutes after taking the tablet (see section 4.4).

Calcium/vitamin D3 (sachet)
Calcium/vitamin D3 sachet should be taken each day for 6 days per week starting on the day after the Optinate 35 mg tablet is taken. The contents of the sachet should be poured into a glass of plain water, stirred and drunk immediately once the fizzing has subsided.

In case the Optinate 35 mg tablet dose is missed, patients should be instructed that the Optinate 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 D3 sachet on the following day. Patients should be instructed that they should never take the tablet and the sachet the same day.

If the calcium/vitamin D3 sachet dose is missed, the patient should be instructed to continue taking one sachet each day beginning on the day the missed dose is remembered. Patient should be instructed that they should not take two sachets on the same day. Any remaining calcium/vitamin D3 sachet 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.

Special populations
Elderly
No dose 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 dose adjustment is required for those patients with mild to moderate renal impairment. The use of risedronate sodium and calcium/vitamin D3 is contraindicated in patients with severe renal impairment (creatinine clearance lower than 30ml/min) (see sections 4.3 and 5.2).

Paediatricpopulation
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 substances, soya, peanut, or to any of the excipients listed in section 6.1
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 <30 ml/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 ≤-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 (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 Optinate Plus Ca & D therapy.Other disturbances of bone and mineral metabolism (i.e. parathyroid dysfunction, hypovitaminosis D) should be treated at the time of starting Optinate Plus Ca & D 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.

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.

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.

This medicinal product contains less than 1 mmol sodium (23 mg) per film-coated tablet, that is to say, essentially 'sodium-free'.

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 and renal function should be monitored through measurement of serum creatinine. Monitoring is especially important in elderly patients on concomitant treatment with cardiac glycosides or diuretics (see section 4.5) and in patients with a high tendency to calculus formation. Treatment must be reduced or suspended if urinary calcium exceeds 7.5 mmol/24 hours (300 mg/24 hours). In case of hypercalcaemia or signs of impaired renal function, treatment with calcium/vitamin D3 sachets should be discontinued.

The dose of vitamin D3 in the sachets should be considered when prescribing other medicinal products containing vitamin D. Additional 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 sachets 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 sachets 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 sorbitol and sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicinal product.

This medicinal product contains potassium (163 mg per sachet). This should be taken into consideration in patients with reduced kidney function or patients on a controlled potassium diet.

This medicinalproduct contains less than 1 mmol sodium (23 mg) per sachet, that is to say,essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interactions

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 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 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.

Calcium carbonate/vitamin D3:

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 D3.

Hypercalcaemia may increase the toxicity of digitalis and other cardiac glycosides (risk of dysrhythmia) during treatment with calcium combined with vitamin D3. 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 D3 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 reduce the 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 pass into breast milk. Risedronate sodium must not be used during pregnancy or by breast-feeding women.

Calcium carbonate/vitamin D3:

During pregnancy the daily intake should not exceed 1500 mg calcium and 600 IU colecalciferol (15microg vitamin D3). 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. Optinate Combi D effervescent granules must not be used during pregnancy and lactation.

4.7 Effects on ability to drive and use machines

Optinate Combi D has no or negligibly influence on the ability to drive and use machines.

4.8 Undesirable effects

Risedronate sodium:

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 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:

Rare: Atypical subtrochanteric and diaphyseal femoral fractures (bisphosphonate class adverse reaction).
Very rare: Osteonecrosis of the external auditory canal (bisphosphonate class adverse reaction).

Calcium carbonate/vitamin D3

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.

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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL – Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

Risedronate sodium:

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 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 D3:

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 D3 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

Pharmacotherapeutic group: Bisphosphonates, combinations, ATC Code: M05BB04.

Risedronatesodium
Mechanism ofaction

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 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.

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 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 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 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 ≤-2.5 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 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.

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.

Calcium carbonate/vitamin D3
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 D3 counteracts the increase in parathyroid hormone (PTH) which is caused by calcium deficiency which causes increased bone resorption.

A clinical study of institutionalised patients suffering from vitamin D deficiency indicated that a daily intake of effervescent granules of 1000 mg calcium/880 IU colecalciferol for six months normalised the value of the 25-hydoxylated metabolite of vitamin D3 and reduced secondary hyperparathyroidism.

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%.

Biotransformation
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 dose 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).

Calcium carbonate:

Absorption
During dissolution the calcium salt contained in the effervescent granules is transformed into calcium citrate. Calcium citrate is well absorbed, approximately 30% to 40% of the ingested dose.

Distribution and biotransformation
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 D3:

Absorption
Vitamin D is readily absorbed in the small intestine.

Distribution and biotransformation
Colecalciferol and its metabolites circulate in the blood bound to a specific globulin. Colecalciferol 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 that 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**,** but 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 D3:

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

Film-coated tablet:
Tablet core: Lactose monohydrate,
Cellulose microcrystalline
Crospovidone A
Magnesium stearate

Film coating: Hypromellose
Macrogol
Hydroxypropylcellulose
Colloidal anhydrous silica
Titanium dioxide E171
Iron oxide yellow E172
Iron oxide red E172

Effervescent granules:
Citric acid anhydrous
Malic acid
Gluconolactone
Maltodextrin
Sodium cyclamate
Saccharin sodium
Sorbitol E420
Mannitol E421
Dextrin
Acacia
Natural Lemon oils
Natural Lime flavour
Rice starch
Potassium carbonate
All-rac--Tocopherol
Soya-bean oil, hydrogenated
Gelatin
Sucrose
Maize starch

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

Combination pack constituted of an outer carton pack containing weekly unit(s) (carton boxes). Each weekly unit contains:
Clear PVC/aluminium foil blister containing one tablet

Six sachets (laminated aluminium paper foil) containing effervescent granules

Pack sizes:
1 weekly unit: 1x(1 film-coated tablet + effervescent granules in 6 sachets)
2 weekly units: 2x(1 film-coated tablet + effervescent granules in 6 sachets)
4 weekly units: 4x(1 film-coated tablet + effervescent granules in 6 sachets)
3x4 weekly units: 12x(1 film-coated tablet + effervescent granules in 6 sachets)
4x4 weekly units: 16x(1 film-coated tablet + effervescent granules in 6 sachets)

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Theramex Ireland Limited
3rd Floor, Kilmore House
Park Lane
Spencer Dock
Dublin 1
D01YE64
Ireland

8 MARKETING AUTHORISATION NUMBER

PA22668/003/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 8th July 2011
Date of last renewal: 13th October 2011

10 DATE OF REVISION OF THE TEXT

November 2019 CRN008J74