Public Assessment Report

Decentralised Procedure

Corica Combi 35 mg + 1000 mg/880 IU Film-coated Tablets + Effervescent Tablets

Risedronate sodium and Calcium/Cholecalciferol 35 mg + 1000 mg/880 IU Film-coated Tablets + Effervescent Tablets

Procedure No: UK/H/3373/001/DC
UK/H/3393/001/DC

UK Licence No: PL 04416/1090-1

Sandoz Limited
LAY SUMMARY

On 18 January 2012, Belgium, Greece, Ireland, Spain, Slovak Republic and the UK agreed to grant Marketing Authorisations to Sandoz Limited for the medicinal products Corica Combi 35 mg + 1000 mg/880 IU Film-coated Tablets + Effervescent Tablets and Risedronate sodium and Calcium/Cholecalciferol 35 mg + 1000 mg/880 IU Tablets (PL 04416/1090-1; UK/H/3373 & 3393/001/DC). The licence was granted via the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS). After the national phase, Marketing Authorisations were granted in the UK on 19 March 2012.

Corica Combi 35 mg + 1000 mg/880 IU Film-coated Tablets + Effervescent Tablets and Risedronate sodium and Calcium/Cholecalciferol 35 mg + 1000 mg/880 IU Tablets are used to treat osteoporosis, even if severe, in women after menopause who also need daily calcium and vitamin D3 supplementation. This combination reduces the risk of spinal and hip fractures.

Risedronate belongs to a group of medicines called bisphosphonates. It works directly on your bones to make them stronger and therefore less likely to break. Calcium/vitamin D3 provides the calcium and the vitamin D3 that your body may need to harden new bone.

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Corica Combi 35 mg + 1000 mg/880 IU Film-coated Tablets + Effervescent Tablets and Risedronate sodium and Calcium/Cholecalciferol 35 mg + 1000 mg/880 IU Tablets outweigh the risks, and Marketing Authorisations were granted.
### TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Module</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Module 1: Information about initial procedure</td>
<td>3</td>
</tr>
<tr>
<td>Module 2: Summary of Product Characteristics</td>
<td>4</td>
</tr>
<tr>
<td>Module 3: Patient Information Leaflets</td>
<td>22</td>
</tr>
<tr>
<td>Module 4: Labelling</td>
<td>24</td>
</tr>
<tr>
<td>Module 5: Scientific Discussion</td>
<td>28</td>
</tr>
<tr>
<td>1 Introduction</td>
<td></td>
</tr>
<tr>
<td>2 Quality aspects</td>
<td></td>
</tr>
<tr>
<td>3 Non-clinical aspects</td>
<td></td>
</tr>
<tr>
<td>4 Clinical aspects</td>
<td></td>
</tr>
<tr>
<td>5 Overall conclusions</td>
<td></td>
</tr>
<tr>
<td>Module 6: Steps taken after initial procedure</td>
<td></td>
</tr>
</tbody>
</table>
Module 1

| **Product Name** | Corica Combi 35 mg + 1000 mg/880 IU Film-coated Tablets + Effervescent Tablets Risedronate sodium and Calcium/Cholecalciferol 35 mg + 1000 mg/880 IU Tablets |
| **Type of Application** | Generic, Article 10.1 |
| **Active Substances** | Risedronate sodium, calcium carbonate, cholecalciferol |
| **Form** | Film-coated tablets |
| **Strength** | 35 mg risedronate sodium (equivalent to 32.5 mg risedronic acid) |
| | 2500 mg calcium carbonate (equivalent to 1000 mg calcium) |
| | 22 micrograms (880 IU) cholecalciferol (vitamin D3) |
| **MA Holder** | Sandoz Limited, Frimley Business Park, Frimley, Camberley, Surrey, GU16 7SR |
| **Reference Member State (RMS)** | UK |
| **Concerned Member States (CMS)** | UK/H/3373/001/DC: Belgium, Greece, Spain, Slovak Republic |
| | UK/H/3393/001/DC: Ireland |
| **Procedure Number** | UK/H/3373/001/DC & UK/H/3393/001/DC |
| **Timetable** | Day 210 – 18 January 2012 |
Module 2
Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Corica Combi 35 mg + 1000 mg/880 IU Film-coated Tablets + Effervescent Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains 35 mg risedronate sodium, (equivalent to 32.5 mg risedronic acid).

Each effervescent tablet contains 2500 mg calcium carbonate (equivalent to 1000 mg calcium) and 22 micrograms (880 IU) cholecalciferol (vitamin D3).

Excipients with known effect: Each film-coated tablet contains lactose-monohydrate 120 mg.

Each effervescent tablet contains lactose-monohydrate 396 mg, sodium 96.1 mg, sucrose 3.68 mg and soya oil 0.73 mg.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet.
Oval biconvex orange film-coated tablet encoded 35 on one side.

Effervescent tablets.
Cylindrical, white or off-white coloured biplane effervescent tablets with bevel-edges on both sides.

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).

Corica Combi is only intended for use in assessed patients for whom the amount of calcium and vitamin D3 included is considered to provide adequate supplementation.

4.2 Posology and method of administration
Corica Combi is a weekly therapy of 1 Risedronate 35 mg film-coated tablet and 6 calcium/vitamin D3 effervescent tablets.

The recommended dose in adults is 1 Risedronate 35 mg tablet on the first day followed on the next day by 1 calcium/vitamin D3 effervescent tablet daily for 6 days. This 7-day sequence is then repeated each week starting with Risedronate 35 mg tablet.

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 Corica Combi on an individual patient basis, particularly after 5 or more years of use.

Risedronate 35 mg (orange tablet):
The Risedronate 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 Risedronate 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 Risedronate 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 D3 (effervescent tablet):
Calcium/vitamin D3 effervescent tablet should be taken each day for 6 days per week starting on the
day after the Risedronate 35 mg tablet is taken. The effervescent tablet is taken dissolved in a glass of
water.

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

If the calcium/vitamin D3 effervescent tablet dose is missed, the patient should be instructed to
continue taking one effervescent tablet each day beginning on the day the missed dose is remembered.
Patient should be instructed that they should not take two effervescent tablets on the same day. Any
remaining calcium/vitamin D3 effervescent tablet at the end of the weekly cycle should be discarded.

**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 D3 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, cholecalciferol, 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 <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 (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.

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 Corica Combi therapy. Other disturbances of bone and mineral metabolism (i.e. parathyroid dysfunction, hypovitaminosis D) should be treated at the time of starting Corica Combi 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.

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.

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 cholecalciferol 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 hour (300 mg/24 hour). In case of hypercalcaemia or signs of impaired renal function, treatment with calcium/vitamin D3 effervescent tablets should be discontinued.

The dose of vitamin D3 in the effervescent tablets should be considered when prescribing other drugs 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 effervescent 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 effervescent 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 and lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, glucose-galactose malabsorption, fructose intolerance or sucrase-isomaltase insufficiency should not take this medicine.

This medicinal product contains 1.90 mmol (or 43.59 mg) sodium per dose. To be taken into consideration by patients on a controlled sodium diet.

### 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 D3:**
Thiazide diuretics reduce the urinary excretion of calcium. Due to increased risk of hypercalcaemia 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 cholecalciferol (15μg 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.
Calcium carbonate 2500 mg/vitamin D3 880 IU dose granules 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.

During post-marketing experience the following reactions have been reported (frequency rare):

Musculoskeletal and connective tissues disorders:
Atypical subtrochanteric and diaphyseal femoral fractures (bisphosphonate class adverse reaction)

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

Eye disorders:
iritis, uveitis

Musculoskeletal and connective tissues disorders:
osteonecrosis of the jaw

Skin and subcutaneous tissue disorders:
hypersensitivity and skin reactions, including angioedema, generalised rash, urticaria and bullous skin reactions, some severe including isolated reports of Stevens-Johnson syndrome 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.

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.
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 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: Drugs affecting bone structure and mineralization, Bisphosphonates, combinations,

ATC Code: M05BB04.

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 anti-resorptive activity, and dose dependently increased bone mass and biomechanical skeletal strength. The activity of risedronate sodium was confirmed by measuring biochemical markers for bone turnover during pharmacodynamic and clinical studies. Decreases in biochemical markers of bone turnover were observed within 1 month and reached a maximum in 3-6 months. 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 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 ≥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 D3:
In case of calcium deficiency, oral intake of calcium supplementation supports the remineralisation of the skeleton. Vitamin D3 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 cholecalciferol for six months normalised the value of the 25-hydoxylated metabolite of vitamin D3 and reduced secondary hyperparathyroidism.

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 (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 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 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.

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 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 D3:
Absorption: Vitamin D is readily absorbed in the small intestine. Distribution and biotransformation: 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-hydroxycholecalciferol. It is then further converted in the kidneys to 1,25 hydroxycholecalciferol. 1,25 hydroxycholecalciferol 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 hypocalcaemia 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 SmPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Film-coated tablet:
- Tablet core: crospovidone
- lactose monohydrate
- magnesium stearate
- microcrystalline cellulose.
- Film coating: hypromellose
- macrogol 400
- titanium dioxide (E171)
- ferric oxide, yellow (E172),
- ferric oxide, red (E172).

Effervescent tablet:
- citric acid anhydrous
- gelatin
- lactose monohydrate
- macrogol 6000
- maize starch
- sodium cyclamate
- sodium hydrogen carbonate
- povidone K25
- saccharin sodium,
- hydrogenated soya oil
- sucrose
- alpha-tocopherol
- methylcellulose
- simeticone
- aromatics; orange juice flavour, PHS-133147 (containing maltodextrin, orange flavouring substances and hydroxyethyl starch)

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years

Calcium carbonate/vitamin D3 effervescent tablets
Shelf life after first opening: 1 month

6.4 Special precautions for storage
Do not store above 25°C. Store in the original package in order to protect from light and moisture!

6.5 Nature and contents of container
Risedronate film-coated tablets: Al/PVC blister
Calcium carbonate/vitamin D3 effervescent tablets: Polypropylene tubes with polyethylene stopper containing a silica gel desiccant

Pack sizes:
4 film-coated tablets + 24 (2 x 12) effervescent tablets
A single carton box contains both the film-coated tablet blister (placed in a carton box) and the effervescent tablets in tubes for one month use.
3 x (4 film-coated tablets + 24 (2 x 12) effervescent tablets)
A single carton box contains both the film-coated tablet blister (placed in carton boxes) and the
effervescent tablets in tubes for three months use.
4 x (4 film-coated tablets + 24 (2 x 12) effervescent tablets)
A single carton box contains both the film-coated tablet blister (placed in carton boxes) and the
effervescent tablets in tubes for four months use.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements

7 MARKETING AUTHORISATION HOLDER
Sandoz Ltd
Frimley Business Park,
Frimley,
Camberley,
Surrey,
GU16 7SR.

8 MARKETING AUTHORISATION NUMBER(S)
PL 04416/1090

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
19/03/2012

10 DATE OF REVISION OF THE TEXT
19/03/2012
1 **NAME OF THE MEDICINAL PRODUCT**
Risedronate sodium and Calcium/Cholecalciferol 35 mg + 1000 mg/880 IU Film-coated Tablets + Effervescent Tablets

2 **QUALITATIVE AND QUANTITATIVE COMPOSITION**
Each film-coated tablet contains 35 mg risedronate sodium, (equivalent to 32.5 mg risedronic acid).

Each effervescent tablet contains 2500 mg calcium carbonate (equivalent to 1000 mg calcium) and 22 micrograms (880 IU) cholecalciferol (vitamin D3).

Excipients with known effect: Each film-coated tablet contains lactose-monohydrate 120 mg.

Each effervescent tablet contains lactose-monohydrate 396 mg, sodium 96.1 mg, sucrose 3.68 mg and soya oil 0.73 mg.

For the full list of excipients, see section 6.1.

3 **PHARMACEUTICAL FORM**
Film-coated tablet.
Oval biconvex orange film-coated tablet encoded 35 on one side.

Effervescent tablets.
Cylindrical, white or off-white coloured biplane effervescent tablets with bevel-edges on both sides

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).

Risedronate sodium and Calcium/Cholecalciferol is only intended for use in assessed patients for whom the amount of calcium and vitamin D3 included is considered to provide adequate supplementation.

4.2 **Posology and method of administration**
Risedronate sodium and Calcium/Cholecalciferol is a weekly therapy of 1 Risedronate 35 mg film-coated tablet and 6 calcium/vitamin D3 effervescent tablets.

The recommended dose in adults is 1 Risedronate 35 mg tablet on the first day followed on the next day by 1 calcium/vitamin D3 effervescent tablet daily for 6 days. This 7-day sequence is then repeated each week starting with Risedronate 35 mg tablet.

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 sodium and Calcium/Cholecalciferol on an individual patient basis, particularly after 5 or more years of use.

Risedronate 35 mg (orange tablet):
The Risedronate 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 Risedronate 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 Risedronate 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 D3 (effervescent tablet):
Calcium/vitamin D3 effervescent tablet should be taken each day for 6 days per week starting on the
day after the Risedronate 35 mg tablet is taken. The effervescent tablet is taken dissolved in a glass of
water.

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

If the calcium/vitamin D3 effervescent tablet dose is missed, the patient should be instructed to
continue taking one effervescent tablet each day beginning on the day the missed dose is remembered.
Patient should be instructed that they should not take two effervescent tablets on the same day. Any
remaining calcium/vitamin D3 effervescent tablet at the end of the weekly cycle should be discarded.

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 D3 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, cholecalciferol, 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 <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 (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
gastro-duodenal 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 instructions and be alert to any signs and symptoms of possible oesophageal reaction. The patients should be instructed to seek timely medical attention if they develop symptoms of oesophageal irritation such as dysphagia, pain on swallowing, retrosternal pain or new/worsened heartburn.

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

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.

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 cholecalciferol 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 hour (300 mg/24 hour). In case of hypercalcaemia or signs of impaired renal function, treatment with calcium/vitamin D3 effervescent tablets should be discontinued.

The dose of vitamin D3 in the effervescent tablets should be considered when prescribing other drugs 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 effervescent 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 effervescent 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 and lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, glucose-galactose malabsorption, fructose intolerance or sucrase-isomaltase insufficiency should not take this medicine.

This medicinal product contains 1.90 mmol (or 43.59 mg) sodium per dose. To be taken into consideration by patients on a controlled sodium diet.

### 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 D3:

Thiazide diuretics reduce the urinary excretion of calcium. Due to increased risk of hypercalcaemia 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 cholecalciferol (15μg 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. Calcium carbonate 2500 mg/vitamin D3 880 IU dose granules 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%),

**Mucoskeletal 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.

During post-marketing experience the following reactions have been reported (frequency rare):

Musculoskeletal and connective tissues disorders:
Atypical subtrochanteric and diaphyseal femoral fractures (bisphosphonate class adverse reaction)

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

Eye disorders:
iritis, uveitis

Musculoskeletal and connective tissues disorders:
osteonecrosis of the jaw

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

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

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.
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 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: Drugs affecting bone structure and mineralization, Bisphosphonates, combinations,

ATC Code: M05BB04.

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 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 ≥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 D3:
In case of calcium deficiency, oral intake of calcium supplementation supports the remineralisation of the skeleton. Vitamin D3 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 cholecalciferol for six months normalised the value of the 25-hydoxylated metabolite of vitamin D3 and reduced secondary hyperparathyroidism.

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 (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 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 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.

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 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 D3:
Absorption: Vitamin D is readily absorbed in the small intestine. Distribution and biotransformation: 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-hydroxycholecalciferol. It is then further converted in the kidneys to 1,25 hydroxycholecalciferol. 1,25 hydroxycholecalciferol 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 hypocalcaemia 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 SmPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Film-coated tablet:
  Tablet core: crospovidone
  lactose monohydrate
  magnesium stearate
  microcrystalline cellulose.
  Film coating: hypromellose
  macrogol 400
  titanium dioxide (E171)
  ferric oxide, yellow (E172),
  ferric oxide, red (E172).

Effervescent tablet:
  citric acid anhydrous
  gelatin
  lactose monohydrate
  macrogol 6000
  maize starch
  sodium cyclamate
  sodium hydrogen carbonate
  povidone K25
  saccharin sodium,
  hydrogenated soya oil
  sucrose
  alpha-tocopherol
  methylcellulose
  simeticone
  aromatics; orange juice flavour, PHS-133147 (containing maltodextrin, orange flavouring substances and hydroxyethyl starch)

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years

Calcium carbonate/vitamin D3 effervescent tablets
Shelf life after first opening: 1 month

6.4 Special precautions for storage
Do not store above 25°C. Store in the original package in order to protect from light and moisture!

6.5 Nature and contents of container
Risedronate film-coated tablets: Al/PVC blister

Calcium carbonate/vitamin D3 effervescent tablets: Polypropylene tubes with polyethylene stopper containing a silica gel desiccant

Pack sizes:
4 film-coated tablets + 24 (2 x 12) effervescent tablets
A single carton box contains both the film-coated tablet blister (placed in a carton box) and the effervescent tablets in tubes for one month use.
3 x (4 film-coated tablets + 24 (2 x 12) effervescent tablets)
A single carton box contains both the film-coated tablet blister (placed in carton boxes) and the
effervescent tablets in tubes for three months use.
4 x (4 film-coated tablets + 24 (2 x 12) effervescent tablets)
A single carton box contains both the film-coated tablet blister (placed in carton boxes) and the
effervescent tablets in tubes for four months use.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements

7 MARKETING AUTHORISATION HOLDER
Sandoz Ltd
Frimley Business Park,
Frimley,
Camberley,
Surrey,
GU16 7SR.

8 MARKETING AUTHORISATION NUMBER(S)
PL 04416/1091

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
19/03/2012

10 DATE OF REVISION OF THE TEXT
19/03/2012
Module 3

Corica Combi 35 mg + 1000 mg / 880 IU Film-coated Tablets + Effervescent Tablets

Risedronate sodium + calcium/cholecalciferol

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet?
1. What is Corica Combi and what is it used for?
2. What you need to know before you take Corica Combi
3. How to take Corica Combi
4. Possible side effects
5. How to store Corica Combi
6. Contents of the pack and other information

1. What Corica Combi is and what it is used for

Corica Combi is used to treat osteoporosis, even if severe, in women after menopause who also need daily calcium and vitamin D3 supplementation. This combination medicine reduces the risk of spinal and hip fractures.

a) Risedronate belongs to a group of medicines called bisphosphonates. It works directly on your bones to make them stronger and therefore less likely to break.

b) Calcium/vitamin D3 provides the calcium and the vitamin D3 that your body may need to maintain new bone.

2. What you need to know before you take Corica Combi

Do not take Corica Combi if you have:
- allergy (hypersensitivity) to risedronate sodium, calcium carbonate, vitamin D3 tablets, peanut or any of the other ingredients of this medicine (listed in section 6)
- blood calcium levels which are below or above normal
- urine calcium levels which are above normal
- blood vitamin D levels which are too low or too high
- pregnant, may be pregnant or planning to become pregnant
- breast-feeding
- severe kidney problems, including kidney stones

Warnings and precautions
Ask your doctor for advice before taking this medicine if any of the following conditions apply to you:
- unable to stand or sit upright for at least 30 minutes
- abnormal bone and mineral absorption, conversion and/or excretion, for example:
  - lack of vitamin D,
  - parathyroid hormone abnormalities
  - height reduction leading to below normal calcium levels.
- previous problems with your gut, such as pain or difficulty in swallowing food
- sarcoidosis, a disorder mainly affecting the lungs, which causes shortness of breath and coughing
- heart failure
- poor kidney function
- heart, lung or kidney disease
- uncontrolled diabetes
- you are under 50 years of age

Tell your doctor that you are being treated with Corica Combi.

Children and adolescents
Risedronate is not recommended for use in children below age 18 due to insufficient data on safety and efficacy.

Other medicines and Corica Combi
Talk to your doctor or pharmacist if you are taking or have recently taken or might take any other medicines.

a) Medicines containing any of the following reduce the effect of Risedronate; if taken at the same time:
- calcium
- magnesium
- aluminium, contained for example in medicines to treat heartburn or indigestion
- iron
- Take these medicines at least 30 minutes after your Risedronate tablet.

b) Calcium/vitamin D3 is known to affect or be affected by the following medicines:
- digitalis: a medicine to treat heart weakness
- naproxen: a painkiller, anti-inflammatory medicine
- medicines to reduce inflammation or prevent organ transplant rejection, such as azathioprine
- calcium: used to strengthen tooth enamel or to treat osteoporosis
- thyroid hormones: medicines to increase water output through your kidneys
- chlorothiazide: a medicine to reduce blood fat levels
- laxatives, such as paraffin wax

Your doctor will give you further instructions, if you take any of the above-mentioned medicines.

Corica Combi with food and drink
a) Do not take your Risedronate tablet with food or drink, other than plain water, to ensure that it works properly. This particularly applies to dairy products, such as milk, as they contain calcium, see section 2. Other medicines and Corica Combi. Food and drinks, other than plain water, may only be taken at least 30 minutes after your Risedronate tablet.

b) Do not take the dissolved Calcium/vitamin D3 effervescent tablets with foods containing high amounts of:
- oxalic acid, such as spinach and rhubarb, or
- phytic acid, such as whole wheat.

Take the dissolved tablets at least 2 hours after eating such foods.

Pregnancy and breast-feeding
Do not take Corica Combi if you are, may be pregnant or plan to become pregnant or if you are breast-feeding.

The risk associated with the use of risedronate sodium in pregnant women is unknown.

Ask your doctor or pharmacist for advice before taking this medicine.

Driving and using machines
Corica Combi is not known to affect your ability to drive or use machines.

Corica Combi contains lactose, sucrose and sodium
The Risedronate tablets contain lactose. The Calcium/vitamin D3 effervescent tablets contain lactose and sucrose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before you take the medicines for this product.

The Calcium/vitamin D3 effervescent tablets contain 1.98 mmol (43.69 mg) sodium per tablet. Be taken into consideration by patients on a controlled sodium diet.

3. How to take Corica Combi

Always take this medicine exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Corica Combi is a weekly therapy of:
- a) 1 Risedronate tablet
- b) 1 Calcium/vitamin D3 effervescent tablets

The recommended dose per weekly cycle is:
- 1 Risedronate tablet (orange tablet):
  - Choose one day of the week that best fits your schedule. This will be the "Day 1" of your weekly cycle.
  - Each week, take the Risedronate tablet on your chosen "Day 1" at the position of the strip which is marked with the corresponding week (i.e. week 1).
- Days 2 to 7
  - 1 Calcium/vitamin D3 effervescent tablet per day for the next 6 days
  - Start Calcium/vitamin D3 intake on the day after the Risedronate tablet has been taken.

Do not take the Risedronate tablet and the Calcium/vitamin D3 effervescent tablet on the same day.

Every 7 days start a new weekly box beginning with the Risedronate tablet on your chosen "Day 1".

Method of use
a) Take your Risedronate tablet whole:
  - In the morning at least 30 minutes before your first food, drink or other medicine
  - whilst you are standing, to avoid heartburn
  - with at least one glass of plain water

Do not be last for 20 minutes after taking your tablets. Small spills, wind, do not suck or chew the tablets.

b) Take the Calcium/vitamin D3 effervescent tablet after dissolving it in a glass of water.
**Duration of use**
This will be decided by your doctor.

**If you take more Corica Combi than you should**

a) Drink one glass of milk and seek medical attention if you have taken more Risedronate tablets than prescribed.

b) Please contact your doctor if you have taken more Calcium/vitamin D3 effervescent tablets than you should.

**If you forget to take Corica Combi**

a) If you have forgotten to take your Risedronate tablet on your chosen day "Day 1".
   1. Take it on the day you remember. Do not take two Risedronate tablets in one day to make up for the tablet you missed.
   2. On the following day take your Calcium/vitamin D3 effervescent tablet.
   3. Do not take your Risedronate tablet and the effervescent tablet on the same day.
   4. Continue taking one Calcium/vitamin D3 effervescent tablet each day until the end of the weekly cycle.
   5. Discard any remaining calcium/vitamin D tablets in the box at the end of the weekly cycle.

   Then start a new weekly cycle: take one Risedronate tablet once a week on your chosen "Day 1".

b) If you have forgotten to take a Calcium/vitamin D3 effervescent tablet:
   1. Take it on the day you remember, but do not take two effervescent tablets on the same day. Do not take the effervescent tablet on the same day as the Risedronate tablet.
   2. Continue taking one effervescent tablet each day until the end of the weekly cycle.
   3. Discard the forgotten effervescent tablet.

**If you stop taking Corica Combi**

If you stop treatment you may begin to lose bone mass. Please talk to your doctor before you consider stopping treatment.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

---

**Possible side effects**

Like all medicines, this medicine can cause side effects, although not everybody gets them.

a) Possible side effects caused by Risedronate

Stop taking Risedronate and contact a doctor immediately if you experience any of the following:

- Severe swelling of deep skin layers (angioedema) characterised by:
  - Swelling of face, tongue or throat
  - Difficulty in swallowing
  - Noses and difficulties in breathing
  - Swollen skin, blisters under the skin

Inform your doctor immediately if you have:

- Eye inflammation, usually with pain, redness and light sensitivity
- Depression which may be associated with delayed healing and infection, often following tooth extraction
- Difficulty and pain in swallowing, chest pain, or new or unusual heartburn.

Common, may affect up to 1 in 10 people:

- Indigestion, feeling sick, stomach pain, stomach cramps or discomfort, constipation, feeling of fullness, bloating, diarrhea
- Pain in your tummy, muscles or joints
- Headache

Uncommon, may affect up to 1 in 100 people:

- Inflammation in the region of the gut causing:
  - Difficulty and pain in swallowing
  - Inflammation in the stomach and the first part of the small bowel immediately beyond the stomach
  - Inflammation of the large bowel, pain, and visual disturbances

Rare, may affect up to 1 in 1,000 people:

- Tongue inflammation with swelling and possible pain
- Narrowing of the gut
- Abnormal liver blood tests
- Reduced blood calcium and phosphorous levels

Other changes are usually small, occur at the beginning of treatment and cause no symptoms.

- Unusual fracture of the hip bone, particularly in patients on long-term treatment for osteoporosis may occur rarely.

Contact your doctor if you experience pain, weakness or discomfort in your thigh, hip or groin as this may be an early indication of a possible fracture of the hip bone.

Not known: frequency cannot be estimated from the available data

- Half-loss
- Liver disorders, some cases were severe

b) Possible side effects caused by Calcium/vitamin D3

Uncommon, may affect up to 1 in 100 people:

- Blood calcium levels above normal

Symptoms are excessive thirst, loss of appetite, fatigue and in severe cases irregular heartbeat.

- Urine calcium levels above normal

Rare, may affect up to 1 in 1,000 people:

- Constipation, wind, nausea, abdominal pain, diarrhoea
- Skin reactions such as itching, rash and hives

If you get any side effects, talk to your doctor or pharmacist. This includes any side effects not listed in this leaflet.
The below package leaflet is provided as text only. However, the marketing authorisation holder has committed to submitting mock-ups to the regulatory authorities before marketing this product.

**Package leaflet: Information for the user**

[Risedronate sodium and Calcium / Cholecalciferol 35 mg + 1000 mg / 880 IU film-coated tablets + effervescent tablets]

Risedronate sodium+calcium/cholecalficorol

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them even if their symptoms are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

**What is in this leaflet:**

1. What Risedronate sodium and Calcium / Cholecalciferol is and what it is used for
2. What you need to know before you take Risedronate sodium and Calcium / Cholecalciferol
3. How to take Risedronate sodium and Calcium / Cholecalciferol
4. Possible side effects
5. How to store Risedronate sodium and Calcium / Cholecalciferol
6. Contents of the pack and other information

1. What Risedronate sodium and Calcium / Cholecalciferol is and what it is used for

Risedronate sodium and Calcium / Cholecalciferol is used to treat osteoporosis, even if severe, in women after menopause who also need daily calcium and vitamin D3 supplementation. This combination medicine reduces the risk of spinal and hip fractures.

a) Risedronate belongs to a group of medicines called bisphosphonates. It works directly on your bones to make them stronger and therefore less likely to break.

b) Calcium/vitamin D3 provides the calcium and the vitamin D3 that your body may need to build new bone.

2. What you need to know before you take Risedronate sodium and Calcium / Cholecalciferol

Do not take Risedronate sodium and Calcium / Cholecalciferol

If you are/are have

- allergic (hypersensitive) to risedronate sodium, calcium carbonate, vitamin D3, soya, peanut or any of the other ingredients of this medicine (listed in section 6)
- blood calcium levels which are below or above normal
- urine calcium levels which are above normal
- blood vitamin D levels which are above normal
- pregnant, may be pregnant or planning to become pregnant
- breast feeding
- severe kidney problems, including kidney stones

**Warnings and precautions**

Ask your doctor for advice before taking this medicine if any of the following conditions apply to you:

- unable to stand or sit upright for at least 30 minutes
- abnormal bone and mineral absorption, conversion and/or excretion, for example:
  - lack of vitamin D
- parathyroid hormone abnormalities
  Both of which lead to below normal calcium levels.
- previous problems with your gullet, such as pain or difficulty in swallowing food
- sarcoidosis, a disorder mainly affecting the lungs, which causes shortness of breath and coughing
- already taking vitamin D
- had or have pain, swelling or numbness of the jaw, a “heavy jaw feeling” or loosening of a tooth
- under dental treatment or will undergo dental surgery
  Tell your dentist that you are being treated with Risedronate sodium and Calcium
  Cholecalciferol.

**Children and adolescents**
Risedronate is not recommended for use in children below age 18 due to insufficient data on safety and efficacy.

**Other medicines and Risedronate sodium and Calcium / Cholecalciferol**
Talk to your doctor or pharmacist if you are taking or have recently taken or might take any other medicines.

a) Medicines containing any of the following reduce the effect of Risedronate if taken at the same time:
- calcium
- magnesium
- aluminium, contained for example in medicines to treat heartburn
- iron
  Take these medicines at least 30 minutes after your Risedronate tablet.

b) Calcium/vitamin D₃ is known to affect or be affected by the following medicines:
- digitalis: a medicine to treat heart weakness
- tetracycline antibiotics
- medicines to reduce inflammation or prevent organ transplant rejection, such as cortisone
- sodium fluoride: used to strengthen tooth enamel or to treat osteoporosis
- thiazides diuretics: medicines to increase water output through your kidneys
- cholestyramine: a medicine to reduce blood fat levels
- laxatives, such as paraffin oil

Your doctor will give you further instructions, if you take any of the above-mentioned medicines.

**Risedronate sodium and Calcium / Cholecalciferol with food and drink**

a) Do not take your Risedronate tablet with food or drinks, other than plain water, to ensure that it works properly. This particularly applies to dairy products, such as milk, as they contain calcium, see section 2. Other medicines and Risedronate sodium and Calcium / Cholecalciferol.

Food and drinks, other than plain water, may only be taken at least 30 minutes after your Risedronate tablet.

b) Do not take the dissolved Calcium/vitamin D₃ effervescent tablets with foods containing high amounts of
- oxalic acid, such as spinach and rhubarb, or
- phytic acid, such as whole cereals

Take the dissolved tablets at least 2 hours after eating such foods.
Pregnancy and breast-feeding
Do not take Risedronate sodium and Calcium / Cholecalciferol if you are, may be pregnant or plan to become pregnant or if you are breast-feeding.

The risk associated with the use of risedronate sodium in pregnant women is unknown.

Ask your doctor or pharmacist for advice before taking this medicine.

Driving and using machines
Risedronate sodium and Calcium / Cholecalciferol is not known to affect your ability to drive or use machines.

Risedronate sodium and Calcium / Cholecalciferol contain lactose, sucrose and sodium. The Risedronate tablets contain lactose. The Calcium/vitamin D3 effervescent tablets contain lactose and sucrose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before you taking this medicinal product.

The Calcium/vitamin D3 effervescent tablets contain 1.90 mmol (43.59 mg) sodium per tablet. To be taken into consideration by patients on a controlled sodium diet.

3. How to take Risedronate sodium and Calcium / Cholecalciferol
Always take this medicine exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Risedronate sodium and Calcium / Cholecalciferol is a weekly therapy of:
 a) 1 Risedronate tablet;
 b) 6 Calcium/vitamin D3 effervescent tablets

The recommended dose per weekly cycle is:
• Day 1
  1 Risedronate tablet (orange tablet)
  Choose one day of the week that best fits your schedule. This will be “Day 1” of your weekly cycle.
  Every week, take the Risedronate tablet on your chosen “Day 1” at the position of the strip which is marked with the corresponding week (e.g. week 1).

• Days 2 to 7
  1 Calcium/vitamin D3 effervescent tablet per day for the next 6 days
  Start Calcium/vitamin D3 intake on the day after the Risedronate tablet has been taken.

Do not take the Risedronate tablet and the Calcium/vitamin D3 effervescent tablet on the same day.

Every 7 days start a new weekly box beginning with the Risedronate tablet on your chosen “Day 1”.

Method of use
 a) Take your Risedronate tablet whole:
 • in the morning at least 30 minutes before your first food, drink or other medicine
 • whilst you sit or stand, to avoid heartburn
 • with at least one glass of plain water
 Do not lie down for 30 minutes after taking your tablet. Swallow it whole, do not suck or chew the tablets.
b) Take the Calcium/vitamin D$_3$ effervescent tablet after dissolving it in a glass of water.

**Duration of use**
This will be decided by your doctor.

**If you take more Risedronate sodium and Calcium / Cholecalciferol than you should**

a) Drink one glass of milk and seek medical attention if you have taken more Risedronate tablets than prescribed.

b) Please contact your doctor if you have taken more Calcium/vitamin D$_3$ effervescent tablets than you should.

**If you forget to take Risedronate sodium and Calcium / Cholecalciferol**

a) If you have forgotten to take your Risedronate tablet on your chosen day “Day 1”:
1. Take it on the day you remember. Do not take two Risedronate tablets in one day to make up for the tablet you missed.
2. On the following day take your Calcium/vitamin D$_3$ effervescent tablet. Do not take your Risedronate tablet and the effervescent tablet on the same day.
3. Continue taking one Calcium/vitamin D$_3$ effervescent tablet each day until the end of the weekly cycle.
4. Discard any remaining calcium/vitamin D tablets in the box at the end of the weekly cycle.

Then start a new weekly cycle: take one Risedronate tablet once a week on your chosen “Day 1”.

b) If you have forgotten to take a Calcium/vitamin D$_3$ effervescent tablet:
1. Take it on the day you remember, but do not take two effervescent tablets on the same day. Do not take the effervescent tablet on the same day as the Risedronate tablet.
2. Continue taking one effervescent tablet each day until the end of the weekly cycle.
3. Discard the forgotten effervescent tablet.

**If you stop taking Risedronate sodium and Calcium / Cholecalciferol**

If you stop treatment you may begin to lose bone mass. Please talk to your doctor before you consider stopping treatment.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. **Possible side effects:**

Like all medicines, this medicine can cause side effects, although not everybody gets them.

a) **Possible side effects caused by Risedronate**

Stop taking Risedronate and contact a doctor immediately if you experience any of the following:
- **severe swellings** of deep skin layers (angioedema) characterized by
  - swelling of face, tongue or throat
  - difficulties in swallowing
  - hives and difficulties in breathing
• severe skin reactions involving blisters under the skin

Inform your doctor immediately if you have:
• eye inflammation, usually with pain, redness and light sensitivity
• degeneration of the jaw bone associated with delayed healing and infection, often following tooth extraction
• difficulty and pain in swallowing, chest pain, or new or worsened heartburn

Common, may affect up to 1 in 10 people
• indigestion, feeling sick, stomach pain, stomach cramps or discomfort, constipation, feelings of fullness, bloating, diarrhoea
• pain in your bones, muscles or joints
• headache

Uncommon, may affect up to 1 in 100 people
• inflammation or ulcer of the gut causing
  - difficulty and pain in swallowing
  - inflammation of the stomach and the first part of the small bowel immediately beyond the stomach
• inflammation of the iris causing red, painful eyes and visual disturbances

Rare, may affect up to 1 in 1,000 people
• tongue inflammation with swelling and possible pain
• narrowing of the gut
• abnormal liver blood tests
• reduced blood calcium and phosphate levels
  These changes are usually small, occur at the beginning of treatment and cause no symptoms.
• Unusual fracture of the thigh bone particularly in patients on long-term treatment for osteoporosis may occur rarely. Contact your doctor if you experience pain, weakness or discomfort in your thigh, hip or groin as this may be an early indication of a possible fracture of the thigh bone.

Not known: frequency cannot be estimated from the available data
• hair loss
• liver disorders, some cases were severe

b) Possible side effects caused by Calcium/vitamin D₃

Uncommon, may affect up to 1 in 100 people
• blood calcium levels above normal
  Symptoms are excessive thirst, loss of appetite, fatigue and in severe cases irregular heartbeat.
• urine calcium levels above normal

Rare, may affect up to 1 in 1,000 people
• constipation, wind, nausea, abdominal pain, diarrhoea
• skin reactions such as itching, rash and hives

If you get any side effects, talk to your doctor or pharmacist. This includes any side effects not listed in this leaflet.

5. How to store Risedronate sodium and Calcium / Cholecalciferol
Keep out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton after EXP. The expiry date refers to the last day of that month.

Do not store above 25 °C. Store in the original package in order to protect from light and moisture!

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What **Risedronate sodium and Calcium / Cholecalciferol** contains

a) Risedronate film-coated tablets
The active substance is risedronate sodium.

One film-coated tablet contains 35 mg risedronate sodium, equivalent to 32.5 mg risedronic acid.

The other ingredients are:
- Tablet core: microcrystalline cellulose, crospovidone, lactose monohydrate, magnesium stearate
- Film coating: hydroxypropyl methylcellulose, macrogol 400, titanium dioxide (E171), ferric oxide yellow (E172), ferric oxide red (E172)

b) Calcium/vitamin D₃ effervescent tablets
The active substances are calcium carbonate and cholecalciferol (vitamin D₃).

One effervescent tablet contains:
- 2500 mg calcium carbonate, equivalent to 1000 mg calcium
- 22 micrograms (880 International Units [IU]) cholecalciferol (vitamin D₃)

The other ingredients are: citric acid, anhydrous, simeticone, gelatine, lactose monohydrate, macrogol 6000, maize starch, methyl cellulose, sodium cyclamate, sodium hydrogen carbonate, povidone K25, saccharin sodium, colloidal silicon dioxide, hydrogenated soya oil, sucrose, alpha-tocopherol, aromatics (orange juice flavour, PHS-133147 (containing maltodextrin, orange flavouring substances and hydroxyethyl starch)).

What **Risedronate sodium and Calcium / Cholecalciferol** looks like and contents of the pack

a) Risedronate film-coated tablets: oval biconvex, orange, encoded 35 on one side. It is packed in a plastic/aluminum strip.

b) Calcium/vitamin D₃ effervescent tablets: cylindrical, white or off-white coloured biplane effervescent tablets with bevel-edges on both sides. It is packed in a tube.

**Risedronate sodium and Calcium / Cholecalciferol** is available in packs containing
- 4 film-coated tablets + 24 (2 x 12) effervescent tablets
A single carton box contains both the film-coated tablet blister (placed in a carton box) and the effervescent tablets in tubes for one month use

- 3 x (4 film-coated tablets + 24 (2 x 12) effervescent tablets)

A single carton box contains both the film-coated tablet blister (placed in carton boxes) and the effervescent tablets in tubes for three months use

- 4 x (4 film-coated tablets + 24 (2 x 12) effervescent tablets)

A single carton box contains both the film-coated tablet blister (placed in carton boxes) and the effervescent tablets in tubes for four months use.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Sandoz Ltd
Frimley Business Park,
Frimley,
Camberley,
Surrey,
GU16 7SR.

This medicinal product is authorised in the Member States of the EEA under the following names:
<To be completed nationally>

This leaflet was last approved in (03/2012).
Module 4
Labelling

Corica Combi
35 mg +
1000 mg/880 IU
Film-coated Tablets *
Effervescent Tablets
Risedronate Sodium +
Calcium/Cholecalciferol
4 film-coated tablets +
24 effervescent tablets
Film-coated and
effervescent tablets for
one month use

Corica Combi 1000 mg/880 IU
Effervescent Tablets
Calcium/Cholecalciferol
12 effervescent tablets

Oral use. Use as directed by your doctor.
Read the package leaflet before use.
Do not store above 25°C. Store in the original package in order to protect from light and moisture.
Take 1 effervescent tablet per day from day 2 to 7 of your weekly cycle.

Keep out of the sight and reach of children.
Each effervescent tablet contains 2500 mg calcium carbonate (equivalent to 1000 mg calcium) and 22 micrograms (880 IU) cholecalciferol [Vitamin D3).
See leaflet for further information.
The below labelling is provided as text only. However, the marketing authorisation holder has committed to submitting mock-ups to the regulatory authorities before marketing this product.

| PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING |
| Carton box of Risedronate Sodium |

1. NAME OF THE MEDICINAL PRODUCT

Risedronate sodium 35 mg film-coated tablets
Risedronate sodium

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Contains lactose.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

4 film-coated tablets
For one month use
3 x (4 film-coated tablets)
For three months use
4 x (4 film-coated tablets)
For four months use

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use. Read the Package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
9. **SPECIAL STORAGE CONDITIONS**

Do not store above 25°C. Store in the original package in order to protect from light and moisture.

10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

11. **NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Sanosan Ltd
Frimley Business Park,
Frimley,
Camberley,
Surrey,
GU16 7SR.

12. **MARKETING AUTHORISATION NUMBER(S)**

PL 04416/1091

13. **BATCH NUMBER**

Lot

14. **GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription

15. **INSTRUCTIONS ON USE**

16. **INFORMATION IN BRAILLE**

[nationally completed name]
MINIMUM PARTICULARS TO APPEAR ON BLISTERS
AL/PVC blisters (Risedronate Sodium)

1. NAME OF THE MEDICINAL PRODUCT

[Risedronate sodium 35 mg film-coated tablets]
Risedronate sodium

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Sandoz Ltd

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. OTHER

“Week 1 to 4”
Take 1 film-coated tablet per week on Day 1 of your weekly cycle.
PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

Tube (Effervescent tablet)

1. **NAME OF THE MEDICINAL PRODUCT**

[Calcium / Cholecalciferol 1000 mg / 880 IU effervescent tablets]

calcium/cholecalciferol

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**

Each effervescent tablet contains 2500 mg calcium carbonate (equivalent to 1000 mg calcium) and 22 micrograms (880 IU) cholecalciferol (vitamin D3).

3. **LIST OF EXCIPIENTS**

Contains lactose, sodium, sucrose and soya oil. Read the package leaflet before use.

4. **PHARMACEUTICAL FORM AND CONTENTS**

12 effervescent tablets

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**

Oral use.

6. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children

7. **OTHER SPECIAL WARNING(S), IF NECESSARY**

8. **EXPIRY DATE**

EXP

9. **SPECIAL STORAGE CONDITIONS**

Do not store above 25°C. Store in the original package in order to protect from light and moisture!

10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**
11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sandoz Ltd
Frimley Business Park
Frimley,
Camberley,
Surrey,
GU16 7SR.

12. MARKETING AUTHORISATION NUMBER(S)

FL 04416/1091

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

Take 1 effervescent tablet per day from day 2 to 7 of your weekly cycle.
PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON BOX (final KIT)

1. NAME OF THE MEDICINAL PRODUCT

[Risedronate sodium and Calcium / Cholecalciferol 35 mg + 1000 mg / 880 IU film-coated tablets + effervescent tablets]

Risedronate sodium + calcium / cholecalciferol

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Film-coated tablet.
Contains lactose.

Effervescent tablets. Contains lactose, sodium, sucrose and soya oil.

See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

4 film-coated tablets + 24 (2 x 12) effervescent tablets
Film-coated and effervescent tablets for one month use
3 x (4 film-coated tablets + 24 (2 x 12) effervescent tablets)
Film-coated and effervescent tablets for three months use
4 x (4 film-coated tablets + 24 (2 x 12) effervescent tablets)
Film-coated and effervescent tablets for four months use

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use. Read the Package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY
8. **EXPIRY DATE**

EXP

9. **SPECIAL STORAGE CONDITIONS**

Do not store above 25°C. Store in the original package in order to protect from light and moisture!

10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

11. **NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Sandoz Ltd
Frimley Business Park,
Frimley,
Camberley,
Surrey,
GU16 7SR.

12. **MARKETING AUTHORISATION NUMBER(S)**

PL 04416/1091

13. **BATCH NUMBER**

film-coated tablets: Batch
effervescent tablets: Batch

14. **GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

15. **INSTRUCTIONS ON USE**

16. **INFORMATION IN BRAILLE**

[nationally completed name]
Module 5

Scientific discussion during initial procedure

I  INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the member states considered that the applications for Corica Combi 35 mg + 1000 mg/880 IU Film-coated Tablets + Effervescent Tablets and Risedronate sodium and Calcium/Cholecalciferol 35 mg + 1000 mg/880 IU Tablets (PL 04416/1090-1; UK/H/3373 & 3393/001/DC) could be approved. These applications were submitted via the decentralised procedure, with the UK as reference member state (RMS), and Belgium, Greece, Ireland, Spain and Slovak Republic as concerned member states (CMS).

These are prescription-only medicines for the treatment of postmenopausal osteoporosis, to reduce the risk of vertebral fractures, and the treatment of established postmenopausal osteoporosis, to reduce the risk of hip fractures.

These are applications made under the decentralised procedure (DCP), according to Article 10.1 of 2001/83/EC, as amended, claiming to be generic medicinal products of Optinate 5 mg film coated tablets, which were initially granted to Sanofi Aventis AB on the 7th October 1999. This was followed by a registration in the UK and other member states via a Mutual Recognition Procedure (SE/H/0192/001-2/MR - Actonel 5 mg & 30 mg film coated tablets), on 16th March 2000. In 2003 Actonel 35 mg film coated tablet was authorised via mutual recognition (SE/H/0192/003/MR). In line with Article 6 of the Directive 2001/83/EC, the additional presentation as a convenience pack in Actonel Combi was granted a marketing authorisation, belonging to the same global marketing authorisation. The medicinal product calcium/vitamin D 1000mg/880 IU effervescent granules has been licensed in the EU for more than 10 years.

These applications concern a convenience pack and not a fixed combination because the two components, Risedronate 35 mg tablets and the effervescent tablets containing 2500 mg calcium carbonate (corresponding to 1000 mg elemental calcium) and 880 IU cholecalciferol (corresponding to 22 μg vitamin D3) are separate medicinal products packed together in a single carton and under a single MA number. The purpose of this convenience pack is to improve patient compliance to dosing instructions.

Risedronate sodium is a pyridinyl bisphosphonate that inhibits osteoclast-mediated bone resorption and modulates bone metabolism. Bone is continually being formed and dissolved. By slowing down the rate at which bone is dissolved, risedronate increases the amount of bone. The administration of calcium/vitamin D in combination with any bisphosphonate in osteoporosis is to avoid secondary hyperparathyroidism and ensure sufficient availability of calcium for the mineralisation of the bone matrix.

No new non-clinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years.

With the exception of the bioequivalence study, no new clinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years.
One bioequivalence study was performed, which compared the pharmacokinetics of Risedronate sodium 35mg film-coated tablets (the test product) and Actonel 35mg film-coated tablets (the reference product - Proctor and Gamble Pharmaceuticals, Germany). The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP). No bioequivalence study was submitted for the calcium carbonate/cholecalciferol effervescent tablets because these are dissolved in a glass of water before ingestion.

The RMS has been assured that acceptable standards of Good Manufacturing Practice are in place for these product types at all sites responsible for the manufacture, assembly and batch release of these products.

The RMS and CMS considered that the applications could be approved with the end of procedure (Day 210) on 18 January 2012. After a subsequent national phase, the licences were granted in the UK on 19 March 2012.

**II. ABOUT THE PRODUCT**

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Corica Combi 35 mg + 1000 mg/880 IU Film-coated Tablets + Effervescent Tablets Risedronate sodium and Calcium/Cholecalciferol 35 mg + 1000 mg/880 IU Tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>35 mg risedronate sodium (equivalent to 32.5 mg risedronic acid)</td>
</tr>
<tr>
<td></td>
<td>2500 mg calcium carbonate (equivalent to 1000 mg calcium)</td>
</tr>
<tr>
<td></td>
<td>22 micrograms (880 IU) cholecalciferol (vitamin D3)</td>
</tr>
<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Bisphosphonates, combinations (M05BB04)</td>
</tr>
<tr>
<td>Pharmaceutical form and strength(s)</td>
<td>35 mg risedronate sodium film-coated tablets 2500 mg calcium carbonate/22 micrograms (880 IU) cholecalciferol effervescent tablets</td>
</tr>
<tr>
<td>Reference numbers for the Mutual Recognition Procedure</td>
<td>UK/H/3373 &amp; 3393/001/DC</td>
</tr>
<tr>
<td>Reference Member State</td>
<td>United Kingdom</td>
</tr>
</tbody>
</table>
| Member States concerned                      | UK/H/3373/001/DC: Belgium, Greece, Spain, Slovak Republic  
UK/H/3393/001/DC: Ireland                                                                 |
| Marketing Authorisation Number(s)            | PL 04416/1090-1                                                                                                   |
| Name and address of the authorisation holder  | Sandoz Ltd, Frimley Business Park, Frimley, Camberley, Surrey, GU16 7SR.                                         |
III SCIENTIFIC OVERVIEW AND DISCUSSION
III.1 QUALITY ASPECTS

S. Active substance – Risedronate sodium

rINN: Risedronate sodium
Chemical name: Monosodium 2-(3-pyridyl)-1-hydroxyethane diphosphonic acid hemipentahydrate

Structure:

```
\[
\begin{align*}
\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{
Calcium carbonate is the subject of a European Pharmacopoeia monograph.

With the exception of the packaging and stability, all aspects of the manufacture and control of the active substance are covered by European Directorate for the Quality of Medicines (EDQM) Certificates of Suitability.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

S. Active substance – Cholecalciferol concentrate (powder form)

rINN: Cholecalciferol

Structure:

Molecular formula: $\text{C}_{27}\text{H}_{44}\text{O}_{4}$

Molecular weight: 384.6 g/mol

Appearance: White or almost white crystals, practically insoluble in water, freely soluble in alcohol, chloroform and fatty acid. The cholecalciferol concentrate powder is, however, soluble in water.

Cholecalciferol concentrate (powder form) is the subject of a European Pharmacopoeia monograph.

With the exception of the packaging and stability, all aspects of the manufacture and control of the active substance are covered by European Directorate for the Quality of Medicines (EDQM) Certificates of Suitability.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.
P. Medicinal Product

Other Ingredients

Other ingredients consist of the pharmaceutical excipients in the risedronate sodium film-coated tablet and the calcium carbonate/cholecalciferol effervescent tablets namely:

Film-coated tablet – crospovidone, lactose monohydrate, magnesium stearate, microcrystalline cellulose, hypromellose, macrogol 400, titanium dioxide (E171), yellow ferric oxide (E172) and red ferric oxide (E172)

Effervescent tablet - citric acid anhydrous, gelatin, lactose monohydrate, macrogol 6000, maize starch, sodium cyclamate, sodium hydrogen carbonate, povidone K25, saccharin sodium, hydrogenated soya oil, sucrose, alphatocopherol, methylcellulose, simeticone, and aromatics (orange juice flavour, PHS-133147 [containing maltodextrin, orange flavouring substances and hydroxyethyl starch])

With the exception of the orange juice flavour/PHS-133147, yellow ferric oxide (E172) and red ferric oxide (E172), all excipients comply with their respective European Pharmacopoeia monographs. Yellow ferric oxide (E172) and red ferric oxide (E172) comply with US National Formulary specifications and current European Directives concerning use of colouring agents in foodstuff. Orange juice flavour/PHS-133147 complies with a suitable in-house specification.

Suitable batch analysis data have been provided for all excipients, showing compliance with their respective specifications.

With the exception of lactose monohydrate and gelatin, none of the excipients are sourced from animal or human origin. Suitable declarations have been provided from the suppliers of lactose monohydrate to show that the lactose is sourced from healthy animals, under the same conditions as milk for human consumption and only calf rennet is used in its preparation. Suitable EDQM certificates of suitability have been provided for all suppliers of gelatin to show that these are produced in line with current European guidelines concerning the minimisation of transmission of BSE/TSE. No genetically modified organisms (GMO) have been used in the preparation of these products.

Pharmaceutical Development

The objective of the development programme was to formulate globally acceptable, stable and bioequivalent products that could be considered generic medicinal products of the innovator product Actonel® (Optinate®) from Aventis Pharma and Procter & Gamble Pharmaceuticals.

A satisfactory account of the pharmaceutical development has been provided.

Comparative in vitro dissolution and impurity profiles have been provided for the proposed risedronate sodium 35mg film-coated tablets and the respective innovator products from different EU member states.

Manufacturing Process

Satisfactory batch formulae have been provided for the manufacture of both the risedronate sodium film-coated tablet and the calcium carbonate/cholecalciferol effervescent tablets. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specification
The finished product specifications proposed for both the risedronate sodium film-coated tablets and the calcium carbonate/cholecalciferol effervescent tablets are acceptable. Test methods have been described and have been adequately validated. Batch data have been provided and comply with the release specifications. Certificates of analysis have been provided for all working standards used.

**Container-Closure System**
Risedronate film-coated tablets are packed in aluminium/polyvinylchloride blisters. Calcium carbonate/vitamin D3 effervescent tablets are packed in polypropylene tubes with polyethylene stoppers, containing a silica gel desiccant.

The finished product is packed in pack sizes of:

- 4 film-coated tablets + 24 (2 x 12) effervescent tablets - A single carton box contains both the film-coated tablet blister (placed in a carton box) and the effervescent tablets in tubes for one month use
- 3 x (4 film-coated tablets + 24 (2 x 12) effervescent tablets) - A single carton box contains both the film-coated tablet blister (placed in carton boxes) and the effervescent tablets in tubes for three months use
- 4 x (4 film-coated tablets + 24 (2 x 12) effervescent tablets) - A single carton box contains both the film-coated tablet blister (placed in carton boxes) and the effervescent tablets in tubes for four months use

It has been stated that not all pack sizes may be marketed, however, the marketing authorisation holder has committed to submitting the mock-ups for any pack size to the relevant regulatory authorities for approval before marketing.

Satisfactory specifications and certificates of analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

**Stability of the product**
Stability studies were performed in accordance with current guidelines on batches of finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 2 years; with the storage conditions “Do not store above 25°C” and “Store in the original package in order to protect from light and moisture”.

The shelf-life reduces to 1 month after opening for the calcium carbonate/vitamin D3 effervescent tablets.

**Bioequivalence/bioavailability**
Satisfactory certificates of analysis have been provided for the test and reference batches used in the bioequivalence study.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels**
The SmPCs, PIL and labels are pharmaceutically acceptable.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups (‘user testing’), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.
Pharmacovigilance System and Risk Management Plan
The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Suitable justification has been provided for not submitting a risk management plan for these products.

Marketing Authorisation Application (MAA) forms
The MAA forms are pharmaceutically satisfactory.

Quality Overall Summary (Expert report)
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion
The grant of marketing authorisations is recommended.

III.2 NON-CLINICAL ASPECTS
As the pharmacodynamic, pharmacokinetic and toxicological properties of risedronate sodium, calcium carbonate and cholecalciferol are well-known, no further non-clinical studies are required and none have been provided.

The applicant’s non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the products’ pharmacology and toxicology.

Suitable justification has been provided for the non-submission of an environmental risk assessment. As these products are intended for generic substitution with products that are currently marketed, no increase in environmental burden is expected.

There are no objections to the approval of these products from a non-clinical viewpoint.

III.3 CLINICAL ASPECTS
Pharmacokinetics
In support of these applications, the marketing authorisation holder has submitted the following bioequivalence study:

An open-label, randomised, two-period, two-treatment, two-sequence, single-dose, crossover study to compare the pharmacokinetics of the test product Risedronate sodium 35mg tablets versus the reference product Actonel (Proctor and Gamble Pharmaceuticals, Germany) in healthy adult subjects under fasted conditions.

Volunteers were dosed with either treatment after an overnight fast of at least 10 hours. Blood samples were taken for the measurement of pharmacokinetic parameters at pre- and up to 72 hours post dose. The two treatment arms were separated by a 28-day washout period.

The pharmacokinetic results (presented as geometric least-squares means, ratios and 90% confidence intervals) are presented below:

<table>
<thead>
<tr>
<th>Parameters (Units)</th>
<th>In-transformed Data</th>
<th>90% Confidence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Geometric Least Squares Mean</td>
<td></td>
</tr>
</tbody>
</table>

51
The 90% confidence intervals for C_{max} and AUC for test versus reference products are within predefined acceptance criteria. The data support the claim that the test product is bioequivalent to the reference product.

No bioequivalence study was submitted for the calcium carbonate/cholecalciferol effervescent tablets because these are dissolved in a glass of water before ingestion. This is acceptable.

**Efficacy**
No new data on the efficacy have been submitted and none are required for these types of applications.

**Safety**
With the exception of the data submitted during the bioequivalence study, no new safety data were submitted and none were required. No new or unexpected safety issues were raised by the bioequivalence data.

**SmPC, PIL and Labels**
The SmPCs, PIL and labels are medically acceptable. The SmPCs are consistent with those for the originator products.

**Clinical Expert Report**
The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

**Conclusion**
The grant of marketing authorisations is recommended.

### IV OVERALL CONCLUSION AND RISK-BENEFIT ASSESSMENT

#### QUALITY
The important quality characteristics of Corica Combi 35 mg + 1000 mg/880 IU Film-coated Tablets + Effervescent Tablets and Risedronate sodium and Calcium/Cholecalciferol 35 mg + 1000 mg/880 IU Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit-risk balance.

#### NON-CLINICAL
No new preclinical data were submitted and none are required for applications of this type.

#### CLINICAL
Bioequivalence has been demonstrated between the applicant’s product and the reference product Actonel (Proctor and Gamble Pharmaceuticals, Germany).

No new or unexpected safety concerns arose from these applications.

The SmPCs, PIL and labelling are satisfactory and consistent with those for the reference products.
RISK-BENEFIT ASSESSMENT
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant’s products and the originator products are interchangeable. Extensive clinical experience with risedronate sodium, calcium carbonate and cholecalciferol is considered to have demonstrated the therapeutic value of the compounds. The benefit-risk is therefore considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>