

## **SUMMARY OF PRODUCT CHARACTERISTICS**

## **1. NAME OF THE MEDICINAL PRODUCT**

Optinate Combi D 1000 mg/880 IU effervescent granules + 35 mg gastro-resistant tablet

## **2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each sachet of effervescent granules contains 1000 mg calcium as 2500 mg calcium carbonate and 22 micrograms (880 IU) cholecalciferol (vitamin D<sub>3</sub>).

Each gastro-resistant tablet contains 35 mg risedronate sodium equivalent to 32.5 mg risedronic acid.

### Excipients with known effect

Each sachet of effervescent granules contains potassium (163 mg), sucrose (1.7 mg), and sorbitol (1.1 mg).

For the full list of excipients, see section 6.1.

## **3. PHARMACEUTICAL FORM**

Effervescent granules

White effervescent granules.

Gastro-resistant tablet.

Oval, yellow, gastro-resistant tablet with “EC 35” engraved on one side.

The dimensions of the tablet are as follows: width 13 mm, length 6 mm.

## **4. CLINICAL PARTICULARS**

### **4.1 Therapeutic indications**

Treatment of osteoporosis in postmenopausal women at increased risk of fractures (see section 5.1).  
Optinate Combi D is only intended for use in assessed patients for whom the amount of calcium and vitamin D<sub>3</sub> included is considered to provide adequate supplementation.

### **4.2 Posology and method of administration**

Optinate Combi D is a combination product consisting of risedronate 35 mg gastro-resistant tablets and calcium/vitamin D<sub>3</sub> sachets in a box.

#### Posology

The recommended dose in adults is one risedronate 35 mg gastro-resistant tablet orally once a week followed on the next day by one calcium/vitamin D<sub>3</sub> sachet daily for 6 days.

The tablet should be taken on the same day each week.

The sequence is repeated each week.

The optimal duration of bisphosphonate treatment for osteoporosis has not been established. The need for continued treatment should be re-evaluated periodically based on the benefits and potential risks of risedronate on an individual patient basis, particularly after 5 or more years of use.

## Special populations

### *Elderly*

Of the patients receiving risedronate 35 mg gastro-resistant tablets in postmenopausal osteoporosis studies, 59% were 65 and over, while 13 % were 75 and over. No overall differences in safety and effectiveness were observed between these patients and younger patients. However, renal function of the elderly patient should be considered (see section 4.4).

### *Patients with renal impairment*

Vitamin D<sub>3</sub> should be used with caution in patients with impairment of renal function and the effect on calcium and phosphate levels should be monitored. The use of risedronate sodium is contraindicated in patients with severe renal impairment (creatinine clearance lower than 30 ml/min) (see sections 4.3 and 5.2).

### *Paediatric population*

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

## Method of administration

Risedronate 35 mg gastro-resistant tablets should be taken orally in the morning immediately after breakfast. Administration under fasting conditions may lead to an increased risk of upper abdominal pain (see section 4.8 and 5.2).

The tablet must be swallowed whole and not sucked or chewed. To aid delivery of the tablet to the stomach, it is to be taken while in an upright position with a glass of plain water ( $\geq 120$  ml). Patients should not lie down for 30 minutes after taking the tablet (see section 4.4).

### *Calcium/vitamin D<sub>3</sub> (sachet)*

Calcium/vitamin D<sub>3</sub> sachet should be taken each day for 6 days per week starting on the day after the risedronate 35 mg gastro-resistant tablet is taken.

The contents of the sachet should be poured into a glass of plain water, stirred, and drunk immediately once the fizzing has subsided.

In case the risedronate 35 mg gastro-resistant tablet is missed, patients should be instructed that the risedronate 35 mg gastro-resistant tablet should be taken on the next day in the morning according to the dosing instructions. In this instance, patients should then take their calcium/vitamin D<sub>3</sub> sachet on the following day. Patients should be instructed that they should never take the tablet and the sachet the same day.

If the calcium/vitamin D<sub>3</sub> sachet dose is missed, the patient should be instructed to continue taking one sachet each day beginning on the day the missed dose is remembered. Patient should be instructed that they should not take two sachets on the same day. Any remaining calcium/vitamin D<sub>3</sub> sachet at the end of the weekly cycle should be discarded.

## **4.3 Contraindications**

Hypersensitivity to the active substance, or to any of the other excipients listed in section 6.1.

Hypocalcaemia (see section 4.4).

Severe renal impairment (creatinine clearance  $< 30$  ml/min).

Diseases and/or conditions resulting in hypercalcaemia and/or hypercalciuria

Nephrolithiasis

Hypervitaminosis D

#### 4.4 Special warnings and precautions for use

Medicinal products containing polyvalent cations (such as calcium, magnesium, iron and aluminium) interfere with the absorption of bisphosphonates and should be taken at a different time of day to risedronate tablets (see section 4.5). In order to achieve the intended efficacy, strict adherence to dosing recommendations is necessary (see section 4.2).

Efficacy of bisphosphonates in the treatment of osteoporosis is related to the presence of low bone mineral density and/or prevalent fracture.

High age or clinical risk factors for fracture alone are not sufficient reasons to initiate treatment of osteoporosis with a bisphosphonate.

The evidence to support efficacy of bisphosphonates including risedronate in the very elderly (>80 years) is limited (see section 5.1).

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

##### Upper gastrointestinal adverse reactions

Bisphosphonates have been associated with oesophagitis, gastritis, oesophageal ulcerations and gastroduodenal ulcerations. Thus, caution should be used:

- In patients who have a history of oesophageal disorders which delay oesophageal transit or emptying e.g. stricture or achalasia.
- In patients who are unable to stay in the upright position for at least 30 minutes after taking the tablet.
- If risedronate is given to patients with active or recent oesophageal or upper gastrointestinal problems (including known Barrett's oesophagus).

Prescribers should emphasise to patients the importance of paying attention to the dosing instructions and be alert to any signs and symptoms of possible oesophageal reaction. The patients should be instructed to seek timely medical attention if they develop symptoms of oesophageal irritation such as dysphagia, pain on swallowing, retrosternal pain or new/worsened heartburn.

##### Osteonecrosis of the jaw

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 judgement of the treating physician should guide the management plan of each patient based on individual benefit /risk assessment.

##### Osteonecrosis of the external auditory canal

Osteonecrosis of the external auditory canal has been reported with bisphosphonates, mainly in association with long-term therapy. Possible risk factors for osteonecrosis of the external auditory canal include steroid use and chemotherapy and/or local risk factors such as infection or trauma. The possibility of osteonecrosis of the external auditory canal should be considered in patients receiving

bisphosphonates who present with ear symptoms including chronic ear infections.

#### Atypical fractures of the femur

Atypical subtrochanteric and diaphyseal femoral fractures have been reported with bisphosphonate therapy, primarily in patients receiving long-term treatment for osteoporosis. These transverse or short oblique fractures can occur anywhere along the femur from just below the lesser trochanter to just above the supracondylar flare. These fractures occur after minimal or no trauma and some patients experience thigh or groin pain, often associated with imaging features of stress fractures, weeks to months before presenting with a completed femoral fracture. Fractures are often bilateral; therefore the contralateral femur should be examined in bisphosphonate-treated patients who have sustained a femoral shaft fracture. Poor healing of these fractures has also been reported. Discontinuation of bisphosphonate therapy in patients suspected to have an atypical femur fracture should be considered pending evaluation of the patient, based on an individual benefit risk assessment.

During bisphosphonate treatment patients should be advised to report any thigh, hip or groin pain and any patient presenting with such symptoms should be evaluated for an incomplete femur fracture.

#### **Risedronate sodium tablets contain sodium**

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

#### Calcium carbonate/vitamin D<sub>3</sub>

Vitamin D<sub>3</sub> should be used with caution in patients with impairment of renal function and the effect on calcium and phosphate levels should be monitored. The risk of soft tissue calcification should be taken into account. In patients with severe renal insufficiency, vitamin D in the form of colecalciferol is not metabolised normally and another form of vitamin D should be used (see section 4.3)

During long-term treatment, serum and urinary calcium levels should be followed and renal function should be monitored through measurement of serum creatinine. Monitoring is especially important in elderly patients on concomitant treatment with cardiac glycosides or diuretics (see section 4.5) and in patients with a high tendency to calculus formation. Treatment must be reduced or suspended if urinary calcium exceeds 7.5 mmol/24 hour (300 mg/24 hour). In case of hypercalcaemia or signs of impaired renal function, treatment with calcium/vitamin D<sub>3</sub> sachets should be discontinued.

The dose of vitamin D<sub>3</sub> in the sachets should be considered when prescribing other medicinal products containing vitamin D. Additional doses of calcium or vitamin D should be taken under close medical supervision. In such cases it is necessary to monitor serum calcium levels and urinary calcium excretion frequently.

Calcium/vitamin D<sub>3</sub> sachets should be used with caution in patients suffering from sarcoidosis because of the risk of increased metabolism of vitamin D to its active metabolite. In these patients, serum calcium levels and urinary calcium excretion must be monitored.

Calcium/vitamin D<sub>3</sub> sachets should be used with caution in immobilised patients with osteoporosis due to the increased risk of hypercalcaemia. The calcium/vitamin D<sub>3</sub> treatment might be discontinued in prolonged immobilization and should only be resumed once the patient becomes mobile again.

#### **Calcium/vitamin D<sub>3</sub> granules contain sorbitol, sucrose, potassium and sodium**

This medicinal product contains 1.1 mg sorbitol in each sachet.

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

May be harmful to the teeth.

This medicinal product contains 4.2 mmol potassium (163 mg) in each sachet. To be taken into consideration by patients with reduced kidney function or patients on a controlled potassium diet.

This medicinal product contains less than 1 mmol sodium (23 mg) in each sachet, that is to say essentially 'sodium-free'.

#### **4.5 Interaction with other medicinal products and other forms of interaction**

##### Risedronate sodium

Medicinal products containing polyvalent cations (such as calcium, magnesium, iron and aluminium) interfere with the absorption of bisphosphonates and should be taken at a different time of day to risedronate tablets (see section 4.4).

Risedronate sodium is not systemically metabolised, does not induce cytochrome P450 enzymes, and has low protein binding.

Co-administration of risedronate 35 mg gastro-resistant tablets with the proton pump inhibitor esomeprazole increased the risedronate bioavailability. The maximum plasma concentration (C<sub>max</sub>) and the area under the plasma concentration time curve (AUC) were increased by 60% and 22% respectively, but the clinical implications measured by body mass density changes were not statistically significant.

If considered appropriate risedronate sodium may be used concomitantly with oestrogen supplementation.

##### Calcium carbonate/vitamin D<sub>3</sub>

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

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

Calcium carbonate may interfere with the absorption of concomitant administered tetracycline preparations. For this reason, tetracycline preparations should be administered at least two hours before or four to six hours after oral intake of calcium carbonate/vitamin D<sub>3</sub>.

Hypercalcaemia may increase the toxicity of digitalis and other cardiac glycosides (risk of dysrhythmia) during treatment with calcium combined with vitamin D<sub>3</sub>. Such patients should be monitored with regard to electrocardiogram (ECG) and serum calcium levels.

If sodium fluoride is used concomitantly, this preparation should be administered at least three hours before intake of calcium carbonate/vitamin D<sub>3</sub> 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**

Optinate Combi D is intended for use in postmenopausal women and should not be used during pregnancy or while breastfeeding.

##### Risedronate sodium

### Pregnancy

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

Optinate Combi D must not be used during pregnancy.

### Breast-feeding

Studies in animals indicate that a small amount of risedronate sodium pass into breast milk. Optinate Combi D must not be used by breast-feeding women.

### Fertility

There are no adequate data on the effects of risedronate on human fertility. Animal studies showed adverse effects at exposures considerably above that in humans (see section 5.3).

### Calcium carbonate/vitamin D<sub>3</sub>

During pregnancy the daily intake should not exceed 1500 mg calcium and 600 IU cholecalciferol (15 µg vitamin D<sub>3</sub>). 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<sub>3</sub> pass into breast milk. Optinate Combi D must not be used during pregnancy and lactation.

## **4.7 Effects on ability to drive and use machines**

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

## **4.8 Undesirable effects**

### Risedronate Sodium

#### Summary of the safety profile

The most commonly reported side effects with risedronate tablets are gastrointestinal disorders including abdominal pain, diarrhoea, dyspepsia, nausea, constipation, musculoskeletal pain and headache.

#### Tabulated list of adverse reactions from clinical studies

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

Adverse experiences reported in phase III clinical studies in postmenopausal women with osteoporosis and considered possibly or probably related to risedronate sodium are listed below using the following convention: very common ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); rare ( $\geq 1/10,000$  to  $< 1/1,000$ ); very rare ( $< 1/10,000$ ).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

**Table 1**

| MedDRA System Organ Class                              | Common                                                                                                                       | Uncommon                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Rare                             |
|--------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------|
| <i>Infections and infestations</i>                     |                                                                                                                              | Influenza                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                  |
| <i>Blood and lymphatic system disorders</i>            |                                                                                                                              | Leukopenia, neutropenia                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                  |
| <i>Immune system disorders</i>                         |                                                                                                                              | Hypersensitivity                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                  |
| <i>Endocrine disorders</i>                             |                                                                                                                              | Hyperparathyroidism secondary                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                  |
| <i>Metabolism and nutrition disorders</i>              |                                                                                                                              | Hypercalcaemia                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                  |
| <i>Psychiatric disorders</i>                           |                                                                                                                              | Depression                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                  |
| <i>Nervous system disorders</i>                        | Headache                                                                                                                     | Dizziness, paresthesia, hypoaesthesia                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                  |
| <i>Eye disorders</i>                                   |                                                                                                                              | Iritis*, ocular                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                  |
|                                                        |                                                                                                                              | hyperaemia, conjunctivitis, vision blurred                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                  |
| <i>Ear and labyrinth disorders</i>                     |                                                                                                                              | Vertigo                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                  |
| <i>Vascular disorders</i>                              |                                                                                                                              | Hot flush, hypotension                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                  |
| <i>Respiratory, thoracic and mediastinal disorders</i> |                                                                                                                              | Cough                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                  |
| <i>Gastrointestinal disorders</i>                      | Abdominal pain including abdominal pain upper and abdominal pain lower, constipation, dyspepsia, nausea, diarrhoea, vomiting | Gastritis, Helicobacter gastritis, oesophagitis, dysphagia, duodenitis, oesophageal ulcer, abdominal discomfort, abdominal distension, erosive esophagitis, gastritis erosive, haematochezia, hyperchlorhydria, eructation, flatulence, gastritis atrophic, gastroesophageal reflux disease, gingivitis, haemorrhoids, hiatus hernia, melaena, abdominal tenderness, aphthous stomatitis, colitis, dry mouth, faecal incontinence, gastric mucosal hypertrophy, gastrointestinal inflammation, gastrointestinal pain, hypoaesthesia oral, lip swelling, odynophagia, swollen tongue | Oesophageal stricture, glossitis |
| <i>Hepatobiliary disorders</i>                         |                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Abnormal liver function tests*   |
| <i>Skin and subcutaneous</i>                           |                                                                                                                              | Erythema, Henoch-                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                  |

|                                                             |                      |                                                                                                                                                                                                                                  |  |
|-------------------------------------------------------------|----------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|
| <i>tissue disorders</i>                                     |                      | Schonlein purpura, urticarial, dermatitis allergic, pruritus, rash                                                                                                                                                               |  |
| <i>Musculoskeletal and connective tissues disorders</i>     | Musculoskeletal pain | Arthralgia, back pain, muscle spasm, myalgia, pain in extremity, bone pain, muscle fatigue, muscular weakness, neck pain, pain in jaw                                                                                            |  |
| <i>Renal and Urinary disorders</i>                          |                      | Nephrolithiasis                                                                                                                                                                                                                  |  |
| <i>Reproductive system and breast disorders</i>             |                      | Ovarian cyst                                                                                                                                                                                                                     |  |
| <i>General disorders and administration site conditions</i> |                      | Asthenia, chills, fatigue, influenza like illness, chest discomfort, chest pain, face oedema, oedema, oedema peripheral, pain, pyrexia                                                                                           |  |
| <i>Investigations</i>                                       |                      | Blood calcium and phosphate decreased, heart rate irregular, urine analysis abnormal, transaminases increased, blood alkaline phosphatase increased, blood parathyroid hormone increased, occult blood, platelet count decreased |  |

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

#### Description of selected adverse events

##### Gastrointestinal disorders

In the Phase III study, comparing risedronate 35 mg gastro-resistant tablets and risedronate sodium 5 mg daily (immediate-release) more patients that used NSAID/aspirin reported upper gastrointestinal treatment-emergent adverse events than non-users.

The frequency of patients that reported such events were:

- 22.0% in NSAID/aspirin users vs 15.7% in the NSAID/aspirin non-users in the 35 mg immediately-following-breakfast group
- 29.8% in NSAID/aspirin users vs 15.3% in the NSAID/aspirin non-users in the 35 mg 30 minutes- before-breakfast group
- 22.4% in NSAID/aspirin users vs 13.4% in the NSAID/aspirin non-users in the 5 mg immediate-release before-breakfast group

A higher incidence of upper abdominal pain was seen when risedronate 35 mg gastro-resistant tablets were taken in a fasted state 30 minutes before breakfast.

The frequency of lower gastrointestinal treatment-emergent adverse events were 22.1% in the 35 mg immediately-following-breakfast group, 20.1% in the 35 mg 30 minutes- before-breakfast group and

15.6% in the 5 mg immediate-release group.

During post marketing experience the following reactions have been reported

Adverse reactions are listed below, by system organ class and frequency following convention: very common ( $\geq 1/10$ ); common ( $\geq 1/100$ ;  $< 1/10$ ); uncommon ( $\geq 1/1,000$ ;  $< 1/100$ ); rare ( $\geq 1/10,000$ ;  $< 1/1,000$ ); very rare ( $< 1/10,000$ ).

| MedDRA System Organ Class                               | Rare                                                                                              | Very rare                                                                            | Frequency not known                                                                                                                                                                                                              |
|---------------------------------------------------------|---------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <i>Eye disorder</i>                                     |                                                                                                   |                                                                                      | Iritis, uveitis, orbital inflammation                                                                                                                                                                                            |
| <i>Hepatobiliary disorders</i>                          |                                                                                                   |                                                                                      | Serious hepatic disorders (In most of the reported cases the patients were also treated with other products known to cause hepatic disorders)                                                                                    |
| <i>Immune system disorders</i>                          |                                                                                                   |                                                                                      | Anaphylactic reaction                                                                                                                                                                                                            |
| <i>Musculoskeletal and connective tissues disorders</i> | Atypical subtrochanteric and diaphyseal femoral fractures (bisphosphonate class adverse reaction) | Osteonecrosis of the external auditory canal (bisphosphonate class adverse reaction) |                                                                                                                                                                                                                                  |
| <i>Skin and subcutaneous tissue disorders</i>           |                                                                                                   |                                                                                      | Hypersensitivity and skin reactions, including angioedema, and bullous skin reactions, some severe including isolated reports of Stevens Johnson syndrome, toxic epidermal necrolysis and leukocytoclastic vasculitis; Hair loss |

### Calcium carbonate/vitamin D<sub>3</sub>

Adverse reactions are listed below, by system organ class and frequency following convention: very common ( $\geq 1/10$ ); common ( $\geq 1/100$ ;  $< 1/10$ ); uncommon ( $\geq 1/1,000$ ;  $< 1/100$ ); rare ( $\geq 1/10,000$ ;  $< 1/1,000$ ); very rare ( $< 1/10,000$ ).

| MedDRA System Organ Class                 | Common | Uncommon                          | Rare                                                           |
|-------------------------------------------|--------|-----------------------------------|----------------------------------------------------------------|
| <i>Gastrointestinal disorders</i>         |        |                                   | Constipation, flatulence, nausea, abdominal pain and diarrhoea |
| <i>Metabolism and nutrition disorders</i> |        | Hypercalcaemia and hypercalciuria |                                                                |

|                                        |  |  |                              |
|----------------------------------------|--|--|------------------------------|
| <i>Skin and subcutaneous disorders</i> |  |  | Pruritus, rash and urticaria |
|----------------------------------------|--|--|------------------------------|

#### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

## **4.9 Overdose**

### Risedronate Sodium

No specific information is available on the treatment of overdose with risedronate sodium.

Decreases in serum calcium following substantial overdose may be expected. Signs and symptoms of hypocalcaemia may also occur in some of these patients.

Milk or antacids containing magnesium, calcium or aluminium should be given to bind risedronate and reduce absorption of the drug.

The impact of this intervention for Optinate Combi D has not been evaluated. The gastro-resistant formulation is less sensitive to the binding effects of divalent cations. Standard procedures that are effective for treating hypocalcaemia, including the administration of calcium intravenously, would be expected to restore physiologic amounts of ionised calcium and to relieve signs and symptoms of hypocalcaemia.

In cases of substantial overdose, gastric lavage may be considered to remove unabsorbed drug if performed within 30 minutes of ingestion.

### 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 D<sub>3</sub> 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 for treatment of bone diseases, Drugs affecting bone structure and mineralization, Bisphosphonates, ATC Code: M05BA07.

## Risedronate Sodium

### Mechanism of action

Risedronate sodium is a pyridinyl bisphosphonate that binds to bone hydroxyapatite and inhibits osteoclast-mediated bone resorption. The bone turnover is reduced while the osteoblast activity and bone mineralisation is preserved.

### Pharmacodynamic effects

In preclinical studies risedronate sodium demonstrated potent anti-osteoclast and anti-resorptive activity, and dose dependently increased bone mass and biomechanical skeletal strength. The activity of risedronate sodium was confirmed by measuring biochemical markers for bone turnover during pharmacodynamic and clinical studies. In studies of postmenopausal women, decreases in biochemical markers of bone turnover were observed at month 3 and at subsequent timepoints. Decreases in biochemical markers of bone turnover were similar with risedronate 35 mg gastro-resistant weekly tablets and risedronate 5 mg daily at all-time points.

### Clinical efficacy and safety

#### *Treatment of Postmenopausal Osteoporosis*

Based on effects on mean change in lumbar spine BMD, risedronate 35 mg gastro-resistant tablets (n=307 following breakfast and n=308 before breakfast) was shown to be equivalent to risedronate 5 mg daily tablets (n=307) in a two-year, double-blind, multicentre study of postmenopausal women with osteoporosis.

Risedronate 35 mg gastro-resistant tablets administered either before or after breakfast was shown to be therapeutically equivalent to risedronate 5 mg daily (immediate-release formulation) in a 2-year, double-blind, multicentre study of postmenopausal women with osteoporosis. The primary efficacy endpoint of percent change from baseline in lumbar spine BMD (LS) at week 52 was met. Secondary efficacy endpoints included percent change from baseline in lumbar spine BMD at week 104; non-vertebral fractures at week 104 which were consistent with the primary outcome measure; and change in bone turnover markers. Table 2 presents the primary efficacy analysis at 1 year (Primary Analysis Population), as well as the 2 year results (Week 104 Endpoint Population).

| <b>Table 2 Lumbar Spine BMD (LS) - Percent Change from Baseline at 1 yr and 2 yr Endpoints [a]</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                      |                                                                                   |                                                                                |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------|-----------------------------------------------------------------------------------|--------------------------------------------------------------------------------|
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | Risedronate 5 mg<br>Daily immediate-release<br>N=307 | Risedronate 35 mg<br>Once a Week gastro-resistant Following<br>Breakfast<br>N=307 | Risedronate 35 mg<br>Once a Week gastro-resistant<br>Before Breakfast<br>N=308 |
| <b>Primary Efficacy (LOCF), at 1 year [c]</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                      |                                                                                   |                                                                                |
| n                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 270                                                  | 261                                                                               | 271                                                                            |
| LS Mean (95% CI)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 3.1* (2.7, 3.5)                                      | 3.3* (2.9, 3.7)                                                                   | 3.4* (3.0, 3.8)                                                                |
| LS Mean Difference [b] (95% CI)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                      | -0.2 (-0.8, 0.3)                                                                  | -0.3 (-0.9, 0.3)                                                               |
| <b>2 year-endpoint [d]</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                      |                                                                                   |                                                                                |
| n                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 274                                                  | 265                                                                               | 273                                                                            |
| LS Mean (95% CI)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 4.1 (3.7, 4.6)                                       | 5.2 (4.7, 5.7)                                                                    | 5.1 (4.6, 5.6)                                                                 |
| LS Mean Difference[b] (95% CI)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                      | -1.1 (-1.8, -0.4)                                                                 | -0.9 (-1.6, -0.2)                                                              |
| N = number of intent-to-treat patients within specified treatment; n = number of patients with values at baseline and at the visit.<br>* Indicates a statistically significant difference from baseline determined from 95% CI unadjusted for multiple comparisons.<br>[a] at 1 year and 2 year LOCF<br>[b] LS Mean Difference is 5 mg daily minus 35 mg weekly treatment.<br>[c] Based on PE Population (all ITT patients who had analyzable lumbar spine BMD data at both baseline and Week 52 LOCF Endpoint)<br>[d] Based on <b>Week 104-Endpoint population</b> (all ITT patients who had analyzable lumbar spine BMD data at both baseline and Week 104 LOCF Endpoint) |                                                      |                                                                                   |                                                                                |

The clinical programme for risedronate sodium administered once daily studied the effect of risedronate sodium on the risk of hip and vertebral fractures and contained early and late postmenopausal women with and without fracture. Daily doses of 2.5 mg and 5 mg were studied and all groups, including the control groups, received calcium and vitamin D (if baseline levels were low). The absolute and relative risk of new vertebral and hip fractures was estimated by use of a time-to-first event analysis.

- Two placebo-controlled studies (n=3661) enrolled postmenopausal women under 85 years with vertebral fractures at baseline. Risedronate sodium 5 mg daily given for 3 years reduced the risk of new vertebral fractures relative to the control group. In women with respectively at least 2 or at least 1 vertebral fractures, the relative risk reduction was 49% and 41% respectively (incidence of new vertebral fractures with risedronate sodium 18.1% and 11.3%, with placebo 29.0% and 16.3%, respectively).
- Two further placebo controlled studies enrolled postmenopausal women above 70 years with or without vertebral fractures at baseline. Women 70-79 years were enrolled with femoral neck BMD T-score <-3 SD (manufacturer's range, i.e. -2.5 SD using NHANES III (National Health and Nutrition Examination Survey)) and at least one additional risk factor. Women >80 years could be enrolled on the basis of at least one non-skeletal risk factor for hip fracture or low bone mineral density at the femoral neck. Statistical significance of the efficacy of risedronate versus placebo is only reached when the two treatment groups 2.5 mg and 5 mg are pooled. The following results are only based on *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  $\leq -2.5$  SD (NHANES III) and at least one vertebral fracture at baseline, risedronate sodium given for 3 years reduced the risk of hip fractures by 46% relative to the control group (incidence of hip fractures in combined risedronate sodium 2.5 mg and 5 mg groups 3.8%, placebo 7.4%);

### Paediatric population

The safety and efficacy of risedronate sodium has been investigated in a 3-year study (a randomized, double-blind, placebo-controlled, multicenter, parallel group study of one year duration followed by 2 years of open-label treatment) in paediatric patients aged 4 to less than 16 years with mild to moderate osteogenesis imperfecta. In this study, patients weighing 10-30 kg received risedronate 2.5 mg daily and patients weighing more than 30 kg received risedronate 5 mg daily.

After completion of its one-year randomized, double-blind, placebo-controlled phase, a statistically significant increase in lumbar spine BMD in the risedronate group versus placebo group was demonstrated; however an increased number of patients with at least 1 new morphometric (identified by x-ray) vertebral fracture was found in the risedronate group compared to placebo. During the one-year double-blind period, the percentage of patients who reported clinical fractures was 30.9% in the risedronate group and 49.0% in the placebo group. In the open-label period when all patients received risedronate (month 12 to month 36), clinical fractures were reported by 65.3% of patients initially randomized to the placebo group and by 52.9% of patients initially randomized to the risedronate group.

Overall, results do not support the use of risedronate sodium in paediatric patients with mild to moderate osteogenesis imperfecta.

### Calcium carbonate/vitamin D<sub>3</sub>

In case of calcium deficiency, oral intake of calcium supplementation supports the remineralisation of the skeleton. Vitamin D<sub>3</sub> increases the intestinal absorption of calcium.

Administration of calcium and vitamin D<sub>3</sub> counteracts the increase in parathyroid hormone (PTH) which is caused by calcium deficiency which causes increased bone resorption.

A clinical study of institutionalised patients suffering from vitamin D deficiency indicated that a daily intake of effervescent granules of 1000 mg calcium/880 IU colecalciferol for six months normalised the value of the 25-hydroxylated metabolite of vitamin D<sub>3</sub> and reduced secondary hyperparathyroidism.

## **5.2 Pharmacokinetic properties**

### Risedronate Sodium

#### *Absorption*

The time to peak concentration (T<sub>max</sub>) for risedronate 35 mg gastro-resistant tablet is ~3 hours when administered in the morning 4 hours prior to a meal. The relative bioavailability of the risedronate 35 mg gastro-resistant tablets administered after a high-fat breakfast was 2 to 4-fold higher than the corresponding immediate-release formulation administered 30 minutes prior to a high-fat breakfast.

#### *Food Effect*

The presence of food did not appreciably affect the bioavailability of the gastro-resistant tablets.

#### *Distribution*

The mean steady state volume of distribution is 6.3 L/kg in humans. Plasma protein binding is about 24%.

#### *Biotransformation*

There is no evidence of systemic metabolism of risedronate sodium.

#### *Elimination*

Approximately half of the absorbed dose is excreted in urine within 24 hours, and 85% of an intravenous dose is recovered in the urine after 28 days. Mean renal clearance is 105 ml/min and mean total clearance is 122 ml/min, with the difference probably attributed to clearance due to adsorption to bone. The renal clearance is not concentration dependent, and there is a linear relationship between

renal clearance and creatinine clearance. Unabsorbed risedronate sodium is eliminated unchanged in faeces. After oral administration the concentration-time profile shows three elimination phases with a terminal half-life of 480 hours.

### *Special Populations*

#### *Elderly*

No dosage adjustment is necessary.

#### *Acetyl salicylic acid/NSAID users*

Among regular acetyl salicylic acid or NSAID users (3 or more days per week) the incidence of upper gastrointestinal adverse events in risedronate sodium treated patients was similar to that in control patients.

### Calcium carbonate

#### *Absorption*

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

#### *Distribution and biotransformation*

99% of calcium in the body is concentrated in the hard structure of bones and teeth. The remaining 1% is present in the intra- and extracellular fluids. About 50% of the total blood calcium content is physiologically active ionised form with approximately 10% being complexed to citrate, phosphate or other anions, the remaining 40% being bound to proteins, principally albumin.

#### *Elimination*

Calcium is eliminated through faeces, urine and sweat. Renal excretion depends on glomerular filtration and calcium tubular reabsorption.

### Vitamin D<sub>3</sub>

#### *Absorption*

Vitamin D is readily absorbed in the small intestine.

#### *Distribution and biotransformation*

Colecalciferol and its metabolites circulate in the blood bound to a specific globulin. Colecalciferol is converted in the liver by hydroxylation to the active form 25-hydroxycolecalciferol. It is then further converted in the kidneys to 1,25-hydroxycolecalciferol. 1,25-hydroxycolecalciferol is the metabolite responsible for increasing calcium absorption. Vitamin D that is not metabolised is stored in adipose and muscle tissues.

#### *Elimination*

Vitamin D is excreted in faeces and urine.

## **5.3 Preclinical safety data**

### Risedronate Sodium

#### Repeat-dose toxicity

In toxicological studies in rat and dog, dose dependent liver toxic effects of risedronate sodium were seen, primarily as enzyme increases with histological changes in rat. The clinical relevance of these observations is unknown. Testicular toxicity occurred in rat and dog at exposures considered in excess of the human therapeutic exposure. Dose related incidences of upper airway irritation were frequently noted in rodents. Similar effects have been seen with other bisphosphonates. Lower respiratory tract effects were also seen in longer term studies in rodents, although the clinical significance of these findings is unclear.

The results of a 13-week repeat-dose toxicity study in dogs comparing the gastro-resistant risedronate formulation with conventional risedronate showed a similar toxicity profile for the two formulations.

#### Reproductive toxicity

A fertility study in male and female rats showed no adverse effects at oral doses up to 16 mg/kg/day, corresponding to systemic exposure (serum AUC 0-24h) about 30 times higher than that in humans dosed at 30 mg/day. At higher dose levels, systemic toxicity, testicular atrophy and reduced fertility were seen in male rats, but these effects are unlikely to have clinical relevance.

In reproduction toxicity studies at exposures close to clinical exposure ossification changes were seen in sternum and/or skull of foetuses from treated rats and hypocalcemia and mortality in pregnant females allowed to deliver. There was no evidence of teratogenesis at 3.2 mg/kg/day in rat and 10 mg/kg/day in rabbit, although data are only available on a small number of rabbits. Maternal toxicity prevented testing of higher doses.

Studies on genotoxicity and carcinogenesis did not show any particular risks for humans.

#### Calcium carbonate/vitamin D3

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

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

#### *Tablet core:*

Microcrystalline cellulose (E460)  
Silica, colloidal anhydrous  
Disodium edetate  
Sodium starch glycolate  
Stearic acid  
Magnesium stearate  
(E470b)

#### *Enteric coating:*

Methacrylic acid – ethyl acrylate copolymer (1:1)  
Triethyl citrate (E1505)  
Talc (E553b)  
Iron oxide yellow  
(E172)  
Simeticone  
Polysorbate 80 (E433)

#### Effervescent granules

Citric acid  
Malic acid (E296)  
Gluconolactone  
Maltodextrin  
Sodium cyclamate (E952)  
Saccharin sodium (E954)  
Lemon flavour (containing sorbitol)  
Rice starch  
Potassium carbonate (E501)

All-rac-alfa-Tocopherol  
Modified starch  
Sucrose  
Sodium ascorbate  
Triglycerides, medium chain  
Silica, colloidal anhydrous

## **6.2 Incompatibilities**

Not applicable.

## **6.3 Shelf life**

3 years.

## **6.4 Special precautions for storage**

This medicinal product does not require any special storage conditions.

## **6.5 Nature and contents of container**

The medicinal product is supplied as a combination product containing gastro-resistant tablet/s in blister and effervescent granules in sachets.

A pack contains monthly units.

Each monthly unit contains:

Clear PVC/aluminium foil blister containing four tablets + Twenty-four sachets (laminated aluminium paper foil) containing effervescent granules

Pack sizes:

1 monthly unit 1 x (4 gastro- resistant tablets + effervescent granules in 24 sachets)

3 monthly units: 3 x (4 gastro- resistant tablets + effervescent granules in 24 sachets)

Not all pack sizes may be marketed.

## **6.6 Special precautions for disposal**

No special requirements for disposal.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

## **7. MARKETING AUTHORISATION HOLDER**

<[To be completed nationally]>

## **8. MARKETING AUTHORISATION NUMBER(S)**

<[To be completed nationally]>

## **9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

<[To be completed nationally]>

## **10. DATE OF REVISION OF THE TEXT**

<{MM/YYYY}>

<{DD/MM/YYYY}>

<{DD month YYYY}>

<[To be completed nationally]>

11-OCT-2024