LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Optinate Combi D
cholecalciferol, calcium carbonate, risedronate sodium

SE/H/732/02/DC

This module reflects the scientific discussion for the approval of Optinate Combi D. The procedure was finalised on 2021-05-12. For information on changes after this date please refer to the module 'Update'.

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Optinate Combi D, 1000 mg/880 IE + 35 mg, Effervescent granules + gastro-resistant tablet.

The active substance is cholecalciferol, calcium carbonate, risedronate sodium. A comprehensive description of the indication and posology is given in the SmPC.

For recommendations to the marketing authorisation not falling under Article 21a/22a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a/22a/ 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

The application is an extension, new pharmaceutical form, of the previously authorised product Optinate Combi D, 35 mg + 1000 mg/ 880 IE, effervescent granules + film-coated tablet marketed by Theramex Ireland Limited since 2005.

The application for Optinate Combi D, 1000 mg/ 880 IU + 35 mg, effervescent granules + gastro-resistant tablet, is submitted according to Article 8(3) of Directive 2001/83/EC. The applicant, Theramex Ireland Limited, applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and DE as concerned member state (CMS).

Potential similarity with orphan medicinal products
According to the application form and a check of the Community Register of orphan medicinal products there is no medicinal product designated as an orphan medicinal product for a condition relating to the indication proposed in this application.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

No new non-clinical data or assessments have been submitted for the current application. The drug product applied for in the present line extension is 35 mg gastro-resistant risedronate tablets and 1000 mg/880 IU calcium/cholecalciferol effervescent granules. The applied combination pack includes previously approved products. The effervescent granules are the same as in the approved drug product Optinate Combi D film-coated tablets and effervescent granules (SE/H/0732/01/DC). The gastro-resistant tablets are the same as Optinate Septimum (SE/H/0192/07).

IV. CLINICAL ASPECTS

Pharmacokinetics
No new pharmacokinetic data have been submitted for the current application. The drug product applied for in the present line extension is 35 mg gastro-resistant risedronate tablets and 1000 mg/880 IU calcium/cholecalciferol effervescent granules. The applied combination pack includes previously approved products. The effervescent granules are the same as in the approved drug product Optinate Combi D film-coated tablets and effervescent granules (SE/H/0732/01/DC).
The gastro-resistant tablets are the same as Optinate Septimum (SE/H/0192/07).

Risedronate Sodium

Absorption
The time to peak concentration (T_{max}) 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.

Cholecalciferol (vitamin D_3)

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-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.

Interaction with other medicinal products
It is known that 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.

Pharmacodynamics
No new data have been submitted for the current application.
The applicant has provided a comprehensive literature overview and summarized key clinical efficacy data from relevant original studies for the separate and combined use of weekly alendronate and calcium/vitamin D3 chewable tablets. The efficacy of weekly alendronate and daily calcium/vitamin D3 chewable tablets is considered well established.
The Applicant has also referred to relevant guidelines and listed comparable compounds authorized in the EU.

A dose of 4,800 IU / week was considered to be is within the limits of well-established dose for maintenance vitamin D therapy in osteoporosis. Vitamin D is possible to be administered once weekly and consequently separating dosing to 6 times per week is also acceptable.
The dose of calcium required in osteoporosis is also individual and the prescriber should estimate a dietary calcium intake before starting therapy. The Applicant amended the SmPC with the statement that due to the lower amount of calcium than the recommended daily intake the product is intended for use by patients with a dietary intake of calcium of 500-1,000 mg per day. Use of the proposed weekly dose of 3 000 mg, divided on 6 days/ week can be appropriate to certain osteoporosis patients who are also treated with alendronate, especially taking into account that calcium and alendronate should not be taken at the same time due to an interaction.

Clinical efficacy

Risedronate

Treatment guidelines recommend the use of bisphosphonates as one of the first-line treatments for the prevention and treatment of osteoporosis (Kanis et al 2019, Cosman et al 2014). Bisphosphonates bind with high affinity to the mineral matrix of the bone and inhibit osteoclast resorption of the bone, leading to a decrease in bone turnover and a net gain in bone mass (McClung et al 2014). Optinate IR 5mg 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) (SmPC EMA, 2016). In practice, a significant proportion of patients (25% – 40%) are non-adherent to dosing instructions when taking bisphosphonates, despite receiving counseling and written instructions that bisphosphonates IR must be taken at least 30 minutes before the first food, other medicinal product or drink (other than plain water) of the day (McClung et al, 2014, Ettinger et al 1998, Cramer et al 2006). In patients who do not follow dosing instructions, bisphosphonates are not absorbed and therefore will not be effective. Literature data suggest that the fracture risk increases with poorer adherence to bisphosphonate (Liu et al, 2018). Optinate Septimum GR 35mg taken before or after breakfast has similar therapeutic benefits as Optinate IR taken after breakfast on increasing the BMD in postmenopausal women with osteoporosis (SmPC EMA, 2016) (14). and the BMD has been shown to be a reliable way of evaluating the risk of hip fracture (Marshall et al 1996, Cummings et al 1993). It can be concluded that patients receiving Optinate Septimum GR will derive the full benefits of bisphosphonates irrespective of dosing with or without food. This is a unique differentiating feature of the GR formulation compared to other bisphosphonates. Furthermore, as Optinate Septimum GR is equivalent to Optinate IR, it is postulated that the reduction in vertebral and hip fractures observed with the IR formulation can be extrapolated to the GR formulation.

Calcium/vitamin D

Calcium and vitamin D are essential nutrients for bone health and maintenance. It is believed that 90% of women may not be getting enough calcium and over 50% of women treated for bone loss have inadequate vitamin D levels (Holick et al 2008). Combined calcium and vitamin D supplements in a daily dose of 0.5–1.2 g and 400–800 IU, respectively, are generally recommended in patients receiving bone protective therapy, since most randomised controlled trial evidence for the efficacy of interventions is based on co-administration of the agent with calcium and vitamin D supplements (Harvey et al 2017).

Indication

The approved indication for Optinate Combi D is the same as for Optinate Septimum, with the addition of a recommendation to consider the use of Optinate Combi D in patients who require supplements of calcium and vitamin D. Treatment of postmenopausal osteoporosis, to reduce the risk of vertebral fractures. Treatment of established postmenopausal osteoporosis, to reduce the risk of hip fractures.-Optinate Combi D is only intended for patients for whom the amount of calcium and vitamin D3 included is considered to provide adequate supplementation, based on individual assessment.

Dosing
The recommended dose in adults is one tablet of risedronate film-coated 35 mg on the first day, followed by the next day by dose of calcium and vitamin D 500 mg/880 IU effervescent granules daily for 6 days. This 7 day sequence is repeated starting with Risedronate 35 mg. No dose adjustment is required in patients with mild to moderate renal failure. Risedronate/calcium/Vitamin D combination is contraindicated in patients with severe renal failure, defined as a creatinine clearance of lower than 30ml/min. No dose adjustment is required in the elderly population, including in patients over 75y in whom there are no clinically significant differences compared to a younger population.

The components of the combination package have been approved in previous applications.

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. It can be argued that patients receiving Optinate Septimum GR will derive the full benefits of bisphosphonates irrespective of dosing with or without food. This is a differentiating feature of the GR formulation compared to other bisphosphonates. Furthermore, as Optinate Septimum GR is equivalent to Optinate IR, it is postulated that the reduction in vertebral and hip fractures observed with the IR formulation can be extrapolated to the GR formulation. Optinate 5mg 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. 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%).

The addition of calcium and cholecalciferol to the Optinate Combi D (gastro-resistant tablet) package can be justified as the patients who participated in the Risedronate trials received calcium and vit D. There is also literature evidence to support the importance of the concomitant supply of 1000 mg calcium and 800 IU vitamin D when postmenopausal women are treated with a bisphosphonate (Brazier et al, 2005).

Clinical safety
Risedronate:
The most commonly reported side effects with risedronate tablets are gastrointestinal disorders including abdominal pain, diarrhoea, dyspepsia, nausea, constipation; musculoskeletal pain and headache. In the Phase III studies, 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. 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. In the post-marketing phase, reports for Risedronate have been consistent and have indicated that gastro-intestinal and musculoskeletal symptoms are the most commonly reported adverse events. In rare cases, Atypical subtrochanteric and diaphyseal femoral fractures (bisphosphonate class adverse reaction). In very rare cases, Osteonecrosis of the external auditory canal (bisphosphonate class adverse reaction).

Calcium/VitD Calcium/vitamin D3:
Calcium carbonate and vitamin D as cholecalciferol are well known products and their safety profiles are also well described in literature. Since initial registration, the product information for Cacit Vitamin D3 has been updated with skin reactions, such as pruritus, rash and urticaria. Other adverse reactions listed are hypercalciuria, constipation, flatulence, nausea, abdominal pain and diarrhoea. Altogether 20 non-serious and six serious adverse events were reported for Cacit Vitamin D3 during the latest PSUR period. Among the serious cases, two were assessed as related to treatment. One of these was hypercalcemia, the other one was urticaria. None was fatal. 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. It should not be used in patients with severe renal insufficiency. The risk of soft tissue calcification should be taken into account. During long-term treatment, serum calcium levels and serum creatinin should be monitored. This is especially important in elderly patients on concomitant treatment with digitalis glycosides or diuretics and in patients with a tendency to calculus formation. Calcium/vitamin D3 sachets should be used with caution in patients with sarcoidosis and in immobilised patients due to the increased risk of hypercalcemia. In conclusion, risedronate, calcium carbonate and vitamin D3 as cholecalciferol are well known products, with well known safety profiles and the combined use is not expected to cause any new safety problems, provided that dosing is as per the SmPC.

Benefit/Risk assessment
Optinate Combi D is presented as a combination pack which consists of Risedronate 35 tablets (once weekly dosing regimen) and calcium/vitamin D 1000 mg/880 IU effervescent granules (daily dosing). Each of the component has a well-established benefit/risk profile and the combination has previously been approved in several EMA countries. The combination pack is designed to simplify the correct dosage regimen compared to the individual products. The sequential dosing reduces the risk of drug-drug interactions and may improve adherence to recommended osteoporosis therapy and optimize the effectiveness of such treatment.

Risk Management Plan
The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to the product.

Safety specification
Summary table of proposed safety concerns (RMP Part II: Module SVIII).

Summary of safety concerns	
Important identified risks	Iritis/Uveitis Hypersensitivity and skin reactions Osteonecrosis of the jaw (ONJ) Hypocalcaemia Interaction with medicinal products containing polyvalent cations (such as calcium, magnesium, iron and aluminium) that affect absorbtion of risedronic acid
Important potential risks	Serious upper GI irritation Severe musculoskeletal pain Serious hepatic disorders Atypical femoral fracture Osteonecrosis of external auditory canal
Missing information	Effect in children Effect in pregnant women Effect in lactating women Effect on fertility Use in patients with severe renal impairment

Pharmacovigilance Plan
There are no on-going or planned additional Pharmacovigilance studies/activities in the Pharmacovigilance Plan.

Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures
Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP
According to GVP V rev 2 (EMA/838713/2011rev2), only important identified and potential risks that require additional Pharmacovigilance studies/activities or additional risk minimisation activities needs to be inclused in the summary of safety concern.
Only missing information where any new information is considered important to collect and review on a regular basis need to be included.

The Applicant is asked to consider revising the summary of safety concerns in the submitted Risk Management Plan According to GVP V rev 2 (EMA/838713/2011rev2). The applicant has already started the revision process of the RMP.

An updated RMP should be submitted:
- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Optinate Septimum , SE/H/192/07/DC. The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The applicant has provided a literature overview and summarized key clinical data from relevant original studies for the separate and combined use of weekly 35 mg gastro-resistant risedronate tablets and 1000 mg/880 IU calcium/cholecalciferol effervescent granules in the treatment of postmenopausal osteoporosis. The efficacy and safety of weekly risedronate and daily calcium/vitamin D3 chewable tablets is considered well established.

The RMS considers that the proposed fixed combination “35 mg gastro-resistant risedronate tablets and 1000 mg/880 IU calcium/cholecalciferol effervescent granules” in a combined pack, could be useful for a limited group of patients. These patients, for whom the actual doses of calcium/vitamin D3 and are optimal, and for whom a combined pack could improve compliance may be identified by the prescribers.

There are no objections to approval of Optinate Combi D, from a quality, non-clinical and clinical point of view. The product information is acceptable. The application is therefore recommended for approval.

List of recommendations not falling under Article 21a/22a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a/22a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The decentralised procedure for Optinate Combi D, 1000 mg/880 IE + 35 mg, Effervescent granules + gastro-resistant tablet was positively finalised on 2021-05-12.

LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se