LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report

Scientific discussion

Optinate Combi D

35 mg tablet and 1000 mg/880 IU effervescent granules

(risedronate sodium and calcium /cholecalciferol)

SE/H/732/01/MR

This module reflects the scientific discussion for the approval of Optinate Combi D. The procedure was finalised at May 4, 2007. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Sanofi-Aventis AB has applied for a marketing authorisation for Optinate Combi D, a combination pack with 35 mg tablet and 1000 mg/880 IU oral effervescent granules. The active substance of the tablet is risedronate sodium (corresponding to 35 mg risedronate sodium) and the active substances of the effervescent granules are 2500 mg calcium carbonate (corresponding to 1000 mg elemental calcium) and 880 IU cholecalciferol (corresponding to 22 µg vitamin D3).

This is a complete application for known active substances. The 35 mg risedronate tablet has been previously approved as Optinate Septimum tablets via MRP SE/H/192/03 (first approval in RMS in July 2002) and as Optinate Combi (a combination pack with calcium 500 mg) via MRP SE/H/192/04 (first approval in RMS in August 2004). Risedronate for treatment of postmenopausal osteoporosis is also available as a 5 mg tablet for once daily dosing.

The aim of the Optinate Combi D combination pack is to help those patients who are advised to take calcium 1000 mg and vitamin D3 880 IU together with risedronate 35 mg to better understand dosing instructions and improve compliance. Patients are instructed to take the 35 mg risedronate sodium tablet on day 1 and the calcium + vitamin D sachets on the following 6 days of each week.

The approved indication for Optinate Combi D is the same as for Optinate Septimum in postmenopausal women, but with addition of a recommendation concerning the calcium and vitamin D3 content in Optinate Combi 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.

II. QUALITY ASPECTS

II.1 Introduction

Optinate Combi D is presented in the form of film-coated tablets containing 35 mg of risedronate sodium and effervescent granules containing 2500 mg calcium carbonate (corresponding to 1000 mg elemental calcium) and 880 IU cholecalciferol (corresponding to 22 µg vitamin D3). The excipients of the film-coated tablets are lactose monohydrate, microcrystalline cellulose, crospovidone, magnesium stearate, Dri-Klear [hypromellose, macrogol 400, hydroxypropylcellulose, macrogol 8000 and silicon dioxide], Chroma-Tone White (DDB-7536W) [titanium dioxide (E171), hypromellose], iron oxide yellow (E172) and iron oxide red (E172). The excipients of the effervescent granules are citric acid anhydrous, malic acid, gluconolactone, maltodextrin, sodium cyclamate, saccharin sodium, Flavour Lemon LCA Code 120 (sorbitol (E420), mannitol (E421), gluconolactone, dextrin, acacia, lemon oils and lime flavour), rice starch, potassium carbonate, all-rac-α-tocopherol, hydrogenated soya-bean oil, gelatin, sucrose and maize starch. The product is packed in an outer carton containing multiples of weekly units. Each weekly unit contains a clear

PVC/aluminium foil blister containing one tablet and six sachets (laminated aluminium paper foil) containing effervescent granules.

II.2 Drug Substance

Risedronate sodium does not have a monograph in the Ph.Eur. whereas cholecalciferol and calcium carbonate have. The manufacturers of cholecalciferol and calcium carbonate drug substance hold a “Certificate of Suitability” (CoS) of the Ph.Eur. monograph.

Sodium risedronate is a white to off-white crystalline powder which is soluble in pH 7.0 potassium phosphate dibasic solution, 0.1 N sodium hydroxide and water. Calcium carbonate is a white powder that is practically insoluble in water. Cholecalciferol consists of off-white to yellowish, free-flowing particles. The concentrate disperses quickly and completely in cold water. The structure of each of the drug substances has been adequately proven and their physicochemical properties sufficiently described. The manufacturing routes have been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The active substances specifications include relevant tests and limits for impurities/degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies have been conducted and the data provided are sufficient to confirm the retest period used.

II.3 Medicinal Product

Optinate Combi D film-coated tablet and effervescent granules is formulated using excipients of which all but gluconolactone and Lemon flavour are tested for compliance to the respective monographs in the European Pharmacopoeia. Gluconolactone is tested for compliance to the corresponding USP monograph and Lemon flavour is tested to an in-house monograph. There is no TSE risk related to any of the excipients. Magnesium stearate is from vegetable origin, the lactose is sourced from milk for human consumption. Declarations are provided. A certificate of suitability of the monographs of the European Pharmacopoeia exist for the gelatine used.

The product development has taken into consideration the physicochemical characteristics of the active substance.

The manufacturing process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.

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 claimed in the SPC, with no special storage precautions.

III. NON-CLINICAL ASPECTS

No new non-clinical data have been submitted for this product. The non-clinical assessment is the same as for the previously approved Optinate 5 mg and Optinate Septimum 35 mg tablets.

Bisphosphonates as a class are characterised pharmacologically by their ability to inhibit bone resorption. The bisphosphonates bind with high affinity to hydroxyapatite crystals in the bone and appear to inhibit bone resorption by inhibiting osteoclast activity. It is suggested that bisphosphonates are incorporated into the crystal structure of the bone, and when during bone resorption osteoclasts dissolve the crystals, the bisphosphonates are released to be taken up by the osteoclasts and exert a direct inhibitory effect on the cells. Some studies suggest also an indirect action on osteoblasts.

Previously assessed pharmacodynamic studies indicated that risedronate has the same mode of action as other bisphosphonates, with positive effects mainly on trabecular/cancellous bone. In a long-term (one year) treatment study in ovariectomised rats, where treatment was initiated when bone loss was established, there were no restoring effects on bone already lost, but risedronate apparently prevented further bone loss. Furthermore, efficacy of risedronate for prevention of ovariectomy-induced bone loss was clearly demonstrated in a one-year prevention study in ovariectomised rats at 0.5 mg/kg/day (treatment initiated one week after ovariectomy). Results from pharmacodynamic studies of risedronate in rats and dogs indicate that risedronate decreases bone turnover at daily as well as intermittent dosing and that the magnitude of the effect depends on total cumulative dose as well as dosing schedule (pulse length and intervals between doses).

There were no signs of impaired bone mineralisation in any of the pharmacological studies with daily or intermittent dosing with risedronate. Contrary to the results in pharmacological studies, in a previously assessed 2-year toxicity study in dogs some bone turnover parameters indicated similar or greater effects at the highest intermittent dose than at the same total dose (56 mg/kg per 28-day cycle) given daily. The pharmacodynamic effect on bone in pronounced cases, led to partial obliteration of the marrow cavity which was observed in all the high-dose groups (2 mg/kg daily and 8 mg/kg intermittently), although there was no deleterious effect on haematology parameters. In previous preclinical pharmacokinetic studies, CL and V_d decreased at higher doses, suggested due to saturation of either renal elimination or binding to bone and non-linear increases in exposure were seen at high doses, likely due to higher absorption. The non-linearity occurred at 4-8 mg/kg, i.e. at doses about 10 times higher than the approved clinical doses. No dose-dependent pharmacokinetics were observed in clinical pharmacokinetic studies at single doses of 30 mg, repeated doses of 5 mg/day or at weekly doses of 35 or 50 mg. Thus, no altered distribution or increases in total exposure would be expected with 35 mg given weekly compared with 5 mg daily, although the initial plasma levels after each dose will be considerably higher.

No new toxicology studies were included in the present application. Previous studies have shown that risedronate treatment resulted in clear effects on bone, kidney, liver, testes and stomach. The main concern was the liver toxicity, which – in contrast to e.g. gastrointestinal and renal toxicity – has not been observed preclinically for bisphosphonates in general but may be specific for risedronate. Results from studies with other dosing schedules indicate no increased toxicity upon intermittent compared with daily dosing. An intermittent dose level (8 mg/kg for 7 consecutive days per 28-day cycle) was clearly toxic when given daily in studies with shorter duration, with signs of hepatotoxicity after 5-6 weeks. The data indicate that toxicity of risedronate is related to systemic exposure over a certain time period and not to

C_{max}. The presented clinical safety database raises no additional cause for concern regarding potentially increased risk for hepatic or other toxicity at weekly dosing.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

There are no new pharmacokinetic data for this application and the pharmacokinetic assessment is the same as for the previously approved Optinate 5 mg and Optinate Septimum 35 mg tablets. In common with other bisphosphonates, the absolute bioavailability of risedronate is very low, <1%. The drug has low protein binding, 24%, and is eliminated unchanged via the kidney. Approximately half of the absorbed dose was excreted in the urine in the first 24 hours, and 85% of the dose is recovered in the urine over 28 days. Since CL_R comprised about 86% of the CL, only a small percentage (approximately 14%) of a systemically available dose was "cleared" or incorporated into bone. It is this fraction of drug that is taken up into bone, and subsequently released, that is responsible for the very long half life of risedronate, around 2 weeks. The pharmacokinetics of risedronate are dose and time independent. Bisphosphonates form an insoluble complex with multivalent cations, such as Ca^{2+}. The presence of food, certain beverages, and calcium-binding medications considerably decreases the absorption of all bisphosphates. The risk for systemic, pharmacokinetic interactions, however, appears to be low. Since the risedronate sodium tablet and the calcium + vitamin D sachets in Optinate Combi D are administered on different days, an absorption interaction between the two products in the combination pack is avoided.

Dosing with 35 mg risedronate once a week resulted in about 6 times higher C_{max} (mean values), approximately similar C_{ave} but lower C_{min} than the 5 mg daily dose regimen. Efficacy and safety data indicate that the lower C_{min} obtained with the 35 mg weekly compared with the 5 mg daily dose will not impair efficacy and that the considerably higher C_{max} is unlikely to increase the risk for risedronate-induced toxicity. Efficacy as well as toxicology appears to be mainly related to systemic exposure, which is approximately the same with the two dosing schedules.

IV.2 Pharmacodynamics

There are no new pharmacodynamic data for this application and the pharmacodynamic assessment is the same as for the previously approved Optinate 5 mg and Optinate Septimum 35 mg tablets.

IV.3 Clinical efficacy

No new clinical efficacy data are presented in this submission and no additional efficacy claims are requested for Optinate Combi D. As all previous efficacy trials with risedronate were performed with supplementation of calcium and vitamin D, additional efficacy data for the combination pack are not considered necessary. However, it is important to discern those patients who have the need for the specific doses of calcium and vitamin D supplied in the combination pack.

Data for the calcium and vitamin D3 sachets have been previously submitted in marketing applications for Cacit Vitamine D3 -, via the MR procedure FR/H/103/02. Clinical efficiency is expected to be equal to what has been established for the products Optinate Septimum and Cacit Vitamine D3.

As the aim of the combination pack is to improve patient’s adherence to dosing instructions, an evaluation of the understanding of the dosing instructions for the combination pack was performed.

The proportion of questions a patient answered correctly was dependent on whether or not she had previously used a bisphosphonate, previous bisphosphonate users having significantly ($p < 0.0001$) higher percentage of correct answers. The proportion of questions a participant answered correctly for the combination pack was significantly higher than the proportion of questions answered correctly for the separate packs ($p < 0.0004$). Persons who had earlier been taking a bisphosphonate had significantly more correct answers to the questions than persons who had not taken bisphosphonates earlier ($p < 0.0001$). Participant's preferences for combined or separate packs were compared and significantly more participants preferred the combination pack ($p < 0.0001$).

IV.4 Clinical safety

Spontaneous post-marketing adverse event reporting for risedronate has been consistent. The types of events most frequently reported by health care professionals are gastrointestinal and musculoskeletal signs and symptoms. Skin disorders, headache/neurological signs and symptoms and abnormal liver enzymes are among the most commonly reported events.
Since initial registration, the product information for Cacit Vitamine 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 Vitamine 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 SPC.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

A user test (including two testing rounds) has been performed for the proposed Package Leaflet (PL). The first testing round resulted in amendments of the PL followed by a second test. The results of the second test were acceptable and no additional changes in the leaflet were needed.
The proposed leaflet of this combination medicine is created based on the leaflet of "Optinate Septimum" 35 mg tablets for weekly dosing, containing only the tablet. This leaflet has been tested previously, also with good results.

The results of the performed user test of the PL can be considered acceptable.

The SPC, package leaflet and labelling are acceptable.

The risk/benefit ratio is considered positive and Optinate Combi D, 35 mg tablet and 1000 mg/880 IU oral effervescent granules, is recommended for approval.

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Public Assessment Report – Update

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)

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