LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Optinate Septimum
(risedronate sodium)

SE/H/192/07/DC

This module reflects the scientific discussion for the approval of Optinate Septimum. The procedure was finalised on 2016-10-12. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Actavis Group PTC ehf. has applied for a marketing authorisation for Optinate Septimum , 35 mg, gastro-resistant tablet. The active substance risedronate sodium is the same as in Optinate , 5 mg, film-coated tablet, marketed by Actavis Group PTC ehf. since 1999.

For approved indications, see the Summary of Product Characteristics.

The marketing authorisation has been granted pursuant to Article 8(3) of Directive 2001/83/EC.

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

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

III.1 Introduction

The non-clinical profile of risedronate has been thoroughly investigated within the frame of previous applications for the approval of Optinate 5 mg, 30 mg and 35 mg tablets. A brief summary of relevance for the present product is given below.

III.2 Pharmacology

Risedronate belongs to the class of bisphosphonates, characterised pharmacologically by their ability to inhibit bone resorption. Results from pharmacodynamic studies 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.

Risedronate did not cause any adverse functional effects on the central nervous system, gastrointestinal or cardiovascular systems at doses sufficiently in excess of clinical exposure.

III.3 Pharmacokinetics

Bisphosphonates as a class display similar qualitative pharmacokinetics, which has been shown also for risedronate. Oral bioavailability is very low in animals as well as in humans. Systemic clearance of risedronate is rapid and comprises renal excretion and distribution to bone. It passes the placenta to a low degree, and, apparently, small amounts pass to the milk during lactation.

III.4 Toxicology

In previous repeat-dose toxicity studies in rats and dogs, the liver, testes, kidney and gastrointestinal tract were identified as target organs for toxicity. In support of the new formulation, a 13-week repeat-dose toxicity study was conducted in dogs, using once weekly administration via oral gelatin capsules. The main purpose of this study was to identify potential changes in gastrointestinal effects due to the combination of risedronate and EDTA versus risedronate alone.

No new target organs of toxicity were identified when risedronate was dosed once-a-week as compared with previous studies in dogs using once daily administration. Addition of EDTA at 12.5 mg/kg increased the exposure of risedronate between 2 to 6 times, accounting for slightly more pronounced effects on target organs as compared with risedronate alone or with EDTA 2.5 mg/kg. No toxicity of EDTA alone was observed at a dose 4 times the clinical dose of 100 mg.

III.5 Ecotoxicity/environmental risk assessment

Risedronate is not considered to pose any risk to the environment.

CLINICAL ASPECTS

Introduction

Bisphosphonates like risedronate, generally exhibit low bioavailability due to low absorption from the gastrointestinal (GI) tract and absorption of oral bisphosphonates is further decreased as they form complexes with food, calcium, and other polyvalent cations. Therefore, a key factor is to ensure that patients adhere to dosing requirements outlined in the product label so that they absorb a sufficient amount of drug. Due to the complexity of these dosing requirements, i.e.must be taken on an empty stomach 30 to 60 minutes before the first food,

drink, or other medication of the day, many patients may fail to adhere to one or more of the dosing requirements, thus failing to absorb the optimal amount of bisphosphonate.

This was an extension application for a new formulation of risedronate; 35 mg delayed-release (DR) once a week formulation of risedronate tablets for the treatment of postmenopausal osteoporosis (PMO).

The scientific rationale for the DR formulation is based on the premise that absorption of risedronate in the presence of food may be improved if risedronate is delivered at sites beyond the stomach; where the concentrations of calcium and other divalent or trivalent cations are anticipated to be lower than in the fed stomach. In addition, any cations present will be bound by a competing chelating agent in the formulation, Ethylenediaminetetraacetic acid (EDTA).

The application was mainly supported by data from the Phase III clinical study 2007008 which was a parallel group non inferiority study of the 35 mg DR once-a-week regimen compared to the currently authorised 5 mg Immediate Release (IR) daily formulation. The primary efficacy endpoint was mean percent change from baseline in lumbar spine Bone Mineral Density (BMD) at a week 52 Endpoint, using a stepwise analysis of 35 mg DR taken immediately following breakfast (DRFB), then of 35 mg DR taken at least 30 minutes prior to breakfast (DRBB).

In Europe, risedronate 5mg daily and 35mg once a week strengths were approved as an IR formulation via Mutual Recognition Procedure (MRP) and the 75 mg on 2 consecutive days (2CDM) strength via the Decentralised Procedure (DCP). The approval of the 5 mg daily formulation, was based on two 3-year, double-blind, multicenter, placebo-controlled Phase III studies in women with PMO that showed risedronate reduces the risk of vertebral and nonvertebral fractures. The subsequent approvals of 35 mg IR once a week and 75 mg IR 2CDM were based on Year 1 data from 2-year, double-blind, multicenter, Phase III non inferiority studies in women with PMO. With respect to increasing lumbar spine BMD after 1 and 2 years of treatment, these studies demonstrated that risedronate 35 mg IR once a week and 75 mg IR 2CDM, are noninferior to risedronate 5 mg IR daily. In addition, the overall safety profiles of 35 mg IR once a week and 75 mg IR 2CDM were similar to 5 mg IR daily.

The 35 mg delayed-release (DR) once-a-week formulation, which were the subject of this line extension, is already approved in the US (2010), Canada (2011), Australia (2011), South-Korea (2012), and Brazil (2013).

The application for Optinate Septimum, 35 mg, gastro-resistant tablet, were a line extension application made according to Article 8(3) Known active substance of Directive 2001/83/EC. The applicant, Actavis Group PTC ehf applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and BE, DE, ES, FR, IE, IT, NL and UK as concerned member states (CMS).

Pharmacokinetics

The pharmacokinetic documentation comprises several studies comparing the pharmacokinetic characteristics of the new formulation with the existing immediate release formulation. Influence of factors affecting the performance of the formulation (e.g. food and certain other drugs that may affect the delayed release) has also been investigated.

Risedronate concentrations in urine and in serum/plasma have been determined with validated LC-MS/MS methods. In most studies the primary pharmacokinetic variables were the

cumulative amount and percentage of risedronate recovered in urine (Ae and Ae% respectively) up to 72 h.

Absorption
Time to peak concentration (Tmax) for risedronate 35 mg DR was approximately 3 hours after administration in the morning 4 hours prior to a meal.

Risedronate 35 mg DR tablet vs risedronate 35 mg IR tablet
Several studies have been conducted to evaluate the relative bioavailability of the new DR tablet compared to the already authorised IR tablet, after single dose as well as after multiple dose administration. When both formulations were administered under fasting conditions, the risedronate exposure from the DR tablet was 1.4-fold higher than from the IR tablet. In most studies the relative bioavailability of risedronate 35 mg DR compared to risedronate 35 mg IR was evaluated when both formulations were administered under proposed label/per-label with regards to food intake; i.e. the DR tablet was administered immediately following breakfast and the IR tablet 30 min before breakfast. There was a large variability in results both within and between studies. Overall, the risedronate exposure was 2-4-fold higher after administration of the DR tablet compared to risedronate IR. Based on comparisons with other formulations, it can be concluded that the monthly exposure of risedronate from the 35 mg DR tablet is expected to be largely comparable to risedronate 75 mg administered on two consecutive days.

Effect of food on risedronate 35 mg DR tablet
The risedronate exposure was approximately 30% lower when the 35 mg DR tablet was administered immediately following a high-fat breakfast compared to administration under strict fasting conditions. Thus, the DR tablet appears to be less affected by food intake than the conventional IR tablet for which the exposure was 54% lower when administered 30 min prior to a high-fat breakfast compared to under fasting condition. The results from the population PK analysis indicate the presence of food did not appreciably affect the bioavailability of the gastro-resistant tablets.

In the Phase III study, risedronate DR was administered either 30 minutes before breakfast or directly following breakfast. Given that administration 30 minutes prior to breakfast resulted in a higher incidence of upper abdominal pain, it is recommended that the DR tablet should be taken with breakfast.

The effect of different types of food has not been evaluated in a single study. In the comparison between studies, there was no indication of a marked difference in exposure after administration of a high-fat and a standard breakfast. Since this is a between-study comparison, this conclusion should however be interpreted with caution. Nevertheless, no specific recommendation regarding type of food is considered to be required.

Administration of risedronate 35 mg DR after dinner resulted in 87% higher exposure than administration following breakfast. Based on the potential for increased exposure for night time dosing, the proposed labelling recommends dosing in the morning with breakfast.

Taken together, it is recommended that the gastro-resistant tablet should be administered in the morning with breakfast.

Bioequivalence between to-be-marketed and Phase III formulation
Bioequivalence between the to-be-marketed and the Phase III formulation has been sufficiently demonstrated.

Variability
The inter-individual variability of the pharmacokinetic parameters was markedly higher for the DR tablet compared to the IR tablet; 98-135% for the IR tablet and 128-594% for the DR tablet. Since efficacy and safety has been sufficiently demonstrated for the new DR tablet, the larger inter-individual variability is not considered to be a concern.

Interactions
In vitro
Two in vitro and three in vivo interaction studies have been performed to evaluate the interaction potential with the new delayed release formulation of risedronate.

The risk that the content of low amounts of di- or trivalent cations included in commonly co-prescribed oral drugs would interfere with the absorption of risedronate to a clinically relevant extent, appears to be low based on in vitro data.

The effect of the excipient EDTA on the solubility of certain NTI and antiviral drugs has been evaluated in vitro. There was no or a relatively modest effect of EDTA on the solubility of the tested drugs at anticipated in vivo EDTA concentrations. Furthermore, in vivo concentrations of EDTA resulting from the DR tablet are not likely to influence the paracellular absorption of other drugs.

In vivo
Esomeprazole: The effect of esomeprazole on risedronate has been evaluated in vivo. Co-administration of risedronate 35 mg gastro-resistant tablets with the proton pump inhibitor esomeprazole increased risedronate Cmax AUC by 60% and 22% respectively. This is not considered to be of clinical relevance.

Calcium supplements: The risedronate exposure was 38% lower after co-administration of risedronate 35 mg DR and 600 mg Ca/400 IU vitamin D. in line with the recommendation for risedronate IR formulations, risedronate DR and calcium supplements should be administered at different times.

In conclusion: The pharmacokinetics of the new delayed release formulation has been sufficiently characterised.

Pharmacodynamics

The primary effect of risedronate on the skeleton is to inhibit bone resorption through inhibition of osteoclasts, the cells responsible for bone resorption. Pyridinyl bisphosphonates inhibit osteoclast activity and induce apoptosis by inhibiting enzymes of the mevalonate pathway, with subsequent disruption of intracellular signalling.

Bone Turnover Markers (BTMs) were studied both in the phase III study 2007008 and in the phase II study 2005107 in order to evaluate the mechanism of action of the drug and its integrated effect on bone.

The phase II study 2005107 was conducted in healthy postmenopausal women and assessed BTMs in the following dosing regimens, each compared to the risedronate 35 mg IR tablet taken per-label (35 mg IRBB):
- 35 mg DRFB: 35 mg DR tablet taken immediately following breakfast;
- 50 mg DRFB: 50 mg DR tablet taken immediately following breakfast;
- 50 mg DRBB: 50 mg DR tablet taken at least 30 minutes before breakfast.

The ITT population included 181 subjects.
Results from this study show that the effect on BMTs by the DR regimens was at least not inferior to the effect on BMTs exerted by the 35 mg IR regimen. Both 50 mg regimens suppressed all BTMs to a similar extent.

The phase III study 2007008 conducted in women with PMO assessed BMTs over a 52-week dosing period in the following dosing regimens, each compared to risedronate 5 mg IR daily taken per-label (i.e., at least 30 minutes prior to breakfast) (5 mg IRBB):
•35 mg DRFB: risedronate 35 mg DR once a week taken immediately following breakfast;
•35 mg DRBB: risedronate 35 mg DR once a week taken at least 30 minutes before breakfast.
The ITT population included 922 subjects.
Overall the three different regimes seem to have a similar effect on bone turnover. There were no clinically relevant differences observed between the two DR groups for any of the BTMs. The size of the BTM changes from baseline were within the range of what can be expected based on data from prior studies with the 5 mg IR regime.

In conclusion, according to data from the phase II and the phase III study indicate that the new DR formulation has similar or at least not inferior effect on bone turnover compared to the authorised IR formulation. BMT data are described in the SmPC 5.1 section.

Clinical efficacy

Clinical efficacy of the new formulation was primarily evaluated in the Phase III study 2007008. This study was designed and executed as a multinational non inferiority lumbar spine BMD study assessing the efficacy of the risedronate 35 mg DR once a week formulation for the treatment of women with PMO compared to the authorised 5 mg IR daily regime. The 5 mg IR daily regime has a proven anti-fracture efficacy.
As both 35 mg DR taken before (35 mg DRBB) and after breakfast (35 mg DRBB) were compared to the 5 mg IR formulation taken per label i.e. before breakfast (5 mg IRBB), the study thus had three different treatment arms.
The inclusion criteria of study 2007008 capture females with PMO defined by pathologic T-score or females with T-score defined osteopenia and overt vertebral fractures and such a population adequately matches the currently proposed indication for the product: “treatment of osteoporosis in postmenopausal women at increased risk of fractures (see section 5.1)”. Also the exclusion criteria, (hypocalcaemia, hypersensitivity, severe renal impairment, GI disorders etc.) are reasonably well reflected in the SmPC in sections 4.3 and 4.4.

The study met its primary objective relating to efficacy in demonstrating that both 35 mg DRFB regimen and 35 mg DRBB regimens were non inferior to the 5 mg IRBB regimen with respect to percent change in lumbar spine BMD at the Week 52-Endpoint in the primary efficacy analysis population. The mean percent change from baseline in lumbar spine BMD was approximately 3 % in all three treatment groups. The size of the treatment effect is within the range of what can be expected based on data from prior studies with the 5 mg IR regime. The results from analyses using the per protocol (PP) population were consistent with the primary efficacy analysis. The results from the secondary analyses, including total proximal femur, femoral neck, and greater trochanter BMD as well as new vertebral fractures were overall in line with the results from the primary analyses.
There was no treatment by age interaction for lumbar spine BMD at Endpoint.

In conclusion, data from the phase III study indicate that Risedronate 35 mg DR, whether taken before or after breakfast, demonstrate similar efficacy for a variety of parameters

compared to the approved 5 mg IR daily regimen. This is overall adequately reflected in the product information.

Clinical safety

Exposure
In total>1500 individuals have been exposed to risedronate 35 mg DR in the Phase I, II and III studies. In the Phase III study > 500 patients were treated for >360 days. Cumulative total exposure from countries were 35 mg DR is already approved is estimated to be approximately 474,548 patient-years. The extent of exposure is judged to be sufficient for an adequate safety evaluation.

Summary of safety data from the phase III study
Treatment-emergent adverse events (TEAEs); AEs recorded from the date of the first dose of the study until the subject's exit from the study, were reported.
The numbers of TEAEs, including Gastrointestinal (GI) TEAEs, were slightly higher with the 35 mg DR weekly regimens compared to the 5 mg IR daily regimen in the Phase III study, see Table 1.

Table 1
Overall Treatment-emergent Adverse Event Profile (Intent-to-treat)
Study 2007008

Category	5 mg IRBB Daily (N=307) n (%) nAE			35 mg DRFB Weekly (N=307) n (%) nAE			35 mg DRBB Weekly (N=308) n (%) nAE			p-value
AEs	**243**	**(79.2%)**	**1025**	**250**	**(81.4%)**	**1138**	**264**	**(85.7%)**	**1219**	0.0971
Serious AEs	**31**	**(10.1%)**	**37**	**32**	**(10.4%)**	**54**	**32**	**(10.4%)**	**46**	1.0000
Deaths	1	(0.3%)	1	1	(0.3%)	1	0	(0.0%)	0	0.5546
Withdrawn due to AEs	**28**	**(9.1%)**	**41**	**37**	**(12.1%)**	**52**	**25**	**(8.1%)**	**39**	0.2391
Possibly/Probably Related AEs	59	(19.2%)	89	60	(19.5%)	132	70	(22.7%)	160	0.5089
Possibly/Probably Related Serious AEs	0	(0.0%)	0	1	(0.3%)	1	1	(0.3%)	1	1.0000
UGI AEs[a]	**56**	**(18.2%)**	**73**	**59**	**(19.2%)**	**85**	**69**	**(22.4%)**	**127**	0.4084
Moderate to severe UGI AEs[a]	**14**	**(4.6%)**	**15**	**19**	**(6.2%)**	**25**	**26**	**(8.4%)**	**33**	0.1605
LGI AEs[a]	**48**	**(15.6%)**	**72**	**68**	**(22.1%)**	**98**	**62**	**(20.1%)**	**93**	0.1071
Moderate to severe LGI AEs[a]	**19**	**(6.2%)**	**23**	**25**	**(8.1%)**	**30**	**23**	**(7.5%)**	**30**	0.6560
Vertebral clinical fracture AEs	1	(0.3%)	1	0	(0.0%)	0	3	(1.0%)	3	0.3319
Non-vertebral clinical fracture AEs	15	(4.9%)	18	13	(4.2%)	15	20	(6.5%)	25	0.4702
OP related non-vertebral clinical fracture AEs[b]	7	(2.3%)	8	8	(2.6%)	9	11	(3.6%)	12	0.6788
Selected musculoskeletal AEs	68	(22.1%)	93	67	(21.8%)	103	77	(25.0%)	95	0.5972
Mean Number of AEs per enrolled patient	3.3			3.7			4.0			_
Mean Number of AEs per patient with AEs	4.2			4.6			4.6			_

Treatment: IRBB = 5 mg/day risedronate immediate-release before breakfast, DRFB = 35 mg/week risedronate delayed-release following breakfast, DRBB = 35 mg/week risedronate delayed-release before breakfast.
N=number of intent-to-treat patients within specified treatment.
n(%) = number (percent) of patients within specified category and treatment.
nAE = number of adverse events within the specified category and treatment.
P-value from Fisher's Exact Test (no adjustment for multiple comparisons).
[a] UGI=Upper GI. LGI=Lower GI.
[b] OP = osteoporosis. Includes fractures at wrist, hip, leg, clavicle, humerus, and pelvis.

The number of Upper GI AEs was higher in the DR groups compared to the IR group. Many of these AEs constituted of abdominal pain or abdominal discomfort while events with documented esophagitis, gastritis, ulcers and melena were rare.
Also lower GI TEAs were somewhat more frequent in the 35 mg DR groups compared to the 5 mg IR group; the most common of these AEs being diarrhoea. Event rates for colitis, sigmoiditis and bleedings were low as well as abnormal colonoscopy findings related to inflammation. Lower GI TEAs are of particular interest since the DR Formulation is designed to release drug beyond the stomach.
The risedronate exposure was 2-4-fold higher after administration of risedronate 35 mg DR tablet compared to risedronate35 mg IR. It was enquired whether the somewhat higher incidence of adverse events for the DR formulation compared to the IR form observed in phase III study may be related to higher risedronate exposure.
The applicant was asked to discuss the relevance of the increased exposure for the frequency of AEs with focus on AEs that are too rare to be captured by the phase III study. It was stated

that from the overall data from the clinical trial program there is no evidence that the somewhat higher rate of AEs reported during phase 3 study with Risedronate 35 mg DR formulations may be related to higher risedronate exposure. From post-marketing safety experience of Risedronate 35 mg DR there is no information that may change the known benefit-risk profile of the product. There are no immediate signals neither from the phase I-III studies, nor the post marketing data, that the higher risedronate exposure associated with the Risedronate DR formulation compared to the IR formulation, would translate into a distinctively different safety profile even though the DR formulation seems associated with a somewhat higher AE frequency, including GI AEs. However, the AEs of interest which are too rare to be captured by the development program will have to continue to be kept under close observation.

The incidence of serious AEs was not higher in the 35 mg DR weekly regimens compared to the authorised 5 mg IR daily regimen. Two deaths, one in the 5 mg IR daily group in Year 1 and one in 35 mg DRFB in Year 2, occurred in the Phase III Study. The first death was a cardiac arrest for unclear reasons in a 68 year old female and the second occurred in 75 year old female who was newly diagnosed with a lung neoplasm. Both deaths were considered doubtfully-related to study drug.

The overall frequency of AEs tended to increase with age which is an expected finding but the difference in overall AE frequency between the different age categories was not more than a couple of percent in absolute numbers. The tendency with a slightly increased number of AEs in the DR groups compared to the IR group was preserved across age categories, i.e. the finding that the DR formulation was associated with somewhat more AEs than the IR formulation was not dependent on age but confirmed for all the age groups. The pattern of AEs was not significantly affected by age.
The available information on safety in elderly is adequately expressed in section 4.2 of the SmPC under the subheading special populations; elderly.

Summary of safety data from the phase II study
In the phase II study both the overall number of AEs and overall number of GI AEs was higher in the 35 mg IRBB group than in the 35 mg DRFB group but UGI AEs were higher in the DR group. However the numbers in each treatment group was small (just 1/9 of the number in the different arms in the phase III study) and thus the events were too few to allow firm conclusions on group differences. No deaths were reported in the phase II study.

Summary of safety data from the phase I study
No unexpected safety information relevant to the current application emerged from the Phase I studies.

Safety data on EDTA
The data on EDTA provided by the MAH are to some extent reassuring:

- 100 mg EDTA/week corresponds to <15 mg/day which is well below the established ADI (ADI=99.5 mg/day for a 40 kg person and 149 mg/day for a 60 kg person).
- Very limited impact is expected on dietary calcium.
- There is a the lack of confirmed interactions except for interactions with drugs containing substantial amounts of cations and for PPI, of which both are already addressed in the proposed SmPC (see pharmacokinetics)

However, with the currently proposed dosing, at one day per week the patient's intake of EDTA will be close to ADI. The company was therefore asked to provide additional data confirming that the EDTA-content of the DR tablets does not pose any health related risks both in the short and long term.

The applicant has provided some support that the part of the EDTA-content of the tablet that is systemically absorbed is not expected to cause important safety problems. The risk that the uptake of cations, other than calcium is affected and could cause AEs was not directly discussed by the applicant. However, the safety data from the phase 3 study 2007008, provides some reassurance regarding the risk that the uptake of cations other than calcium is affected since there are indications that at least not iron and Magnesium uptake are significantly influenced by this new EDTA-containing drug. The number of patients that dropped from a normal Haemoglobin value at baseline to a low Haemoglobin value after 2 years of treatment was not higher in the DR-groups than in the IR group and neither was the number that dropped from normal to low Magnesium. It was therefore judged that the issue does not need to be further pursued.

Safety related to interactions
The safety profile of risedronate 35 mg DR does not seem to be significantly impacted by neither PPI inhibitor treatment nor whether the tablet is taken before breakfast or after a meal.

In conclusion, data from phase I-III studies indicate that the safety profile of the 35 mg DR weekly regimen is essentially similar to the currently approved 5 mg IR daily regimen even though the AE frequency, including the GI AE frequency, is slightly higher. The frequency of GI AEs associated with endoscopic findings appears low.
It is recommended that the DR tablet should be taken with breakfast.
The safety profile is overall adequately reflected in the proposed product information .

Risk Management Plans

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 Optinate Septimum.

Safety specification

Table 2: Summary table of safety concerns in the approved RMP

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

Summary of safety concerns	
	Effect in lactating women Effect on fertility Use in patients with severe renal impairment

Pharmacovigilance Plan

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

Risk minimisation measures

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

Summary of the RMP

The RMP is approvable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates 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.

IV. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was english.
The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Quality
From a quality point of view the application can be recommended for approval.

Non-clinical
From a non-clinical point of view the application can be recommended for approval.

Pharmacokinetics
The pharmacokinetics of the new delayed release formulation has been sufficiently characterised.

Clinical

Efficacy
Regarding clinical efficacy, the new 35 mg risedronate DR formulation dosed once weekly, whether taken before or after breakfast, demonstrates similar efficacy for a variety of parameters , compared to the approved 5 mg IR daily regimen. Thus, the benefit of this new formulation in terms of its effect on PMO is considered similar to the authorised comparator regimen. Compared to the authorised regime, the new DR formulation has the benefit that patients do not have to take the tablets fasting.
Safety
Regarding clinical safety, study data indicate that the overall safety profile of the new formulation is similar to the authorised product but the AE frequency, including the GI AE frequency, is slightly higher. However, the frequency of GI AEs associated with endoscopic findings appears low.
Conclusions:
The application is approvable from a clinical perspective.

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

N/A

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

N/A

VI. APPROVAL

The Decentralised procedure for Optinate Septimum , 35 mg, gastro-resistant tablet was positively finalised on 2016-10-12.

LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report – Update

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

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

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