LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

# Public Assessment Report

# Scientific discussion

# Norsed

# 75 mg film-coated tablets

# (risedronate sodium)

# SE/H/194/05/DC

**This module reflects the scientific discussion for the approval of Norsed 75 mg tablets. The procedure was finalised at Dec 5, 2007. 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.mpa.se E-mail: registrator@mpa.se

# I. INTRODUCTION

sanofi-aventis S.p.A has applied for a marketing authorisation for Norsed 75 mg tablets. The active substance risedronate sodium is the same as in Norsed 5 mg tablets marketed by sanofi-aventis S.p.A since 1999. For approved indications, see the Summary of Product Characteristics.

The 75 mg tablet is intended to be administered on two consecutive days each month (75 mg 2CDM) for a total dose of 150 mg per month and provides an alternative to the previously approved 5 mg once daily or 35 mg once weekly dosing regiments.

# II. QUALITY ASPECTS

## II.1 Introduction

Norsed is presented in the form of film-coated tablets containing 75 mg of risedronate sodium which corresponds to 69.6 mg risedronic acid. The excipients are microcrystalline cellulose, crospovidone, magnesium stearate, hypromellose, macrogol, hydroxypropylcellulose, silicon dioxide, titanium dioxide (E171) and ferric oxide red (E172).
The film-coated tablets are packed in PVC/Al blister.

## II.2 Drug Substance

Risedronate sodium does not have a monograph in the Ph Eur.

Risedronate sodium is a fine, white to off-white, crystalline powder which is soluble in pH 7.0 potassium phosphate dibasic solution, 0.1N sodium hydroxide and water; very slightly soluble in 0.1N hydrochloric acid; practically insoluble in ethanol and insoluble in isopropanol. The structure of risedronate sodium has been adequately proven and its physico-chemical properties sufficiently described. Relevant information on polymorphism and chirality is presented. The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

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

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

## II.3 Medicinal Product

Norsed film-coated tablet is formulated using excipients described in the current Ph Eur, except for silicon dioxide in the Dri-Klear coating and ferric oxide red, which are controlled in accordance with the USP/NF. No raw materials used in the product are of human or animal origin.

The product development has taken into consideration the physico-chemical characteristics of the active substance, such as hydrate form and particle size.

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 under ICH conditions have been performed and data presented support the shelf life claimed in the SPC, with no special storage precautions.

# III. NON-CLINICAL ASPECTS

## III.1 Introduction

Risedronate is a bisphosphonate for treatment of postmenopausal osteoporosis. Norsed 75 mg represents a new dose and regimen of risedronate and should be administered on 2 consecutive days every month providing a total monthly dose of 150 mg. Risedronate is a nitrogen containing bisphosphonate that inhibits bone resorption and its cellular actions may include inhibition of mevalonate pathway enzymes and stimulation of apoptosis of osteoclasts. The predominant mechanism of bisphosphonates *in vivo* is not conclusively established and the mechanisms may be different for each bisphosphonate.

## III.2 Pharmacology

The pharmacological properties of risedronate are well-known. No new data are available. The new dose is expected to produce Cmax levels x2 higher than for the approved 35 mg weekly dose. The extent to which previously conducted safety pharmacology studies cover any Cmax dependent toxicity has been discussed and sufficiently addressed. No specific concerns related to this issue were identified.

## III.3 Pharmacokinetics

No new animal pharmacokinetic data are available; however, toxicokinetic data are included in the two new dog repeated dose toxicity studies.

## III.4 Toxicology

Data from previous studies to support the daily dosing regimens have shown that risedronate was 1) not genotoxic; 2) no evidence of teratogenicity in rats or rabbits; and 3) not carcinogenic in lifespan studies in rodents (32 mg/kg/day in mice and 24 mg/kg/day in rats). The design (daily dosing) of the studies for these endpoints is considered adequate for the monthly dosing as well and it is acceptable that no new studies were conducted to cover these endpoints for monthly dosing regimens.

Previously submitted studies in earlier marketing authorization approvals are not reviewed in this report, except selected repeat-dose toxicity information in relation to newly submitted studies. Standard daily repeat-dose toxicity studies used to support earlier approvals of risedronate were conducted primarily in rat and dog. Both oral and intravenous daily administrations were used, and study durations varied from 7 days to 2 years. The NOAELs for oral administration were 16 mg/kg/day in rats, and 4 mg/kg/day in dogs for 13 weeks or longer. Oral daily risedronate treatment resulted in effects on the liver, kidney, testes, and stomach as well as the expected pharmacological effects on bone. Toxicity increased with

increasing dose. There were no significant sex differences. The dog exhibited all the adverse effects observed, at a lower dose and lower exposure than the rat. There was no evidence for cumulative toxicity with increasing duration of treatment beyond 13 weeks. In dogs, liver toxicity was observed at daily doses above 4 mg/kg/day in repeat-dose studies. In 2 year studies in dogs with either daily doses of 2 mg/kg/day or intermittent doses (7 days risedronate followed by 21 days placebo) of 8 mg/kg/dose, did not result in any toxicological effects, although the expected pharmacological effect, normal lamellar bone, was confirmed with non-decalcified tissue. Though 8 mg/kg was clearly toxic in daily repeat-dose studies of shorter duration (13 weeks to 1 year), it was not toxic when administered intermittently during the 2-year study. Specific to this submission to support the use of a new clinical dosing regimen (75 mg risedronate given orally on 2 consecutive days per month), the toxicity of monthly oral dosing of risedronate was investigated in 6-month and 1-year bridging studies in dogs. Dogs received either placebo or risedronate in gelatin capsules at 16, 32, and 64 mg/kg/dose for a total of 7 once-a-month doses (6-month study) or 13 once-a-month doses (1-year study). No new toxicities from those observed in the once-a-day dosing studies were observed following once-a-month dosing. Consistent with the once-a-day dosing, toxicity was observed in the liver and kidney, and a local irritation effect was observed in the stomach. The systemic NOAEL values in dogs increased from 4 mg/kg/day given once a day, to 16 mg/kg/dose given once-a-month, and did not change when the duration increased from 6 months to 1 year with once-a-month dosing. At the NOAEL the exposure multiple to the expected clinical exposure, corrected for unbound drug was approximately 31.

The SPC sections dealing with non-clinical data are acceptable.

### III.5 Ecotoxicity/environmental risk assessment

An environmental assessment for risedronate sodium indicates that Norsed 75 mg film-coated tablets are unlikely to represent a risk to the environment. The phase I PECsurfacewater for risedronate sodium is estimated to be 0.009 µg/L and no other environmental concerns are apparent.

### III.6 Discussion on the non-clinical aspects

Previous studies to support the daily dosing regimens showed that risedronate was 1) not genotoxic; 2) not teratogenic; and 3) not carcinogenic. The design (daily dosing) of the studies for these endpoints is considered adequate for the monthly dosing as well and it is acceptable that no new studies were conducted to cover these endpoints for monthly dosing regimens.

## IV. CLINICAL ASPECTS

### IV.1 Introduction

Risedronate is a bisphosphonate, indicated for treatment of osteoporosis in postmenopausal women at increased risk of fractures. Approval of the 5 mg daily dose of risedronate for treatment of postmenopausal osteoporosis (PMO) was based on four 3-year double-blind multicenter phase III studies. These studies showed that risedronate significantly reduced the risk of vertebral and nonvertebral/hip fractures in women with PMO. A previous approval for the 35 mg once weekly dose was based on a 2-year double-blind multicenter phase III study in women with PMO. This study demonstrated that risedronate 35 mg once weekly was equivalent to risedronate 5 mg daily with respect to increasing lumbar spine bone mineral density (BMD) after one and two years of treatment. Overall safety and tolerability of the two compared dosing regimens were found to be similar between treatments.

The clinical data supporting the new 75 mg tablet and the dosing regimen are discussed below.

## IV.2 Pharmacokinetics

The pharmacokinetics of risedronate after 5 mg daily and 75 mg 2CDM dosing were compared in a multiple-dose study with 4 months dosing to healthy postmenopausal women. The results indicate that the total exposure to risedronate (AUC), amount excreted in urine and average plasma concentration over one month were similar with the two dosing regimens, which support the chosen 2CDM dosing regimen. The $C_{max}$ was approximately 11 times higher after the 75 mg dose than after the 5 mg dose. Compared with the 35 mg weekly dose, $C_{max}$ for the 75 mg dose is estimated to be about 2 times higher.

Previously assessed studies have demonstrated dose linearity for risedronate in the dose range 5 mg to 50 mg. The results of a new single-dose, dose-ranging study in healthy postmenopausal women indicated that pharmacokinetics of risedronate are linear between a 50 mg and a 75 mg single dose, but at higher doses (100-250 mg), AUC increases more than dose proportionally (~2 fold and constant over the range of 100 to 250 mg).

In another part of the dose-ranging study, it was shown that AUC decreased by approximately 30% and 60% when a 150 mg risedronate tablet was swallowed with 240 ml medium-hard and hard water, respectively, compared with administration with soft water. There were no significant differences between the different water hardness groups concerning changes in the bone resorption marker urinary NTX/creatinine. The pivotal phase III study included 61 different sites and differences in water hardness between regions have likely added to the variability in risedronate exposure in the study. Although differences in water hardness by itself may not significantly influence efficacy of risedronate, a combination with other factors that also negatively affect risedronate bioavailability, e.g. a high-fat or high-calcium breakfast at no more than 30 minutes after the risedronate dose, might in an individual patient lead to clinically relevant decreases in exposure.

The effect of a high-fat breakfast given 30 minutes after administration of a 150 mg risedronate tablet was also evaluated in a separate cohort of subjects. The mean AUC of risedronate in this group was only 25% of that in another group of subjects that fasted for 4 hours after administration of 150 mg risedronate. This food effect is slightly larger than the effect observed for a 30 mg dose in a previous study, where the AUC with a meal 30 minutes after risedronate administration was 44% of the AUC when subjects were fasted for 4 hours after administration. In the 150 mg study, there were also indications of decreased pharmacodynamic effect in the fed group, based on the bone resorption marker urinary NTX/creatinine. However, in the 150 mg study the fed and fasted groups were dosed at different study sites, and the results were likely confounded by the higher water hardness at the site for the fed subjects (297.9 mg/L $CaCO_2$ equivalents, hard water) compared to the site for the fasting subjects (21.4 mg/L $CaCO_2$ equivalents, soft water). The effects of food and hard water therefore appear to be additive.
In the pivotal phase III study, the efficacy of the 75 mg 2CDM dosing has been evaluated using the “30 minutes before first food and drink of the day” instruction, so the overall variable food effect has been taken into account in the efficacy assessment.

## IV.3 Pharmacodynamics

In a single-dose, dose-ranging study with doses from 50 to 250 mg in healthy postmenopausal subjects, the area under effect curve (AUEC) for the bone resorption marker urinary

NTX/creatinine showed a statistically significant decrease as plasma AUC increased, with a decrease from approximately -19,6%*hr to approximately -49,7%*hr over the range of AUC values (mean values 56.5 to 1172 ng*hr/ml). Emax also showed a statistically significant decrease as AUC increased, with a decrease from approximately -50% to approximately -76% over the range of AUC values. Thus, the concentration-effect relationship does not appear to be very steep, as also indicated by the lack of significant effects of water hardness on the pharmacodynamic marker, despite a relatively large effect on plasma AUC of risedronate.

Urinary NTX/creatinine was also compared after the 75 mg 2CDM and the 5 mg daily regimen in healthy postmenopausal subjects treated for 4 months. The time course of effect differed between the two dosing regimens and appeared to approximately follow the risedronate plasma concentration-time course, with a more constant suppression during the once daily dosing and a higher initial suppression and lower suppression at the end of the month with the 75 mg 2CDM dosing. The 75 mg 2CDM group showed a greater reduction in median area under the effect curve (AUEC$\tau$) for NTX/creatinine compared to the 5 mg daily group over a 30-day dosing period but there was no significant difference in median E30 (i.e., the effect on Day 30) at Month 1 or Month 4.

## IV.4 Clinical efficacy

Study **2004012, HMR4003M/3001** is a multicenter phase III 2 year, double-blind active-controlled parallel group non-inferiority study to compare the 75 mg 2CDM regimen of risedronate to the 5 mg daily regimen in the treatment of postmenopausal osteoporosis. Data from the first 12 months of the study were submitted for this application and the 24-month data were submitted in the day 106 response to questions. Women included in the study were to be at least 50 years of age and to be postmenopausal for at least 5 years and have at least three evaluable lumbar spine vertebral bodies, L1 – L4, without fracture or degenerative disease. BMD was to be > 2.5 SD below the young adult female mean value *or* > 2.0 SD below the young adult female mean value with at least one prevalent vertebral body fracture (T4-L4). The daily regimen group received 5 mg risedronate tablets daily on each day of the month during the period. The 2CDM group received 75 mg risedronate tablets on 2 consecutive days each month, followed by matching placebo tablets all other days of the month. All study patients received 1000 mg elemental calcium daily and also 400 to 800 IU vitamin D per day. The study is adequately sized and designed; inclusion criteria are considered to be adequate. The inclusion criteria with regard to BMD and the high number of patients with previous fractures support the presumption that these women were at high risk of fracture.

The **primary objective** was to determine the efficacy of a 75 mg 2CDM regimen of risedronate compared to a 5 mg daily dosing regimen by demonstration of non-inferiority of the 2CDM regimen to the daily regimen assessed by percent change from baseline in lumbar spine BMD at month 12 in women with postmenopausal osteoporosis.
Baseline parameters were comparable between groups, with the exception that patients in the 2CDM group were statistically significantly older than patients in the daily dose group (65.1 versus 64.2 years). This difference is not considered to be of clinical importance. Withdrawal rates at both 1 and 2 years were approximately 23% overall, and evenly distributed between treatment arms.

Mean percent change from baseline to months 12 and 24 in lumbar spine BMD is shown in the following table:

| Analysis population Visit | 75 mg 2CDM | | 5 mg daily | | LS mean difference[a] (95% CI) |
|---|---|---|---|---|---|
| | N | LS mean | N | LS mean | 5 mg daily - 75 mg 2CDM |
| Primary efficacy[b] | | | | | |
| Baseline lumbar spine BMD (g/cm²) | 524 | 0.744 | 527 | 0.745 | |
| Percent change from baseline | | | | | |
| Month 12 | 524 | 3.386[c] | 527 | 3.600[c] | 0.214 (-0.189; 0.618) |
| Month 24 lumbar spine BMD | | | | | |
| Baseline lumbar spine BMD (g/cm²) | 479 | 0.745 | 474 | 0.745 | |
| Percent change from baseline | | | | | |
| Month 24 | 479 | 4.181[c] | 474 | 4.348[c] | 0.167 (-0.345; 0.679) |

BMD = bone mineral density; LS = least squares, N = Number of patients in the indicated population with values at baseline and the relevant visit.

[a] Adjusted means, mean differences, and confidence intervals are from an ANOVA model containing Treatment and Pooled Investigative Center.

[b] Due to additional lumbar spine BMD data available after Month 12, data at Month 6 and Month 12 in the Month 24 database are slightly different from that in the Month 12 database. The primary efficacy endpoint result based on the primary efficacy population (reported in the year 1 CSR) is considered as final and is presented for Month 12 in the table.

[c] Indicates a statistically significant difference from baseline determined from a 95% confidence interval unadjusted for multiple comparisons. 95% CI = 95% two-sided confidence interval.

The pre-defined non-inferiority margins of 1.5 % at year 1 and 2.0% at year 2 for the 2CDM regimen were reached and the 2CDM regimen was thus considered to be non-inferior to the daily regimen. This was shown for the PE at year 1 as well as for the PP and ITT populations at year 1 and year 2, indicating that the result was robust.
The change from baseline lumbar spine BMD at 12 and 24 months were also analysed using a 2-way ANOVA model with fixed effects for treatment, pooled investigative center and the treatment by pooled center interaction to assess the homogeneity of the treatment effects across centers. The treatment by pooled center interaction was not significant which indicated that the treatment effect was consistent across various geographic regions.
The numbers of patients with new vertebral fractures were similar between groups at all timepoints [at month 24 2CDM 16 patients (3.34 %) and daily 13 patients (2.79 %)]. At month 24 there were no clinically meaningful differences between the treatment groups for change from baseline in any of the five categorical health state measures or for health status measured by the VAS.

Efficacy endpoints did not significantly differ between the 75 mg 2CDM and the 5 mg daily treatment groups at 24 months.

## IV.5 Clinical safety

More than 15 000 patients have been involved in phase III clinical studies with risedronate. The combined total exposure for risedronate during the latest PSUR period from 1 April 2005 to 31 March 2006 was estimated to be 3.5 million patient-years.

91.1% of patients in the 2CDM treatment arm, compared to 89.9 %in the 5 mg daily treatment arm experienced TEAEs at 24 months. At 24 Months, overall the rate of serious TEAEs was 14.4 % (2CDM treatment arm) compared to 10.8 % but there was no difference in rate of withdrawal due to TEAE between treatment arms (75 mg 2CDM regimen, 12.8%; 5 mg daily regimen, 13.9%). Especially nervous system disorders and “Injury, poisoning and procedural complications” were more common in the 2CDM group.

Gastrointestinal TEAEs were slightly more common in the 2CDM group but the difference to the daily dose group was small. Seven patients in the 75 mg 2CDM group and 2 patients in the 5 mg daily group had endoscopically confirmed upper GI ulcers. A majority of these patients continued in the study. No laboratory findings specific for the 2CDM regimen was seen. At 24 months, nine deaths occurred in the Phase III study 2004012, three in the 2CDM group and six in the daily dosing group. None of the deaths were considered by the investigators to be possibly or probably related to the investigational product. No deaths were reported in the other studies 2004051, 2002086 or 2003080.
The majority of patients in the pivotal study as well as in the supportive studies were Caucasian which is common for PMO studies. TEAEs were summarised according to age, < 65 years, 65 to < 75 years and ≥ 75 years. Type of events and number of patients reporting TEAEs were not different between treatment group for any age category.

No special Risk Management plan was provided with this application. No additional significant risks or safety concerns that would call for a special risk management plan are found to be linked to this application. However, due to CMS concerns regarding potential risk for dosing errors with the new dosing regimen, the Applicant has committed to closely analyse global post-marketing reports of lack of efficacy/lack of effect as well as medication/dosing errors with risedronate 75 mg 2CDM compared with the 35 mg once a week and 5 mg daily regimens and to include these findings in the periodic safety update report.

Adynamic bone has been described in the literature after long time treatment with bisphosphonates and due to the potential negative long-term effect on bone. The Applicant has presented an adequate literature review on the subject of delayed fracture healing and/or increased fracture risk after longer-term treatment with bisphosphonates. No clinically significant such risk has been found. Very few bone biopsies were collected from patients in the 2004012 study and no firm conclusions can be drawn from these biopsies.

The theoretical risk of delayed fracture healing and/or increased fracture risk after longer-term treatment with bisphosphonates should be highlighted in coming PSURs.

## IV.6 Discussion on the clinical aspects

Risedronate is a well known medicinal product. The current application concerns a new dosing regimen, in addition to the previously approved once daily and once weekly regimens, namely 75 mg administered on two consecutive days each month (75 mg 2CDM) for a total dose of 150 mg per month. Clinical pharmacokinetic data demonstrate similar total exposure over one month with the 5 mg once daily and the 75 mg 2CDM regimens and may be considered supportive to the efficacy data.

In the pivotal phase III study 2004012, clinical efficacy, measured as mean % change in lumbar spine BMD from baseline to month 24, was demonstrated to be non-inferior to the 75 mg 2CDM regimen when compared to the 5 mg daily regimen, using pre-defined non-inferiority criteria.

Minor differences in the frequency of TEAEs between treatment groups persisted at month 24 but did not lead to different withdrawal rates due to TEAEs between treatment groups and are not considered to be important.
No serious safety issues have been identified that are considered to outweigh the benefit of having an additional dosing option for patients who might find it difficult to comply with more frequent dosing. The theoretical risk of delayed fracture healing and/or increased fracture risk after longer-term treatment with bisphosphonates should be highlighted in coming PSURs. In

addition, the Applicant has agreed to analyse post-marketing reports of lack of efficacy/lack of effect as well as medication/dosing errors with risedronate 75 mg 2CDM compared with the 35 mg once a week and 5 mg daily regimens in the PSURs.

In conclusion, the benefit risk of this new risedronate product is considered to be positive from a clinical point of view.

# V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

User testing of the package leaflet has been performed.
The risk/benefit ratio is considered positive and Norsed 75 mg tablet is recommended for approval.

List of follow-up measures:

| | |
|---|---|
| **Clinical** | The sponsor agrees to closely analyse global post-marketing reports of lack of efficacy/lack of effect as well as medication/dosing errors with risedronate 75 mg 2CDM compared with the 35 mg once a week and 5 mg daily regimens and to include these findings in the periodic safety update report (PSUR). |
| **Clinical** | The Applicant is already monitoring closely gastrointestinal events as listed above and events of osteonecrosis of the jaw as part of the routine pharmacovigilance and careful reviews and assessement through the 6-monthly corporate PSURs. Specific safety analysis pertaining to the 75 mg exposure will be conducted when spontaneous data will be available |
| **Clinical** | As is it already done as routine assessment of the PSUR, the applicant will continue to evaluate cumulative/new non-vertebral fractures and any indication of associated delayed or abnormal fracture healing. Specific safety analysis pertaining to the 75 mg exposure will be conducted when spontaneous data will be available |

# VI. APPROVAL

The Decentralised Procedure for Norsed 75 mg tablets was successfully finalised on Dec 5, 2007.

LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

# 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) |

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.mpa.se E-mail: registrator@mpa.se