

**Rapporteur's
Public Paediatric Assessment Report
for paediatric studies submitted in accordance
with Article 45 of Regulation (EC) No1901/2006, as amended**

**Risedronate Sodium
(Optinate / Actonel)**

UK/W/009/pdWS/001

Rapporteur:	UK
Date of the Final report (Day 120)	11.03.2010
Date of finalisation of PAR	14.09.2010

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	Actonel / Optinate
INN (or common name) of the active substance(s):	Risedronate sodium
MAHs:	See section VI
Currently approved Indication(s)	<p>Treatment of postmenopausal osteoporosis, to reduce the risk of vertebral fractures.</p> <p>Treatment of established postmenopausal osteoporosis, to reduce the risk of hip fractures.</p> <p>Prevention of osteoporosis in postmenopausal women with increased risk of osteoporosis.</p> <p>To maintain or increase bone mass in postmenopausal women undergoing long-term (more than 3 months), systemic corticosteroid treatment at doses ≥ 7.5 mg/day prednisone or equivalent.</p> <p>Treatment of Paget's disease of bone.</p>
Pharmaco-therapeutic group (ATC Code):	Drugs affecting bone metabolism Bisphosphonate
Pharmaceutical form(s) and strength(s):	Film-coated tablets 5mg,30mg,35mg and 75mg risedronate, Film-coated tablets 35 mg risedronate + 500g calcium, Film-coated tablets 35 mg risedronate + sachet 1000 mg calcium/880 IU vitamin D3, Film-coated tablets 35 mg risedronate + 500 mg calcium/400 IU vitamin D3

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I EXECUTIVE SUMMARY

The bisphosphonates, as potent inhibitors of bone resorption, are currently the class of drugs of first choice in the management of skeletal disorders with high bone turnover, whether localised or generalised. Risedronate sodium is a pyridinyl bisphosphonate that inhibits osteoclast-mediated bone resorption and modulates bone metabolism. This anti-resorptive activity leads to the consequent decrease in bone turnover, which constitute the rationale for the use of this drug in many disorders of bone metabolism.

Osteogenesis imperfecta (OI) is characterized by genetic alterations in type I collagen. This alteration is associated with an increase in bone turnover and an uncoupling between the processes of bone resorption and formation of new bone, responsible for the worsening features of the skeleton. Recently several bisphosphonates have been investigated for the treatment of patients with OI.

Risedronate sodium has been approved in several dose strengths (5, 30, 35, and 75 mg film-coated tablets) for the indications of postmenopausal osteoporosis (treatment and prevention), for steroid-induced osteoporosis in postmenopausal women and for Paget's disease.

No specific paediatric formulation is available as risedronate is not currently licensed in children.

The data package submitted by the MAHs under article 45 of the Paediatric Regulation comprised documents relevant to the paediatric use of risedronate, with special reference in OI. The MAH concluded that based on the available information including 2 clinical studies conducted in the paediatric population with OI, the use of risedronate in children (0 to 18 years) should not be recommended and therefore proposed changes to the SmPC for all risedronate containing products.

Based on the review of the presented paediatric data in the day 89 preliminary PdAR the rapporteur concluded that the data justified a variation application regarding the restriction of the use of risedronate sodium in the paediatric population. It was also recommended that all risedronate containing products' SmPCs/PILs across the EU should include a statement in section 5.1 for paediatric patients with OI, which would reflect the data from the Phase III 2003100 study. Furthermore the rapporteur suggested that the SmPC/PIL might be further revised in the light of any future findings from the on-going clinical study 2003100 in paediatric OI patients following the 2-years open-label phase of treatment with risedronate.

The response from the MAH was received in December 2009 and included the MAH's response to the comments raised in the Preliminary PdAR and an updated version of the SmPC/PIL for risedronate containing products. The rapporteur reviewed the MAH's proposals and concluded that the changes in the SmPC and PIL of risedronate sodium should comprehensively reflect the available paediatric information. An amended version of sections 4.2 and 5.1 of the SmPC/PIL was circulated to the CMSs as part of the draft final PdAR (Day 90 report). Comments were received for CMSs who fully endorsed the rapporteur's recommendations.

II RECOMMENDATION

Based on the review of the presented paediatric data the rapporteur considers that:

For all products containing Risedronate sodium across the EU, it is recommended that SmPCs and PILs contain the following statement:

4.2 Posology and method of administration

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

5.1 Pharmacodynamic properties

Paediatric population: The safety and effectiveness of risedronate sodium is being investigated in an on-going study of paediatric patients aged 4 to less than 16 years with osteogenesis imperfecta. After completion of its one-year randomized, double-blind, placebo controlled period, a statistically significant increase in lumbar spine BMD in the risedronate group versus placebo group was demonstrated; however an increased number of at least 1 new morphometric (identified by x-ray) vertebral fracture was found in the risedronate group compared to placebo. Overall, results do not support the use of risedronate sodium in paediatric patients with osteogenesis imperfecta.

III INTRODUCTION

On 6 May 2009, the MAHs submitted the following documents for Risedronate sodium, in accordance with Article 45 of the Regulation (EC) No 1901/2006, as amended on medicinal products for paediatric use:

- Cover letters from both MAHs confirming the alliance to develop risedronate sodium and the combined approach on submitting the paediatric data in accordance to the above mentioned procedure.
- The currently approved European Summary of Product Characteristics (SmPCs) for all dosage strengths of the licensed risedronate products, approved via mutual recognition or decentralised procedure.
- The MAH's response to article 45 paediatric work-sharing procedure with an overview of submitted clinical data, outlining the proposed changes to the SmPCs for all risedronate containing products.
- The findings from literature search of published bibliography conducted by one of the MAHs, which retrieved 64 references (abstracts provided).
- Reports of 2 clinical trials completed or on-going, sponsored by the MAH investigating the use of risedronate in children with osteogenesis imperfecta.
- A brief summary of post-marketing reports of paediatric exposure received by the MAHs.

Based on the information provided, the MAH is proposing the following changes to the SmPC for all risedronate containing products:

4.2 Posology and method of administration

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

5.1 Pharmacodynamic properties

Paediatric patients: The safety and effectiveness of risedronate sodium was assessed in a one-year, randomized, double-blind, placebo controlled study of 143 paediatric patients aged 4 to less than 16 years (94 received risedronate) with osteogenesis imperfecta.

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

IV SCIENTIFIC DISCUSSION

IV.1. Information on the pharmaceutical formulation used in the clinical studies

Risedronate is an orally administered third generation pyridinyl bisphosphonate currently licensed in Europe and the United States. It is suggested that it is approximately 100 times more potent than pamidronate in terms of inhibiting bone resorption. Risedronate sodium has been approved in several dose strengths (5, 30, 35, and 75 mg film-coated tablets). In addition, the 35 mg film-coated tablets are also approved under 3 combination packs with calcium and/or vitamin D₃. The original Marketing Authorisations for risedronic acid/ risedronate sodium in Europe were granted for 5 mg and 30 mg film-coated tablets on 7 October 1999 in Sweden, the Reference Member State (RMS), and in a first wave of Concerned Member States (CMSs) through a Mutual Recognition Procedure (MRP) in February 2000. Risedronate sodium in the different formulations has been approved for the indications noted in the table below:

Dosage	Indications
5 mg daily	Treatment of postmenopausal osteoporosis, to reduce the risk of vertebral fractures. Treatment of established postmenopausal osteoporosis, to reduce the risk of hip fractures. Prevention of osteoporosis in postmenopausal women with increased risk of osteoporosis. To maintain or increase bone mass in postmenopausal women undergoing long-term (more than 3 months), systemic corticosteroid treatment at doses \geq 7.5 mg/day prednisone or equivalent.
30 mg daily	Treatment of Paget's disease of bone.
35 mg once a week	Treatment of postmenopausal osteoporosis, to reduce the risk of vertebral fractures. Treatment of established postmenopausal osteoporosis, to reduce the risk of hip fractures. Treatment of osteoporosis in men at high risk of fractures.
35 mg once a week + 500 mg calcium tablets	Treatment of postmenopausal osteoporosis to reduce the risk of vertebral fractures. Treatment of established postmenopausal osteoporosis to reduce the risk of hip fractures.
35 mg once a week + 1000 mg calcium/880 IU vitamin D ₃ (gramules)	Treatment of postmenopausal osteoporosis to reduce the risk of vertebral fractures. Treatment of established postmenopausal osteoporosis to reduce the risk of hip fractures. This combination product is only intended for use in assessed patients for whom the amount of calcium and vitamin D ₃ included is considered to provide adequate supplementation.
35 mg once a week + 500 mg calcium/400 IU vitamin D ₃ (tablets)	Treatment of postmenopausal osteoporosis to reduce the risk of vertebral fractures. Treatment of established postmenopausal osteoporosis to reduce the risk of hip fractures. This combination product is only intended for use in assessed patients for whom the amount of calcium and vitamin D ₃ included is considered to provide adequate supplementation.
75 mg taken orally on 2 consecutive days each month	Treatment of osteoporosis in postmenopausal women at increased risk of fractures.

IV.2. Non-clinical aspects

1. Introduction

Non-clinical studies in juvenile animals have not been conducted by the MAH on risedronate. A review of literature based on Medline database was done by the MAH using documented search criteria and limitations. No relevant nonclinical data were found in the literature.

Assessor's Comment

No information relevant to paediatric use of risedronate is available at the currently approved SmPC in section 5.3. From conducted toxicology studies, liver, testicular, respiratory toxicity is noted in high doses. In reproduction toxicity studies at exposures close to clinical exposure ossification changes were seen in sternum and/or skull of foetuses from treated rats and hypocalcemia and mortality in pregnant females allowed to deliver. However the clinical significance of these findings for the paediatric population could not be assessed due to lack of non-clinical studies in age appropriate animals.

2. Discussion of non clinical aspects

The main biological action of bisphosphonates consists of the inhibition of osteoclastic bone resorption, without any significant inhibition of bone mineralization. This effect is not expected to be different in paediatric population. There is now evidence suggesting an increased bone turnover in both adults and children with OI, providing a pharmacodynamic rationale for the use of bisphosphonates in this disease. From review of the recently published literature, various concerns have been raised regarding possible effects on the human embryo and foetus. Animal studies have revealed unfavourable effects of bisphosphonate treatment on the foetus, mainly in the skeleton. Since bisphosphonates are retained for a long time in the human skeleton, concerns have been raised that even pre-pregnancy administration of bisphosphonates may result in embryofetal exposure and alter fetal bone modelling (Djokanovic et al 2008). From the information submitted for this work-sharing procedure, the effect of risedronate especially after long-term treatment in the developing skeleton does not appear to have been investigated by the MAH.

IV.3. Clinical aspects

1. Introduction

The MAH has provided a very useful overview of the paediatric use of risedronate. This includes a detail review of the published literature as well as detailed information of the 2 large clinical studies conducted by the MAH in paediatric OI patients. Additionally a broad-based search strategy has been utilised to identify cases of paediatric exposure in the global post-marketing safety database from the start of marketing up until 31-Mar-2009 and the findings are included as an overview of the drug's safety profile. The evidence from published papers and the conducted clinical studies summarized in this overview is identified as information for the efficacy and safety of risedronate mainly in the treatment of paediatric OI patients but also in other paediatric conditions associated with osteoporosis (i.e. the effects of risedronate treatment in children with cerebral palsy).

2. Literature review of published information

A comprehensive literature search was performed to identify published articles and abstracts from 1987 to 14 April 2009 that are relevant to risedronate in a paediatric population. The MAH has provided the details of the conducted literature search in relevant databases with detail information of the search criteria and limitations. The bibliography and abstracts of the 64 articles that met the search criteria were provided as Annexes. The MAH has further reviewed the results and from the 64 possibly relevant articles, 7 were identified as significantly relevant to the use of risedronate in a paediatric population. Of these 7 articles, 6 reported use of risedronate in patients with OI, and 1 reported use of risedronate in patients with cerebral palsy and secondary osteoporosis. It was also noted as initially included in the submitted line-listings that the MAH has sponsored 2 investigator-initiated grant studies investigating the use of risedronate in children, and results from these studies have been included in the retrieved published articles:

- Dr. James E. Heubi and colleagues: assessing the efficacy of risedronate in the treatment of cerebral palsy associated osteoporosis in non-ambulatory children and adults (Cohran 2006);
- Dr. Glorieux F. and colleagues: assessing the safety and efficacy of risedronate in children with mild OI (Cheung 2007). This study has also recently been published electronically by Rauch et al (2009).

The 7 identified articles with a paediatric interest are listed below and were summarized by the applicant:

1. **Risedronate in the treatment of mild paediatric osteogenesis imperfecta: A randomized placebo controlled study** (scientific meeting abstract). Cheung, M, S, et al. Bone Jun 2007; 40 (6):S33-S34.
2. **Risedronate in the Treatment of Mild Pediatric Osteogenesis Imperfecta: A Randomized Placebo - Controlled Study**. Rauch F et al. J Bone Miner Res 2009Jul ;24(7):1282-9.
3. **Safety and efficacy of the use risedronate in children and adults with osteogenesis imperfecta type I** (scientific meeting abstract).Galesanu C et al. Bone Jun 2007a; 40 (6):S184-S185.
4. **Effects of risedronate on bone change at children with osteogenesis imperfecta** (scientific meeting abstract). Galesanu C et al. Journal of Bone and Mineral Research Sep 2007b; 22 (Supp.[1]):S362-S362.
5. **Secondary osteoporosis in long-term bedridden patients with cerebral palsy**. Iwasaki T et al. Pediatrics international Jun 2008; 50 (3):269-275.
6. **Risedronate pharmacokinetics in children with osteogenesis imperfecta**. Thompson GA. Bone Jun 2005; 36 (Supp. [1]):S82-S82 and (Supp. [2]):S223-S224
7. **Oral bisphosphonates improve bone mass in non-ambulatory children and adults with severe bone disease**. Cohran V et al Journal of pediatric gastroenterology and nutrition Oct 2006;43(4): 66

From the identified articles, 2 of them (Cheung 2007 and Rauch 2009) were for the same investigator-initiated grant study discussed above (Dr. Glorieux). This was a single centre, randomised, double-blind, placebo-controlled study in 26 children and adolescents (aged 6.1 to 17.7 years) with mild OI type I. Thirteen patients received risedronate (either 15 mg once a week in patients weighing < 40 kg or 30 mg once a week in patients weighing > 40 kg), and 13 patients received placebo for 2 years. After 2 years of treatment, risedronate significantly increased lumbar spine bone mineral content (BMC) (45% versus 19%, $p=0.02$) and lumbar spine areal bone mineral density (BMD) Z-scores (0.65 versus 0.15, $p=0.002$) compared to placebo. Risedronate treatment also significantly decreased serum levels of the bone resorption marker type I collagen N-telopeptide compared to placebo (35% versus 6%, $p=0.003$). Risedronate was generally well-tolerated, and the incidence of clinical and laboratory adverse events (AEs) was similar in the 2 treatment groups.

Two scientific meeting abstracts have been published by Galesanu and colleagues presenting results from 2 clinical studies in patients with OI. In the first study (Galesanu 2007a), members of 2 families (sisters, mothers, and daughters) with OI type I were treated with risedronate (35 mg once a week in 7 patients \geq 16 years old and 35 mg every 2 weeks in the 2 patients <16 years old) for 1 year. After 1 year of treatment, risedronate significantly increased lumbar spine BMD by 3.8% in the 5 adult women (\geq 21 years old) and 6.3% in the 4 girls (5, 7, 16, and 17 years of age). One woman and 1 girl each experienced a fracture during the study. There were no gastrointestinal adverse effects reported. Risedronate therapy was found to be safe and effective in children and adults with OI.

In the other study (Galesanu 2007b), 8 children (6 girls and 2 boys) with OI were treated with risedronate (35 mg once a week in patients weighing >30 kg and 35 mg every 2 weeks in patients weighing <30 kg) for 1 year. After 1 year of risedronate treatment, the mean percent increase in lumbar spine BMD was 15%. There were no new fractures and no gastrointestinal adverse effects reported. Risedronate therapy was found to be safe and effective in children with OI.

One article has reported a randomised clinical study with risedronate treatment in 20 Japanese children between 1 and 16 years of age with cerebral palsy and secondary osteoporosis (Iwasaki 2008). Patients received either vitamin D (alfacalcidol) alone or in combination with risedronate for 6 months. Treatment with vitamin D was effective for secondary osteoporosis. Treatment with risedronate and vitamin D was even more effective in improving BMD than vitamin D alone.

Additional 2 meeting abstracts have presenting results from the risedronate pharmacokinetic (PK) Study 2002020 in children (Thompson 2005a, Thompson 2005b) and the findings and results of this study will be summarized in Section 3 “Clinical studies” of this report.

The other investigator-initiated grant study performed by Dr. Heubi and colleagues was not indexed in the external databases but was previously identified; results from this study are also summarized by Cohran et

al (2006). A single centre, double-blind, randomised controlled study was performed in 24 non-ambulatory children and adults (ages 10-39 years) with cerebral palsy (CP) associated osteoporosis. Patients were randomised to receive either risedronate (5 mg daily for patients weighing >30 kg or 5 mg every other day for patients weighing <30 kg) or placebo for 2 years. After 2 years of treatment, risedronate significantly increased lumbar spine BMD compared to placebo (0.62 gm/cm³ versus 0.57 gm/cm³; p=0.03). There were minimal side effects reported with risedronate treatment.

Assessor's Comment

The MAH has provided the extended results of a literature research regarding the use of risedronate in the paediatric population. From the total number of articles retrieved the MAH has chosen to summarize 7 publications, mainly reviewing the use of risedronate in children with OI. In addition to the above mentioned studies, there were 4 recent review articles identified which investigated the published literature for the effects of bisphosphonates in children with OI (Castillo et al 2009, Gordon et al 2004, Phillipi et al (Cochrane) 2008 and Somalo & Santos 2007). From those reviews it becomes evident that despite the large body of published literature, there is very little robust evidence to guide the treatment of these patients with any bisphosphonate including risedronate. It is clear that treatment improves bone mineral density (BMD) in these children but it is still not proven that this has a direct positive effect on rate of fractures or the clinical status (pain, growth and functional mobility). From the above mentioned studies, in the most recent published paper by Rauch et al (2009) the author concludes that "results suggest that the skeletal effects of oral risedronate are weaker than those that are commonly observed with intravenous pamidronate treatment". It is also noted that in most of the mentioned OI studies different dosing regimes have been used, including daily doses according to weight, once weekly or even once every 2 weeks according to a cut-off weight. From these inconsistencies it becomes evident that the optimal dose of risedronate has not been established.

The use of bisphosphonates including risedronate has also been investigated in other paediatric conditions associated with deficits in bone mineral density, such as corticosteroid-induced osteoporosis, cystic fibrosis osteopenia, osteoporosis in chronic renal disease and secondary osteoporosis due to immobilization in CP patients. In the paper for Iwasaki et al (2008) quoted by the MAH, the monotherapy with vitamin was proven to be equally effective to risedronate for the treatment of secondary osteoporosis, although the duration of the treatment was limited to 6 months in both arms. In the assessor's opinion, the identified papers are very limited studies that partly confirm findings of improvement of BMD from the risedronate treatment but the clinical significance of these findings has not been established.

3. Clinical studies

Study Number: 2002020. An Open Label, Randomized, Multi-centre, Parallel Group Study to Investigate the Safety, Tolerability and Pharmacokinetics of Risedronate Administered as a Single Oral Dose of 2.5 mg or 5 mg in Children ≤ 30 kg and 5 mg or 10 mg in Children > 30 kg with Osteogenesis Imperfecta

➤ Methods

- **Objective**

The objective of this study was to examine the safety, tolerability, and pharmacokinetics of risedronate administered as a single oral dose of 2.5 mg or 5 mg in children weighing ≤ 30 kg and 5 mg or 10 mg in children weighing > 30 kg with OI.

- **Study design**

Open label, single oral dose, randomized, multi-centre (4 UK centres included), parallel group study in children aged 4-16 years, diagnosed with OI.

- Study population /Sample size

A total of 28 OI patients who had a history of at least one radiographically-confirmed non-traumatic or low impact fracture, were randomized into the study in order to ensure the completion of 24 patients. This sample size was not chosen based on any statistical power considerations but is a typical sample size for an investigative pharmacokinetic study. At a later stage, through an amendment to the protocol, patients who had one or more bone fractures or orthopaedic surgery within 6 weeks of dosing were excluded. There were 15 females and 13 males enrolled in this study. Children were not eligible to participate if they were not in general good health as evidenced by their history and physical examination or weighed less than 10 kg. Patients that have been treated with bisphosphonates in the last 6 months, calcitonin or calcitriol in the last 3 months, anabolic steroids/androgens, systemic glucocorticoids or fluoride were excluded for the trial. All 28 patients that were enrolled completed this study.

- Treatments

Patients were randomized to receive a single oral dose of risedronate 2.5 mg, 5 mg, or 10mg (two 5 mg tablets) based on weight at the time of admission into the study. Patients were stratified into 2 strata by weight and then randomized into treatment groups as follows:

- patients weighing 10-30 kg were randomized to receive 2.5 mg or 5 mg of risedronate
- patients weighing > 30 kg were randomized to receive 5 mg or 10 mg risedronate

The usual administration protocol for oral bisphosphonates was applied in these patients and included a single dose of risedronate orally administered with at least 120 mL of plain water, following an overnight fast of at least 8 hours, at least 2 hours before the first food or drink (except plain water) of the day. Patients were instructed to remain in an upright position for at least 30 minutes after taking the drug and were encouraged to drink up to an additional 120 mL of water, if possible, following treatment administration. For those patients who could not swallow tablets or had history of oesophageal disorders, risedronate was administered as a solution in which 1 or 2 tablets (depending on dose) were added and dispersed in 10 mL of water. Additional water was given to the patient to ensure a minimum of 120 mL.

- Outcomes/endpoints

Pharmacokinetic assessment

Serum and urine samples were analyzed for risedronate sodium (NE-58095) using a validated, Enzyme-Linked Immunosorbent Assay (ELISA). Blood samples were obtained pre-dose and at 0.5, 1, 2, 4, 8, 12, and 24 hours post-dose and urine samples for risedronate analysis were obtained over the following collection intervals: pre-dose and 0-1, 1-4, 4-12, and 12-24 hours post-dose. Patients were discharged from the study centres 24 hours after dosing. Additional timed urine collections (over 4 to 12 hours) were obtained on Days 4 and 6 post-dose and then twice a week for the next 3 weeks with a minimum of 2 days between each collection. It is noted that it was due to a protocol amendment dated Nov 2002, that the timed urine collections were extended from 4–6 hour collections to 4–12 hour collections, and the minimum time required between each timed urine collection was reduced from a minimum of 3 days to a minimum of 2 days between collections.

Safety and Tolerability assessment

Adverse events (AEs) were recorded for each patient throughout the study, from the time written informed consent was obtained through the end of sample collection. Blood pressure, pulse rate, respiratory rate, and oral temperature were obtained during the study.

- Statistical Methods

Baseline characteristics were summarized with descriptive statistics to provide a description of the study population and to check the comparability of treatment groups. Descriptive statistics including mean, standard deviation, coefficient of variation, minimum, maximum and number of relevant observations were provided for each parameter by treatment group and sampling time. To

assess the impact of baseline covariates such as age, weight, gender, and creatinine clearance on PK parameters, a multiple linear regression analysis was conducted for each PK parameter. In each linear regression model, the PK parameter was used as the dependent variable and treatment, gender, age, weight, and creatinine clearance were treated as covariates. An intercept was also fitted in these models. Each of the covariates was tested for significance at a < 0.05 level.

➤ Results

• Risedronate Pharmacokinetics

Risedronate PK following a single oral dose in children with OI demonstrated that the median peak concentrations occurred (t_{max}) between 0.3 and 0.7 hours across all dose groups, maximum serum risedronate concentration (C_{max}) increased as the risedronate dose increased (ranging from 0.25 to 3.68 ng/mL), and risedronate area under the serum concentration-time profile (AUC) ranged from 3.49 to 19.18 ng*h/mL across the 4 treatment groups. The PK results in children exhibited high intersubject variability, which has also been observed in previous risedronate PK studies with adults evaluating oral risedronate 5 mg. Median t_{max} in children and adults was similar, occurring within less than 1 hour. In addition, C_{max}, AUC, and t_{1/2,z} for children are within the ranges previously observed for adults given risedronate 5 mg as summarized in the table below:

PK parameter	Children with OI				Adults Normal and with PMO
	2.5 mg Ris 10-30 kg body weight	5 mg Ris 10-30 kg body weight	5 mg Ris >30 kg body weight	10 mg Ris >30 kg body weight	5 mg Ris
C _{max} (ng/mL)	0.25-1.66	0.91-1.96	1.32-1.56	1.26-3.68	0.32-4.13
AUC (ng*h/mL)	3.49-9.37	4.16-7.74	12.54-14.48	10.27-19.18	1.11-20.44
t _{1/2,z} (hr)	78-745	123-579	100-406	238-661	36-955
Ris=Risedronate PMO=postmenopausal osteoporosis *Data presented as ranges.					

As expected, dose related parameters (cumulative amount of risedronate recovered from 0 to 12 or 24 hours, area under the risedronate serum concentration-time curve and risedronate maximum serum concentration) increased with dose. Also as expected, there was no evidence of dose dependence on the amount of risedronate recovered in urine, once dose normalized. The only pharmacokinetic parameters significantly influenced by creatinine clearance were the cumulative amount recovered in urine and volume of distribution. Body weight significantly influenced the cumulative amount of drug recovered in urine and time of occurrence of maximum serum concentration.

• Safety results

A total of 27 AEs were reported by 13 of the 28 enrolled patients (46.4%). No one withdrew from the study and only one serious AE (Crohn's Disease in one patient in the 10 mg group and assessed as doubtfully drug-related) was reported. All AEs were mild or moderate in severity and 7 (25.9%) of the AEs were thought by the Investigator to be related to study drug. The most commonly reported AEs were nausea and diarrhoea, each was reported by 3 patients. Two patients (2.5 mg group) reported upper GI AEs (both upper abdominal pain). Both events were mild and both patients recovered and completed the study. Four AEs (3 fractures and 1 Crohn's disease) were ongoing at study completion. No trend was observed for AEs across treatment groups, although the 10 mg group had the greatest proportion of patients with AEs.

Most out-of-range laboratory values noted during this study were at baseline or considered not clinically significant by the Investigator (Appendix 3.7, Tables 4 and 5). Six patients had an

abnormal laboratory value that the Investigator believed was clinically significant. Of these 6 patients, 3 patients had elevated glucose levels, 1 patient had elevated triglycerides and eosinophils, 1 patient had elevated serum sodium and chloride, and platelet values, and 1 patient had decreased haemoglobin including mean corpuscular volume and mean corpuscular haemoglobin. These laboratory values were isolated single values without any clinical signs. Fourteen patients had lower than expected estimated creatinine clearance values but had normal serum creatinine levels reported. No clinically significant change in vital signs compared to baseline was observed.

Assessor's Comment

In the assessor's opinion the main finding of this study is that the PK parameters in the tested paediatric population appear to be extremely and unpredictably variable, although the MAH concludes that the mean values are comparable to those of adults. The initial selection of the doses under investigation is not adequately justified. As the results of this study were used to provide the dosing regime for the safety and efficacy 2003100 study, a proper dose finding design should have been utilized as part of the whole paediatric development plan. As mentioned earlier in this report, the literature is also inconclusive for the most appropriate dosing regime for the paediatric population. However the assessor agrees that based on the findings of the PK study, the used dosing in phase III study of 2.5 mg/day for children with body weight 10-30 kg and 5mg/day for children with body weight >30 kg appears to be appropriate to ensure safety; nevertheless it is unclear if it is the optimal dose for efficacy demonstration in long-term use in OI paediatric patients.

Study Number: 2003100. A randomized, double-blind, placebo-controlled, multicenter, parallel group study of one-year duration followed by 2 years of open-label treatment to determine the safety and efficacy of orally administered 2.5 mg or 5 mg daily risedronate in children >4 to <16 years old with osteogenesis imperfecta.

Assessor's Comment

This phase III safety and efficacy study is still on-going (the first year is completed and the 2-year open label period is currently on-going). The final study report will be submitted to the competent authorities in accordance with the Article 46 of Regulation 1901/2006 within 6 months of its completion (ie, September 2010). However, the year 1, double-blind study report has been provided by the MAH and discussed in this report as it provides relevant clinical information regarding the requested amendments of the SmPC for the use of risedronate in paediatric OI patients.

➤ **Methods**

- **Objective**

The primary objective of this study was to determine the efficacy of risedronate compared to placebo in children ≥ 4 to < 16 years of age with osteogenesis imperfecta (OI) as assessed by percent change from baseline in lumbar spine bone mineral density (BMD) after 12 months of treatment.

- **Study design**

This is a 1-year, randomized, double-blind, placebo-controlled, multicenter, parallel group study with 2 additional years of open-label treatment. At the end of 1 year of treatment, without the unblinding of individual patients, all patients will take open-label risedronate for the 2 additional years.

- Study population

One-hundred and forty-seven (147) children ≥ 4 to < 16 years of age with OI were enrolled at 20 study centres in North America, Australia, Europe, South America, and South Africa. For inclusion in this study, a child must have met the following:

- diagnosed with OI as based on a modified Sillence classification scale,
- had an increased risk of fractures, defined by a history of at least 1 radiographically confirmed, non-traumatic or low impact fracture, plus low BMD [Z-score ≤ -1 at either total body or lumbar spine sites] or very low BMD [Z-score ≤ -2.0 at either total body or lumbar spine sites] with or without a history of fractures
- had at least 2 evaluable lumbar spine vertebral bodies (L1-L4, namely without fracture or degenerative disease).

Patients weighing less than 10 kg were not enrolled into the study. A placebo control group was utilized in this study in order to assess the efficacy and safety of risedronate in the treatment of children with OI since there is no approved active-comparator therapy. Due to ethical considerations, a 2:1 randomization of risedronate/placebo was used so that fewer patients would receive placebo.

- Determination of sample size

A total of 123 patients were to be randomized to the risedronate and placebo groups in a 2:1 ratio. This sample size allowed detection of a difference of at least 5% in lumbar spine BMD percent change from baseline at 12 months between the risedronate and placebo groups with 90% power. The calculation was based on the assumptions that the common within-group standard deviation (SD) would be approximately 7% and the dropout rate within Year 1 would be 20%. A difference of 5% in lumbar spine BMD percent change from baseline was considered a clinically meaningful difference. Historical data based on placebo-controlled studies on adults have suggested the within-group SD for lumbar spine BMD percent change at Month 12 is approximately 1.04-1.12 times the observed mean. The 7% SD assumed in this study was below 1.2 times the observed mean we assumed in the risedronate group (6%).

- Treatments

Patients were stratified by age (age at the time of informed consent) within each country into 2 age groups:

- 4 through 9 (≥ 4 to < 10) years, and
- 10 through 15 (≥ 10 to < 16) years

Patients were then randomized (2:1, active versus placebo) to receive either risedronate (2.5 mg or 5 mg tablet) daily or matched placebo daily for the first year. Even though patients were randomized in this study by age group within each country, patients were dosed according to their baseline weight. Patients weighing 10-30 kg received risedronate 2.5 mg or placebo daily and patients weighing more than 30 kg received risedronate 5 mg or placebo daily. The selection of the used doses for this study was based on the previous completed PK study and the experience from adult dosing regimes. Independent of how the dose was administered all patients were to take the study drug at least 30 minutes before the first food and drink (except plain water) of the day and remain in an upright position for 30 minutes after dosing.

All patients were required to take a daily supplement of calcium and vitamin D; patients were encouraged to remain on their present formulation of calcium and vitamin D, as long as the dose fell within a range of 500-1000 mg of calcium and 200-600 IU of vitamin D. Since calcium can interfere with the absorption of risedronate, calcium and vitamin D were to be administered at a different time of the day than the study drug.

- Outcomes/endpoints

The primary objective of this study was to determine the efficacy of risedronate compared to placebo in children ≥ 4 to < 16 years with OI as assessed by percent change from baseline in lumbar spine BMD at Month 12.

The secondary objectives of the year 1, placebo-controlled period of study were:

a) to evaluate the efficacy of risedronate compared to placebo in children ≥ 4 to < 16 years with OI as assessed by:

- percent change from baseline in lumbar spine BMD at Month 6
- percent change from baseline in total body BMD
- percent change from baseline in total body and lumbar spine BMC
- change and percent change from baseline in total body and lumbar spine BMD Z-score
- percent change from baseline in lumbar spine and total body bone area
- incidence and rate of new vertebral fractures (Genant 1993)
- incidence and rate of clinical vertebral and non-vertebral fractures
- percent change from baseline in bone turnover markers (BTMs) (serum bone-specific alkaline phosphatase [BAP] and urine type-I collagen N-telopeptide [NTX])
- improvement from baseline in musculoskeletal pain relief as determined by FACES (Wong 2001) pain rating scale
- improvement from baseline in quality of life (QOL) as determined by PedsQL (Varni 2001, Varni 1999) Pediatric QOL questionnaire.

b) to evaluate the safety and tolerability of risedronate treatment in children ≥ 4 to < 16 years with OI as assessed by:

- adverse events
- laboratory profiles including bone biopsy
- change from baseline in bone age
- annualized growth velocity from baseline.

At the end of 1 year of treatment, without the unblinding of individual patients, all patients received open-label risedronate for 2 additional years. During the 2-year, open-label period of the study (which is ongoing), the secondary objectives are to evaluate risedronate treatment as assessed by:

- percent change from baseline in lumbar spine BMD
- percent change from baseline in total body BMD
- percent change from baseline in total body and lumbar spine BMC
- change and percent change from baseline in total body and lumbar spine BMD Z-score
- percent change from baseline in lumbar spine and total body bone area
- incidence and rate of new vertebral fractures
- incidence and rate of clinical vertebral and non-vertebral fractures
- percent change from baseline in BTMs
- adverse events
- laboratory profiles
- change from baseline in bone age
- annualized growth velocity from baseline.

- Statistical Methods

The primary efficacy analysis compared the percent change in lumbar spine BMD of the risedronate group versus the placebo group based on the endpoint analysis using the ITT population. The ITT population for the endpoint analysis includes all patients who were randomized, took at least one dose of study drug, and had post-baseline lumbar spine BMD percent change data during the first year.

The primary statistical analysis was conducted using an analysis of covariance (ANCOVA) model with the corresponding baseline values as a covariate and treatment, age group, and pooled-country as fixed effects. If the p-value for the comparison between the 2 groups was less than 0.05, the 2 treatment groups were to be declared statistically significantly different. To quantify the treatment difference, a two-sided 95% confidence interval (CI) for the mean difference in

lumbar spine BMD percent change was constructed using the error term from the ANCOVA model. In addition, a two-sided 95% CI for the within-group mean lumbar spine BMD percent change was constructed for each treatment group. Statistically significant differences from baseline were declared if 0 was not included in the interval.

The primary analysis was also repeated for the per-protocol population as supportive analyses to check the robustness of the results from the ITT analysis.

All secondary efficacy analyses were based on the ITT population. In order to control the type-I error rate at 0.05 level on the secondary efficacy endpoints, a closed testing procedure was used to evaluate a list of pre-specified secondary endpoints.

➤ Results

• Analysis of efficacy

Regarding the primary efficacy endpoint of the study, the risedronate group had a statistically significant mean percent increase in lumbar spine BMD compared to placebo ($p < 0.0001$). The mean percent change from baseline in lumbar spine BMD was 7.594% for the placebo group and 16.289% for the risedronate group at 12 months. Both groups had a statistically significant mean percent increase from baseline in lumbar spine BMD at all time points (Months 6, 12, and Endpoint). The risedronate group had a statistically significant mean percent increase in lumbar spine BMD compared to placebo at all time points. The results from this secondary analysis were consistent with the primary efficacy analyses.

The risedronate group had a statistically significant mean percent increase from baseline in lumbar spine Z-scores at all time points. The risedronate group had a statistically significant mean percent increase compared to placebo at all time points.

The placebo group had a mean percent decrease from baseline in total body Z-score at all time points; the risedronate group had a mean percent increase from baseline in total body Z-score at all time points, although these changes were not statistically significant for either group at any time point. The risedronate group had a statistically significant mean percent increase compared to placebo at Month 12 and Endpoint.

A total of 37 patients experienced at least 1 new vertebral fracture at Endpoint (based on x-ray measurements - a patient is considered to have a morphometric vertebral fracture if any post-baseline vertebral x-ray indicates the patient had a fracture, with or without clinical symptomatology). The incidence of new morphometric vertebral fractures at Endpoint is summarized in the table below. A numerically higher percentage of patients in the risedronate group had at least 1 new vertebral fracture compared to the placebo group, but it was not statistically significant. The data by OI type (Type I or Type III and IV) are consistent with these overall results.

**Patients with New Morphometric Vertebral Fractures at Endpoint
(Intent-to-treat)**

	Placebo (N=49)	Risedronate (N=94)	p-value
n	48	91	
At Least One New Fractured Vertebra	8 (16.7%)	29 (31.9%)	0.0693 ^a
No New Fractured Vertebra	40 (83.3%)	62 (68.1%)	
No New Fractured Vertebrae	40 (83.3%)	62 (68.1%)	0.3764 ^b
1 Fractured Vertebra	3 (6.3%)	18 (19.8%)	
2 Fractured Vertebrae	2 (4.2%)	8 (8.8%)	
≥3 Fractured Vertebrae	3 (6.3%)	3 (3.3%)	

N=number of intent-to-treat patients within specified treatment.

n=number of patients with at least one vertebra evaluated at baseline and post-baseline.

Patients new fracture status determined by semi-quantitative score.

^aP-value corresponds to Fisher's Exact Test.

^bP-value corresponds to Savage Exact test.

Corresponding data can be found in Appendix 13.2.6 Listing 9.

/RISEDRONATE/phseiiiib/2003100_poise/ANAL/xrxf1.sas; SAS 8.2 19JUN08 16:46 f23may08 TZ6411.

/RISEDRONATE/phseiiiib/2003100_poise/ANAL/newfrc3.sas; SAS 8.2 19JUN08 16:59 f23may08 TZ6411.

A total of 20 new morphometric vertebral fractures were experienced by 8 placebo-treated patients (average of 2.5 vertebral fractures/placebo patient who had a new vertebral fracture). On the other hand, there were a total of 45 new morphometric vertebral fractures experienced by 29 risedronate-treated patients (average of 1.6 vertebral fractures fractures/risedronate patient who had a new vertebral fracture). The rate of new morphometric vertebral fractures was analyzed using a generalized linear model with a negative binomial distribution link. There was no significant difference between treatment groups in the rate of new morphometric vertebral fractures for risedronate patients as compared to patients in the placebo group. The estimated risedronate to placebo odds ratio was 1.39 (95% CI [0.60, 3.23]) at Endpoint ($p=0.45$). Clinical vertebral and non-vertebral fractures are fractures reported as treatment-emergent adverse events (TEAEs) and include all non-vertebral fractures and symptomatic, radiographically-confirmed vertebral fractures that occurred after randomization. No patients reported a clinical vertebral fracture.

A majority of patients in the placebo group reported no change in their pain score based on the Wong-Baker FACES pain rating scale; a higher percentage of patients in the risedronate group compared to placebo reported an “improvement” at all time points (eg, 22.9%, placebo; 32.6%, risedronate at Month 12); however, there was no statistically significant differences between the 2 groups at any time point.

The change from baseline in overall quality of life was assessed by the PedsQL Pediatric QOL questionnaire at Month 12. The risedronate group had a statistically significant increase from baseline in the Emotional Function Domain Score, School Function Domain Score, Psychological Health Summary Score, and Total Scale Score; the placebo group had no statistically significant changes from baseline. There were no statistically significant differences between the 2 groups for any of the domain scores, including the mean change from baseline in Total Scale Score (100 point score).

There were statistically significant increases in percent change from baseline in height in both treatment groups; the risedronate group had a numerically higher percent change from baseline in height compared to the placebo group (Table 45). When patients who sustained at least one new vertebral fracture during the study were evaluated separately, both treatment groups continued to have a statistically significant increase from baseline in height and although more patients in the risedronate group had vertebral fractures during the study, the risedronate group continued to have a numerically higher percent increase in height compared to placebo.

There were no statistically significant differences between the groups for change from baseline in bone age and annualized growth velocity.

- Analysis of safety

No patients in the placebo group and 7 (7.4%) patients in the risedronate group discontinued on or prior to Month 12.

4 patients voluntarily withdrew, 1 was lost in follow up, 1 had a protocol violation and 1 discontinued due to an AE (Crohn’s disease).

The percent of patients with treatment-emergent adverse events (TEAEs), TEAEs leading to withdrawal, serious TEAEs, upper GI TEAEs, moderate-to-severe upper GI TEAEs, and selected musculoskeletal TEAEs were similar for the 2 groups. Over 90% of patients in each group experienced a TEAE within the first 12 months of this study and 1 patient (risedronate group) was withdrawn from the study due to a TEAE (Crohn’s disease).

The groups were generally comparable overall in the percent of most frequently reported TEAEs. The most frequently reported TEAEs ($\geq 10\%$) by preferred term (PT) were:

- placebo group: gastroenteritis, fall, femur fracture, pain in extremity, back pain, arthralgia, abdominal pain, nausea, and pain
- risedronate group: fall, pain in extremity, back pain, vomiting, abdominal pain upper, pain, and headache.

The serious TEAEs by MedDRA system organ class (SOC) and PT are summarized in the table below

**Serious Treatment-emergent Adverse Events by MedDRA SOC and PT
(Intent-to-treat)**

System Organ Class Preferred Term	Placebo (N=49) n (%) nAE	Risedronate (N=94) n (%) nAE	p-value
OVERALL	8 (16.3%) 15	11 (11.7%) 18	0.4468
Injury, poisoning and procedural complications	8 (16.3%) 15	8 (8.5%) 14	0.1723
Femur fracture	6 (12.2%) 7	4 (4.3%) 7	0.0915
Forearm fracture	0 (0.0%) 0	2 (2.1%) 2	0.5463
Tibia fracture	1 (2.0%) 1	2 (2.1%) 2	1.0000
Fibula fracture	0 (0.0%) 0	1 (1.1%) 1	1.0000
Ulna fracture	2 (4.1%) 2	1 (1.1%) 1	0.2703
Upper limb fracture	0 (0.0%) 0	1 (1.1%) 1	1.0000
Lower limb fracture	1 (2.0%) 2	0 (0.0%) 0	0.3427
Radius fracture	2 (4.1%) 2	0 (0.0%) 0	0.1158
Wrist fracture	1 (2.0%) 1	0 (0.0%) 0	0.3427
Gastrointestinal disorders	0 (0.0%) 0	2 (2.1%) 2	0.5463
Crohn's disease	0 (0.0%) 0	1 (1.1%) 1	1.0000
Gastritis	0 (0.0%) 0	1 (1.1%) 1	1.0000
Infections and infestations	0 (0.0%) 0	2 (2.1%) 2	0.5463
Cellulitis	0 (0.0%) 0	1 (1.1%) 1	1.0000
Mastoiditis	0 (0.0%) 0	1 (1.1%) 1	1.0000

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).

Corresponding data can be found in Appendix 13.2.7 Listing 4.

/RISEDRONATE/phsejib/2003100_poise/ANAL/aesys_ser.sas; SAS 8.2 19JUN08 16:59 f23may08 TZ6411.

Eight (16.3%) patients in the placebo group and 11 (11.7%) patients in the risedronate group experienced a serious TEAE during the first 12 months of the study. The most frequent serious TEAE (> 2 patients) was femur fracture in both the placebo and risedronate groups (6 patients, 12.2% placebo; 4 patients, 4.3% risedronate).

A total of 13 (26.5%) patients in the placebo group and 23 (24.5%) patients in the risedronate group reported an upper GI TEAE. The most frequent upper GI TEAEs (> 10%) were abdominal pain in the placebo group and abdominal pain upper in the risedronate group. A total of 2 (4.1%) patients in the placebo group and 2 (2.1%) patients in the risedronate group reported a moderate-to-severe upper GI TEAE; no patients reported a severe upper GI TEAE.

Clinical vertebral and non-vertebral fractures are fractures reported as TEAEs and include all non-vertebral fractures and symptomatic, radiographically-confirmed vertebral fractures that occurred after randomization. No patients reported a clinical vertebral fracture. Overall fewer patients in the risedronate group reported clinical fractures than in the placebo group (49% placebo; 30.9% risedronate). The Investigators were queried about fracture healing time. According to investigator reports, there were 28 reports of normal healing time and 27 reports that healing time could not be evaluated. There was 1 report (risedronate group: patient 6 years ♀ with atraumatic femur fracture) of abnormal healing time (delayed union of fracture- after 6 weeks of conservative treatment).

A higher percentage of patients in the risedronate group experienced a selected musculoskeletal TEAE compared to placebo. The most frequent selected musculoskeletal TEAEs (≥ 10%) were arthralgia and back pain in the placebo group and back pain in the risedronate group.

- Laboratory evaluation

There were no clinically relevant differences between treatment groups for liver function, renal function, or serum calcium and phosphorus levels.

There were few markedly abnormal haematology results. Several patients in both groups had markedly high lymphocyte and/or eosinophil counts at baseline and during the study. Mean

percentages of patients with high baseline lymphocytes were 23.3% placebo and 14.3% risedronate. Mean percentages of patients with high baseline eosinophils were 18.6% placebo and 14.3% risedronate.

Assessor's Comment

The results of this study support the previously documented effects of risedronate in children with OI. The anti-resorptive effects and favourable safety profile are consistent with those demonstrated in risedronate clinical trials in adults with osteoporosis using various doses and dosing regimens. However, a higher percentage of patients had new morphometric vertebral fractures in the risedronate group versus placebo; these data were unexpected and are difficult to explain given that the rate of new vertebral fractures was similar in the risedronate and placebo groups. The present study was neither designed nor powered to estimate the efficacy of risedronate on fractures. In the assessor's opinion the effect of risedronate on BMD should provide robust evidence on the advantages of treatment for these patients. The results are rather disappointing as the demonstrated increase of the BMD in the lumbar spine does not appear to have clinical significance and does not appear to protect the patients for new vertebral fractures. The MAH states that the following 2 years of the study will offer additional safety data that will help clarify the finding of the increased vertebral fractures. However the design for this period of the study is open label without a placebo comparator group. The efficacy endpoints including lumbar BMD are going to be reviewed against the findings from baseline, which will offer very limited additional proof of risedronate's effect. The incidence and rate of new fractures will be recorded but the uncontrolled model of this period of the study will limit the robustness of these findings. Additionally the findings of the first year of the study revealed that the patients' life does not appear to be improved from treatment as the overall quality of life evaluation did not demonstrate any difference from the placebo group. A fracture outcome study would have been the study of choice as the efficacy data are based on changes in bone mineral density, which are surrogates for bone health rather than indicators of reduction in fracture events. It is noted that very young patients (<4 years) which often have much serious type of the disease and suffer more commonly from atraumatic fractures are not included. Overall the follow up period (currently 1 year) is limited in order to assess a likely positive long term effect of treatment in the progress of the disease. Also regarding the safety of the paediatric use of risedronate, surprisingly, both in the PK and in the efficacy study occurrence of Crohn's disease as a serious adverse event has been reported. The relevance of this finding is not further discussed by the MAH.

4. Post-marketing report of paediatric exposure

Risedronate sodium is approved in over 90 countries, and the estimated global post-marketing exposure to risedronate since start of marketing is estimated to be more than 21,000,000 patient-years. The majority of the use is associated with post-menopausal women as this is the primary licensed indication of this drug.

A broad-based search strategy has been utilised by the MAHs to identify cases of paediatric exposure in the global post-marketing safety database from the start of marketing up until 31-Mar-2009. This cumulative review identified a total of 16 reports concerning patients aged from 2, up to 17 years. Eight (50%) reports were received from healthcare professionals and 8 (50%) from consumers. Four (25%) reports concerned accidental exposure/maladministration and had no AE reported as an outcome. One of these was a serious report (CIP07000995) involving a 10-year old male patient who was hospitalised for observation after accidentally taking one 35 mg tablet. Of the 12 reports where AE information was reported, 1 was serious. This report concerned a 5-year-old male patient with a history of OI who took risedronate 5 mg. The patient was hospitalised with meningitis caused by haemophilus influenza B. Action taken and outcome of the event were unknown.

7 of the 12 reports were non-serious unlisted reports describing events of mouth ulceration, suspected gastritis, no breast development, eye pain, dysphagia, diarrhoea and vomiting. Of these cases, 5 reports stated that risedronate was discontinued, 1 stated that risedronate was continued. Action taken with the drug was unknown in 1 report. 3 cases reported an outcome of improved or recovered, and 1 event was

reported as ongoing. Three reports had an unknown outcome. One report described a positive re-challenge where a 10-year-old female patient experienced pain in her right eye and headache since the beginning of treatment with risedronate 5 mg twice weekly to treat spinal fracture. The treatment was interrupted for 1 month, and the event regressed. The re-challenge was positive at the reintroduction of risedronate.

The remaining 4 reports were non-serious listed reports describing events of lack of effect, bone mass decreased, musculoskeletal pain, and femur fracture.

The MAH concluded that the review of the case reports in children does not suggest any new safety signals with risedronate use.

Assessor's Comment

The data provided in this safety review confirm that risedronate is generally well tolerated. No unexpected ADRs have been identified from these reports and no additional cases of Crohn's disease associated with risedronate treatment have been identified.

Within the past 2 years, an increasing body of literature has suggested that bisphosphonates, especially intravenous zoledronic acid and pamidronate preparations, may be associated with osteonecrosis of the jaws. Recently reports have documented this extremely rare complication after treatment with oral bisphosphonates including risedronate. In this current procedure the MAHs do not submit any evaluation of such a risk associated with risedronate treatment. However it is noted that other bisphosphonates, such as neridronate which is licensed in Italy for OI treatment have included a statement for the risk of osteonecrosis of the jaw as a warning in the SmPC, although this adverse effect of long term bisphosphonates administration is mostly associated with adult use. In addition, review of the literature in the use of bisphosphonates in OI has revealed that pamidronate therapy is associated with delayed healing of osteotomy sites after intramedullary rodding procedures and possibly delayed healing after fractures. This effect has not been investigated in the paediatric use of risedronate. In the recent years some concerns have also been raised regarding less favourable effects on long bones from chronic bisphosphonate use, including osteopetrosis and defective bone modelling (Whyte et al 2008, Rauch et al 2007).

5. Discussion on clinical aspects

The use of bisphosphonates in children with OI has become a common clinical practice, although there is no drug licensed specifically for this indication in UK. In a recent review of bisphosphonate use in childhood osteoporosis (Bachrach and Ward 2009) the authors concluded that the use of bisphosphonate therapy in paediatric patients remains controversial because of inadequate long-term efficacy and safety data. For this reason, many experts recommend limiting use of these agents to those children with recurrent extremity fractures, symptomatic vertebral collapse, and reduced bone mass. More research is needed to define appropriate indications for bisphosphonate therapy and the optimal agent, dose, and duration of use in paediatric patients. Similarly a systematic review of the effects of bisphosphonate treatment in children with osteogenesis imperfecta (Castillo et al 2009) concluded that despite a large body of published literature, there have been only eight studies with a sufficiently high level of internal validity to be truly informative. These studies confirm improvement in bone density. Some, but not all studies, demonstrate reduction in fracture rate and enhanced growth. There has been extremely limited evaluation of broader treatment impacts such as deformity, need for orthopaedic surgery, pain, functioning, or quality of life. As an example a 2-year randomized placebo-controlled trial (Kok et al 2007) has found only slight differences in quality of life in favour of the bisphosphonate group. Short-term side effects were minimal. This body of evidence would be strengthened by a larger controlled trial, because many studies lacked adequate power to evaluate stated outcomes. Additional research is needed particularly into treatment of infants. More studies evaluating medication choices, optimal dosing, duration of treatment, post-treatment impacts, and long-term side effects are necessary before the wider use of bisphosphonates (including neridronate) is supported for the licensed indication of OI in children.

The efficacy data from the studies reviewed here as part of the Article 45 work-sharing procedures, confirm the effect of risedronate, expected from other bisphosphonates on the skeleton. After 1 year, a statistically significant increase in lumbar spine BMD in the risedronate group versus placebo group was observed in the on-going Phase III study. However, treatment with risedronate did not result in an overall

benefit in the risk of fracture in paediatric patients with OI. Risedronate has been generally well-tolerated, and the incidence of clinical or laboratory adverse experiences was similar among patients treated with risedronate or placebo. Some concern is raised from the 2 reported cases of Crohn's disease among the patients treated with risedronate. The MAH concludes that the clinical meaningfulness of the finding of a higher percentage of patients with new vertebral fractures during the first year of Study 2003100 is unclear.

V RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION ON DAY 89

The use of bisphosphonates in children with OI has become a common clinical practice; however there are some concerns on the efficacy and safety of the use of risedronate that still remain after the review of the submitted data in this article 45 European work-sharing procedure.

The presented data justifies a variation application regarding the restriction of the use of risedronate sodium in the paediatric population. It is recommended that all risedronate containing products across the EU should include the following statement in the SmPC:

4.2 Posology and method of administration

Paediatric patients: Risedronate sodium is not recommended for use in children below age 18 due to insufficient data on safety and efficacy in conditions associated with paediatric osteoporosis (also see section 5.1).

Regarding the proposed by the MAH statement in section 5.1 for paediatric patients with OI, the rapporteur considered that the following statement should be included in order to reflect the data from the Phase III 2003100 study:

5.1 Pharmacodynamic properties

Paediatric patients: The safety and effectiveness of risedronate sodium is been investigated in an on-going 3-year multi-centre safety and efficacy study of paediatric patients aged 4 to less than 16 years with osteogenesis imperfecta. Interim analysis after completion of its one-year randomized, double-blind, placebo controlled period has demonstrated a statistically significant increase in lumbar spine BMD in the risedronate group versus placebo group; however the incidence of at least 1 new morphometric (identified by x-ray) vertebral fracture was numerically higher but not statistically significant in the risedronate group compared to placebo.

The SmPC might be further revised in the light of any future findings from the on-going clinical study 2003100 in paediatric OI patients following the 2-years open-label phase of treatment with risedronate. Due to the concerns regarding the new vertebral fracture rate raised during the first year of the study, interim analysis in year 2 and 3 of the 2003100 study should be provided by the MAHs through appropriate regulatory procedures to minimize inappropriate inefficacious exposure of children. The MAH should ensure that the vertebral fracture rate is appropriately assessed in relation to the previous findings of the placebo controlled period, considering amendments of the current study protocol.

Following circulation of the draft preliminary paediatric assessment report (Day 70 report), comments were received from 4 member states who fully endorsed the conclusions and recommendations of the Rapporteur. The final preliminary PdAR (day 89) was circulated to the MAH in September 2009.

VI MAH RESPONSE TO THE PRELIMINARY PDAR DAY 89

The MAH submitted a response to the Preliminary PdAR, dated 11/12/2009. In the submitted document the MAH's response to the rapporteur and CMS comments was provided. Based on the points raised, the MAH also submitted an updated version of the SmPC to better reflect the information that became available from the study 2003100 in children with OI.

In details, regarding section 4.2, the MAH did not agree with the Rapporteur comments to add "in conditions associated with paediatric osteoporosis" to the dosage information for paediatric patients. It was concluded that "this wording could be misinterpreted as restrictive and taken to mean that it is only in children with osteoporosis that risedronate sodium is not recommended. However, risedronate is not recommended for use in children regardless of the indication." Based on this, the MAH proposed the following wording for section 4.2 of the SmPC:

4.2 Posology and method of administration

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

Assessor's Comment

The MAH overall accepted the rapporteur's opinion that the available data is still insufficient to support the efficacy and safety of risedronate in the paediatric population. It is accepted that the wording "in conditions associated with paediatric osteoporosis" could be misinterpreted by prescribers. In conclusion the rapporteur considers that the proposed wording for section 4.2 is acceptable.

Regarding the information from the study 2003100 as reflected in section 5.1 of the SmPC, the applicant did not agree with the proposal from the rapporteur. It was argued that the primary objective of the study was to determine efficacy of risedronate compared to placebo in children with Osteogenesis Imperfecta after 1 year, based on a randomized, double-blind, placebo controlled study design. After 1 year of treatment, the study has continued with open label treatment (all patients receive risedronate) for 2 years to assess safety. In this context, the MAH does not endorse the rapporteur's recommendation ("The safety and effectiveness of risedronate sodium is been investigated in an on-going 3-year multi-centre safety and efficacy study of paediatric patients aged 4 to less than 16 years with osteogenesis imperfecta."), which would imply that the study is continuing in a double label design. Furthermore the MAH considers that it is more relevant to emphasize results relating to overall fracture risk rather than to focus only on vertebral fractures. Based on these conclusions, the MAH proposed the following wording for section 5.1 of the SmPC:

4.1 Pharmacodynamic properties

Paediatric population: The safety and effectiveness of risedronate sodium was assessed after one-year in a randomized, double-blind, placebo controlled study of 143 paediatric patients aged 4 to less than 16 years (94 received risedronate) with osteogenesis imperfecta. After one year, an increase in lumbar spine BMD in the risedronate group compared to the placebo group was observed. However, treatment with risedronate did not result in a reduction in the risk of fracture in paediatric patients with osteogenesis imperfecta.

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

Assessor's Comment

The MAH has strongly argued against the rapporteur's proposal regarding the details from the study 2003100 which are necessary to be included in section 5.1. It is accepted that the evidence on efficacy has been generated from the first year of the study, i.e. the double blinded placebo controlled phase. However as documented in the protocol submitted, this is an on-going study that is expected to be completed in mid 2010. The data generated from the open label phase will still need to be formally assessed for further establishing the safety profile of risedronate in OI.

The rapporteur also does not agree with the phrasing "a reduction in the risk of fracture" regarding the findings of the placebo controlled phase of the study as it can not be supported by the evidence. Generally the individual's risk of fractures in patients with OI is influenced by many confounders including the type of the disease, the age of the patients, the mobility status and the existing bone deformities to mention just a few. The study 2003100 as most OI clinical studies, unfortunately has not been design to assess this risk. The efficacy endpoint was selected to be the BMD of lumbar spine and any information on the effect of treatment in clinical fracture rate was only collected as treatment emergent adverse reaction. For long bones fractures, the difference between those documented in the risedronate group (11.7%) and those in the untreated patients (16.3%) was not statistically significant. The finding of the increased morphometric lumbar fractures can not be ignored but it is very difficult to interpret. It is noted that according to the adult licensed indication in postmenopausal osteoporosis, risedronate is considered to actually reduce the risk of vertebral fractures by increasing the BMD. A similar mechanism should be relevant to the paediatric population and therefore the finding from study 2003100 should be interpreted with caution. However the rapporteur is of the view that this information should be made available to the prescribers and this view has also been supported by the CMSs.

The applicant has stated that "The MAH also commits to update the SPC at completion of this study, if considered necessary." In association to the safety concerns (rate of lumbar fractures) raised by the rapporteur regarding the remaining time of the open label phase of the study, the MAH has highlighted that "study 2003100, was not designed to have an interim analysis at year 2 of the study, and therefore no analysis of the 2 year study data will be submitted to the regulatory agencies. The study has been run with a Data Safety Advisory Board who has reviewed the safety data throughout the study. The study will be completed in March 2010 and the final report will be submitted as per article 46 of the paediatric legislation."

Assessor's Comment

The rapporteur strongly supports the need to assess the overall safety conclusions from the 2003100 study in paediatric patients with OI. As new evidence become available from the completion of the study, it is essential that MAH has committed to submit this data to the competent authorities in due time and further changes to the SmPC/PIL might be considered necessary at that stage.

VII MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION

Overall the proposed changes in the SmPC and PIL of risedronate sodium should reflect the paediatric information available. Based on the review of the presented paediatric data the rapporteur considers that: For all products containing Risedronate sodium across the EU, it is recommended that SmPCs and PILs contain the following statement:

4.2 Posology and method of administration

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

5.1 Pharmacodynamic properties

Paediatric population: The safety and efficacy of risedronate sodium is being investigated in an on-going study of paediatric patients aged 4 to less than 16 years with osteogenesis imperfecta. After completion of its one-year randomized, double-blind, placebo controlled phase, a statistically significant increase in lumbar spine BMD in the risedronate group versus placebo group was demonstrated; however an increased number of at least 1 new morphometric (identified by x-ray) vertebral fracture was found in the risedronate group compared to placebo. Overall, results do not support the use of risedronate sodium in paediatric patients with osteogenesis imperfecta.

The applicant is therefore requested to submit a Type IB C.I.3 a) variation to update the SmPCs and PILs of products containing the active ingredient Risedronate sodium in line with the above work-sharing recommendations within 60 days of this report.

VIII MEDICINAL PRODUCTS AND MARKETING AUTHORISATION HOLDERS INVOLVED

Actonel / Optinate

MAHs: Procter & Gamble Pharmaceuticals, Sanofi-aventis, Aventis Pharma, Gruppo Lepetit SRL.