

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

ALENDRONATE SODIUM

Fosamax / Adronat / Dronal

Tablets 5mg, 10mg and 70mg alendronate sodium

UK/W/022/pdWS/001

Rapporteur:	UK – Shirley Norton
Finalisation procedure (day 120):	25 May 2011
Date of finalisation of PAR	2 June 2011

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product(s):	See section VI
INN (or common name) of the active substance(s):	Alendronate sodium
MAH (s):	See section VI
Pharmaco-therapeutic group (ATC Code):	Drugs affecting bone metabolism Bisphosphonate M05BA04
Pharmaceutical form(s) and strength(s):	Tablets 5mg, 10mg and 70mg alendronate,

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. Alendronate is a potent amino-bisphosphonate which 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.

Alendronate has been approved in several dose strengths (5, 10 and 70 mg tablets) for the treatment and prevention of postmenopausal osteoporosis and steroid-induced osteoporosis in postmenopausal women and for treatment of osteoporosis in men to prevent fractures. Alendronate is not licensed for use in children and therefore no specific paediatric formulation is available. Only very limited information is available in the literature on the use of Alendronate in children with low bone mass, though doses of up to 10mg daily have been used off-label in a small number of children with osteoporosis due to a variety of causes.

In 2005 one MAH submitted data to the FDA in respect of the treatment of Osteogenesis imperfecta (OI) in children, which didn't result in a labelling change. The data on the use of Alendronate in children with OI were also assessed through a European paediatric work-sharing procedure in 2005-2006 (UK as a Rapporteur and Czech Republic as Co-Rapporteur). The following 2 studies were reviewed during that procedure:

- Protocol 135 – A multi-centre, randomised, double-blind, placebo controlled, parallel group study of oral Alendronate sodium in paediatric patients with severe OI, followed by an open label extension.
- Protocol 172 – An open label study to investigate the pharmacokinetic profile of Alendronate in paediatric patients with OI.

As an outcome of this work-sharing procedure, a variation was submitted to update Section 4.2 of the SmPC of Alendronate with the following wording:

"Use in children (under 18 years): Alendronate has been studied in a small number of patients with osteogenesis imperfecta under 18 years of age. Results are insufficient to support its use in children."

On 20 August 2010, the MAH submitted the study report of one completed phase-I clinical trial sponsored by the MAH investigating the oral bioavailability as well as the safety and tolerability of Alendronate in glucocorticoid-treated paediatric patients.

- Protocol 155. An Open-Labeled Study to Investigate the Pharmacokinetic Profile of Alendronate in Glucocorticoid-Treated Paediatric Patients

Based on the review of the presented paediatric data in the day 89 preliminary PdAR the rapporteur concluded that the presented data were insufficient to support a variation regarding the use of Alendronate sodium in the paediatric population with glucocorticoid-induced osteoporosis. In addition, the findings from the study indicating that the oral bioavailability of alendronate is slightly lower in glucocorticoid-treated paediatric patients compared with historical adult bioavailability data were considered to be inconclusive. As appropriate dosing recommendation does not exist for children, the inclusion of the PK findings in section 5.2 "Pharmacokinetic properties" could be potentially misleading for the prescribers and could be

interpreted as a need for higher doses of alendronate in glucocorticoid-treated paediatric patients. Therefore the rapporteur was of the view that the information from study Protocol 155 should not be included in the SmPC/PIL of alendronate containing products.

The response from the MAH was received in March 2011 and included the MAH's agreement to the changes to sections 4.2 and 5.1 of the SmPC as proposed in the Preliminary Paediatric Assessment Report.

II. RECOMMENDATION

Based on the review of the presented paediatric data on pharmacokinetics and safety it is recommended that all alendronate containing products across the EU should include the following statements in the SmPC:

4.2 Posology and method of administration

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

5.1 Pharmacodynamic properties

Paediatric patients: *Alendronate sodium has been studied in a small number of patients with osteogenesis imperfecta under the age of 18 years. Results are insufficient to support the use of alendronate sodium in paediatric patients with osteogenesis imperfecta.*

Regarding the information included in the PIL of alendronate containing products, the following statement should be included:

Children and adolescents

Alendronate should not be given to children and adolescents.

The applicant is therefore requested to submit a Type IB C.1.3 variation to update sections 4.2 and 5.1 of the SmPCs and the appropriate section of the PILs of products containing Alendronate sodium in line with the above work-sharing recommendations

III. INTRODUCTION

On 20 August 2010, one MAH submitted the following documents for Alendronate sodium, in accordance with Article 45 of the Regulation (EC)No 1901/2006, as amended on medicinal products for paediatric use:

- Cover letter from the MAH
- A list of all EU marketing authorisations for Alendronate.
- The MAH's response to article 45 paediatric work-sharing procedure with an overview of submitted clinical data and a brief overview of Alendronate's safety profile.
- The study report of one completed phase-I clinical trial sponsored by the MAH investigating the oral bioavailability as well as the safety and tolerability of Alendronate in glucocorticoid-treated paediatric patients.
- 4 published articles as supporting documentation to the clinical study protocol.

Based on the information provided, the MAH concludes that the data from the submitted study do not warrant any update of the currently approved SmPC for all alendronate containing products.

IV. SCIENTIFIC DISCUSSION

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

Alendronate sodium (monosodium salt of 4-amino-1-hydroxybutylidene-1, 1-bisphosphate) is a member of the class of drugs known as bisphosphonates which are analogs of inorganic pyrophosphate, a naturally occurring inhibitor of both calcium phosphate crystallization and dissolution in vitro. Alendronate sodium is one of the most potent bisphosphonates currently available without impairing bone mineralization at doses that maximally inhibit bone resorption. Alendronate has been approved in several dose strengths (5, 10 and 70 mg tablets) for the treatment and prevention of postmenopausal osteoporosis and steroid-induced osteoporosis in postmenopausal women and for treatment of osteoporosis in men to prevent fractures. Alendronate is not licensed for use in children and therefore no specific paediatric formulation is available.

In 2005 one MAH submitted data to the FDA in respect of the treatment of OI in children, which didn't result in a labelling change. The data on the use of Alendronate in children with OI were also assessed through a European paediatric work-sharing procedure in 2005-2006 (UK as a Rapporteur and Czech Republic as Co-Rapporteur). The following 2 studies were reviewed during that procedure:

- Protocol 135 – A multi-centre, randomised, double-blind, placebo controlled, parallel group study of oral Alendronate sodium in paediatric patients with severe OI, followed by an open label extension.
- Protocol 172 – An open label study to investigate the pharmacokinetic profile of Alendronate in paediatric patients with OI.

As an outcome of this work-sharing procedure, a variation was submitted to update Section 4.2 of the SmPC of Alendronate with the following wording:

"Use in children (under 18 years): Alendronate has been studied in a small number of patients with osteogenesis imperfecta under 18 years of age. Results are insufficient to support its use in children."

Assessor's Comment

The applicant does not provide detailed information regarding the mentioned previous work-sharing procedure although the data from the paediatric use of Alendronate in those studies are considered relevant to this Article 45 procedure. A Phase I open-label, two period, randomised, single dose, crossover pharmacokinetic study (Protocol 135) was conducted in 24 paediatric patients. Comparison was made with adult historical controls and it was concluded that "oral bioavailability of alendronate in paediatric patients is low and of a similar order to that previously demonstrated in adults." No serious adverse experiences were reported and nor did any study participant discontinued treatment due to a clinical adverse experience

Protocol 135 was a Phase V multi-centre, double-blind, placebo controlled, parallel group two year RCT followed by an open-label extension. The primary efficacy endpoint was change in mean lumbar spine (L1 to L4), bone mineral density (BMD) at month 24. The other primary objective was to determine safety and tolerability. Fracture rate was not chosen as the primary efficacy endpoint due to the challenges of accurate fracture quantification and excessive radiation exposure concerns. Patients included in the study were 4-18 years old at entry, with moderate to severe OI with chronic pain and/or more than 3 fractures/year (with minimal trauma for the previous two years) or with limb deformity requiring surgery. An increase in lumbar spine BMD z-score of >1 unit was observed in 57% of the patients in the Alendronate group vs. 8% of the placebo group. However, there was no demonstrable advantage over placebo in the clinically important outcome measure of reduction in fracture risk, whether determined by blinded radiological assessment, or by investigator assessment, with or without radiological confirmation. Nor was there any advantage over placebo in respect of bone pain, disability, or parental assessment of physical activity. Clinical adverse events occurred in 95 patients (87.2%) in the alendronate group and 27 patients (90%) in the placebo group, with no significant difference between groups. Three (6.8%) alendronate and one (9.1%) placebo patients had at least one fracture with delayed union, and four (9.1%) alendronate and no placebo patients had at least 1 fracture that was characterised as a "non-union" fracture.

Overall it was concluded that *"There is as yet inadequate evidence of efficacy of alendronate in osteogenesis imperfecta and there is concern over impaired bone formation and fracture healing. A clear case that BMD is an adequate surrogate marker for fracture risk in this condition has not been made and there are concerns over safety in children generally, particularly in the long term, because of the long retention time of alendronate in bone."*

IV.2 Non-clinical aspects

1. Introduction

Non-clinical studies have not been provided or summarized by the MAH on Alendronate. It is noted that no literature review has been conducted by the MAH to identify preclinical studies relevant for the paediatric use of bisphosphonates or Alendronate.

Some preclinical information is available at the currently approved SmPC in section 5.3. *"In test animal species the main target organs for toxicity were kidneys and gastro-intestinal tract. Renal toxicity was seen only at doses >2 mg/kg/day orally (ten times the recommended dose) and was evident only on histological examination as small widely scattered foci of nephritis, with no evidence of effect on renal function. The gastro-intestinal toxicity, seen in rodents only, occurred at doses >2.5 mg/kg/day and appears to be due to a direct effect on the mucosa."* Furthermore significant lethality has been reported in animals after very high single oral doses.

The USA labelling contains the following preclinical information:

“The relative inhibitory activities on bone resorption and mineralization of alendronate and etidronate were compared in the Schenk assay, which is based on histological examination of the epiphyses of growing rats. In this assay, the lowest dose of alendronate that interfered with bone mineralization (leading to osteomalacia) was 6000-fold the antiresorptive dose. The corresponding ratio for etidronate was one to one. These data suggest that alendronate administered in therapeutic doses is highly unlikely to induce osteomalacia.”

2. Discussion of non clinical aspects

No information relevant to paediatric use of Alendronate is available in the currently approved SmPC in section 5.3. 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. From the information submitted for this work-sharing procedure, the effect of Alendronate especially after long-term treatment in the developing skeleton does not appear to have been investigated by the MAH. From the published literature some concerns have been raised regarding the consequence of treatment on bone healing in animal models (Aguirre JI et al, 2010). Furthermore there have been some reports linking alendronate and a specific pattern of subtrochanteric insufficiency fractures but these have been reported only in adult female patients. Bisphosphonates decrease bone formation as well as resorption, as confirmed by the reduction in alkaline phosphatase in the paediatric RCT (protocol 135) assessed in the previous European work-sharing procedure. This may have an impact on linear growth and indeed a non-significant ($p=0.073$) trend was seen towards lower growth velocity in the alendronate group, during the first year, albeit measurement is difficult in this condition and the trend was not confirmed during the second year of the trial. There was also a suggestion that fracture healing was less complete in the alendronate group, with non-union occurring only in this group and persisting in two cases to 36 months. The overall effect of Alendronate on growth and skeletal and pubertal development has not been assessed and therefore there are safety concerns regarding the long-term use of Alendronate in the paediatric population.

IV.3 Clinical aspects

1. Introduction

The MAH has provided a brief overview of the information available regarding the paediatric use of alendronate. This includes a short review of the clinical pharmacology and a very brief overview of the safety findings on Alendronate obtained from the clinical studies Protocol 172, 155 and 135 which have been reported in previous PSURs.

2. Clinical study

Protocol 155. An Open-Labeled Study to Investigate the Pharmacokinetic Profile of Alendronate in Glucocorticoid-Treated Paediatric Patients

➤ Methods

- **Objective**

The objective of this study was to estimate the oral bioavailability of alendronate in paediatric patients 4 to 11 years and 12 to 17 years old following a 35-mg oral dose compared to adult data from historical controls and to estimate the safety and tolerability of a single 35-mg oral dose and a single 125- μ g IV dose in paediatric patients 4 to 17 years old.

- Study design
Open-label, 2-period, randomized, crossover study including 24 paediatric patients.
- Study population /Sample size
A total of 24 patients between the ages of 4 and 17 who received glucocorticoid therapy at a stable dose over the course of the study period when pharmacokinetic determinations were being made were included in the study. Patients had to be able to stand or sit upright for at least 2 hours (at least at a 45° angle) following dosing to comply with all dosing instructions. Excluding criteria included patients with serum calcium abnormalities, renal impairment, GI disorders or history of bone disease. Patients who received previous treatment with any bisphosphonates within 12 months preceding the screening visit were also excluded from this study.
An appropriate adult historic control group of patients was selected and obtained by combining the data from appropriate bioavailability studies across the MK-0217 program for both male and females. Since short-term treatment of glucocorticoid was an additional factor which may have influenced the bioavailability, a comparison of the paediatric patients relative to the adult controls who had received short-term treatment with steroids was also made.
- Treatments
A single 35-mg oral dose of alendronate in paediatric patients was selected for this study. This dose was based on the once-weekly dose for treatment of glucocorticoid-induced osteoporosis in adults. Once-weekly dosing is likely to provide the optimal dosing recommendation for this population. A 125-µg IV dose had been used in previous studies to determine the bioavailability of oral doses of alendronate, and represents a systemic exposure of alendronate generally similar to that following the 35-mg oral dose.
All patients received 2 single doses of alendronate: the 35-mg tablet and a 125-µg IV dose, each separated by at least 7 days.
An overnight fast from all food and liquid except water (beginning at 2100 hours) prior to dosing was required. The oral treatment (35-mg tablet) of alendronate was administered at approximately 9:00 AM with 180 mL of tap water. Patients remained upright for the first 2 hours following administration of the alendronate tablet and continued to fast until the first meal of the day provided 2 hours post-dose.
The 125-µg IV dose was initiated at approximately 0900 hours and infused over 2 hours. At the start of the alendronate infusion, 180 mL of tap water was given to the patients to drink. Patients remained upright during the infusion. The first meal of the day was provided at the end of the 2-hour infusion.
- Outcomes/endpoints
Pharmacokinetic assessment
For each patient, the mean oral bioavailability of alendronate based on total urinary excretion of alendronate over 8 or 24 hours following the 35-mg tablet relative to the 125-µg IV dose was estimated.
Urine was collected in the intervals of -2 to 0 hours pre-dose, 0 to 8 and an optional 8 to 24 hours following the initiation of each treatment for determination of urinary alendronate concentration

Safety and Tolerability assessment
Safety and tolerability were evaluated throughout the study by physical examinations, a 12-lead electrocardiogram (ECG), vital signs (blood pressure, pulse rate and temperature) and laboratory safety measurements (haematology, blood, chemistry,

and urinalysis). Adverse events (AEs) were recorded for each patient throughout the study.

- **Statistical Methods**

For each age category (4 to 11 years old, 12 to 17 years old) the total urinary excretion data of alendronate was analyzed using an ANOVA model appropriate for a 2-period, crossover design and contained the factors: age category, sequence, age category by sequence interaction, subject within age category by sequence interaction, period, treatment and treatment by age category interaction. A log transformation was applied to the total urinary excretion data.

The oral bioavailability (using total urinary excretion) and 90% confidence interval (CI), using the t-distribution, on the dose-adjusted least-squares mean ratio (GMR) between the oral tablet and the 125- μ g IV (dose adjusted to a common 1-mg dose) were computed for each paediatric age category (4 to 11 years old, 12 to 17 years old). Additionally since there were no significant differences in the bioavailability estimates, a pooled bioavailability estimate (across age categories) and corresponding 90% CI was also computed using appropriate linear contrasts from the above ANOVA model. Additional comparisons between each of the age categories for the total urinary excretion following the oral 35-mg tablet and IV were also performed using appropriate contrasts from the above ANOVA model.

Estimation of both paediatric age categories (4 to 11 years old, 12 to 17 years old) relative to the adult historical data on the bioavailability GMR (paediatric age category/adults) was computed along with the corresponding 90% CI using the t-distribution. Again the bioavailability of alendronate was analyzed using an ANOVA model appropriate for a parallel group study. The 1-way ANOVA model contained the factors: group (4 to 11 years old, 12 to 17 years old and adult historical controls). An exploratory analysis investigating the relative bioavailability of Early/Late stage Tanner stage relative to the historical adult bioavailability data was also conducted.

➤ **Results**

- **Alendronate Pharmacokinetics**

The bioavailability of alendronate was estimated by comparing the total urinary excretion of alendronate following a 125- μ g IV dose, to that following an oral dose of 35-mg. In the younger age group (age 4 to 11 years) the mean oral bioavailability (90% CI) was 0.43% (0.27%, 0.67%), and in the older age group (age 12 to 17 years) it was 0.39% (0.26%, 0.60%). The results indicated that there was no difference in oral bioavailability between the younger and older age groups. In addition, the oral bioavailability of alendronate was generally similar across Tanner Stage, as well as between early and late Tanner Stage patients (early Tanner Stage defined as 1 to 3 in females and 1 to 4 in males).

When the paediatric bioavailability obtained in this study is compared with historical adult bioavailability data, the bioavailability is slightly lower in these paediatric patients (Table 1). The least squares geometric mean ratio (90% CI) for bioavailability of paediatric to adult patients is 0.64 (0.44, 0.94) for ages 4 to 11 years, and 0.58 (0.39, 0.85) for ages 12 to 17 years. This decrease is statistically significant in the older group ($p=0.020$), and of borderline statistical significance in the younger group ($p=0.057$). It should be noted that the variability in individual alendronate bioavailability, which is known to be high in adults, is of similar magnitude in paediatric patients in both age groups.

Table 1

**Summary Statistics for Total Urinary Excretion (μg) of Alendronate After an Oral Dose
(Dose-Adjusted to 1 mg) for Pediatric Patients by Age Category Relative to
Historical Adult Data**

Population	N	Least-squares Mean [†]	Median	Min	Max	Between-Subject SD	GMR [‡]	90% CI GMR [‡]	Between-Group p-Value	Between-Subject CV (%) [§]
Age 4- to 11-year-old	12	1.62	1.51	0.67	11.95	1.94	0.59	(0.40 , 0.86)	0.021	70.22
Age 12- to 17-year-old	12	1.12	1.26	0.30	3.71	1.79	0.41	(0.28 , 0.59)	<0.001	
Historical Adult	52	2.75	2.70	0.61	8.05	2.41	.			

[†] Back-Transformed from Log-Scale.
[‡] Least-Squares Mean Ratio (Pediatric Age Category/Historical Adult).
[§] Root Mean Square Error on the log scale from ANOVA model x 100; CV=coefficient of variation.
SD=Standard Deviation, CI=Confidence Interval.

Data Source: [2.2]

The bioavailability of alendronate in glucocorticoid-treated paediatric patients observed in this study compares favourably with the bioavailability of alendronate observed in paediatric OI patients studied previously (Protocol 172). In paediatric OI patients, the mean oral bioavailability of alendronate (95% CI) was 0.43% (0.28%, 0.64%) for paediatric patients weighing less than 40 kg, and 0.56% (0.36%, 0.87%) for paediatric patients weighing at least 40 kg (compared to the current study in which bioavailability (90% CI) was 0.43% (0.27%, 0.67%) for glucocorticoid-treated patients age 4 to 11 years, and 0.39% (0.26%, 0.60%) for patients age 12 to 17 years). Thus, oral bioavailability was generally similar in all 4 paediatric groups.

A decrease in urinary excretion in these paediatric patients following an IV dose reflects increased uptake by the bone in this patient group, albeit slight (table 2).

Table 2

**Summary Statistics for Total Urinary Excretion (μg) of Alendronate After an IV Dose
(Dose-Adjusted to 1-mg) for Pediatric Patients by Age Category Relative to
Historical Adult Data**

Population	N	Least-Squares Mean [†]	Median	Min	Max	Between-Subject SD	GMR [‡]	90% CI GMR [‡]	Between-Group p-Value	Between-Subject CV (%) [§]
Age 4- to 11-year-old	12	369.37	362.09	200.16	1103.0	181.48	0.91	(0.71 , 1.16)	0.531	45.92
Age 12- to 17-year-old	12	284.01	414.25	68.48	949.84	363.19	0.70	(0.55 , 0.90)	0.018	
Historical Adult	52	405.18	418.21	157.93	856.73	158.81	.			

[†] Back-Transformed from Log-Scale.
[‡] Least-Squares Mean Ratio (Pediatric Age Category/Historical Adult).
[§] Root Mean Square Error on the log scale from ANOVA model x 100; CV=coefficient of variation.
SD=Standard Deviation, CI=Confidence Interval.

Data Source: [2.2]

The MAH concludes that the results of this study indicate that glucocorticoid-treated paediatric patients have a slightly lower oral bioavailability of alendronate, but a slightly

increased bone uptake of alendronate once it reaches the plasma, compared to the historic adult controls used in this study. These 2 opposing effects suggest that following an oral dose of 35 mg, the amount of alendronate reaching the site of pharmacologic activity, the bone surface, is generally similar in paediatric patients and adults. The MAH suggests that these findings support the selection of 35-mg alendronate once weekly as an appropriate dose for glucocorticoid-treated paediatric patients.

- **Safety results**

Three serious adverse experiences were reported in 2 patients. Both patients experienced an overdose with one of them (AN 015) receiving an IV dose of 395.7µg alendronate, and the other (AN 014) receiving an IV dose of 438.7µg. The first patient had no symptoms reported as a result of the overdose, while AN 014 reported mild leg pain following the overdose. All 3 of these serious adverse experiences resolved. Fifteen patients reported a total of 37 clinical adverse experiences, 14 of which were considered to be probably not and 9 were considered definitely not related to study drug. The most common clinical adverse experiences were headache (N=13), stomach ache (N=3) [occurred in one patient], loose stools/diarrhoea (N=2), swelling-ankle/knees (N=3) [occurred in one patient], and leg, ear, hand, arm, neck and facial pain (N=6). All of the clinical adverse experiences were mild or moderate in intensity. No patients were discontinued due to a clinical adverse experience and no study participant died during the study.

All 24 patients were included in the laboratory safety evaluation. One patient experienced a laboratory adverse experience on Day 1 following the 125-µg IV dose in Period 2. The non-serious laboratory adverse experience (decreased lymphocyte count) was considered possibly drug related. No further follow-up was conducted in this patient. Some haematology and blood chemistry values were outside of the normal range in some patients. With the exception of the haematology lymphocyte laboratory adverse experience listed in (Table 23), these abnormal haematology and blood chemistry values were not considered clinically significant changes by the investigator and were not considered as adverse experiences. No patient discontinued due to a laboratory adverse experience.

In some patients, abnormalities were noted at the physical examinations for the vital signs and in 12-lead ECGs. Individual transient increases in temperature, blood pressure and/or heart rate were not considered clinical adverse experiences or clinically significant by the investigator. With the exception of one patient who experienced a clinical adverse experience of arm and hand pain at the IV site, no symptoms of local intolerance were seen at the site of drug administration.

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 significantly variable, although the MAH concludes that the paediatric bioavailability is comparable to those of adults. The initial selection of the doses under investigation is not adequately justified. As mentioned by the MAH, while alendronate is indicated for treatment of glucocorticoid-induced osteoporosis in adults, the drug has not previously been investigated in paediatric patients receiving glucocorticoids. The literature is also inconclusive for the most appropriate dosing regime for the paediatric population or indeed the need to prophylactically or therapeutically treat these patients. It is therefore unclear if it is the optimal dose for efficacy demonstration for alendronate's use in paediatric patients with glucocorticoid-induced osteoporosis. Regarding the safety of the paediatric use of alendronate, the single oral or IV dose appears to be well tolerated and no unusual AEs have been reported during this study. The 2 cases of overdose are considered significant as they demonstrate the

lack of clear dosing regime and the high risk of dosing errors in paediatric patients even within the carefully monitored environment of a clinical study.

3. Literature review of published information

A comprehensive literature search to identify published articles and abstracts relevant to alendronate use in the paediatric population was not performed by the MAH.

The 4 identified articles with a paediatric interest identified by the applicant as supporting information to the conducted clinical trial (Protocol 155) are listed below:

1. Brumsen C, Hamdy NAT, Papapoulos SE. **Long-term effects of bisphosphonates on the growing skeleton: studies of young patients with severe osteoporosis.** Med 1997;76(4):266-83.
2. Glorieux FH, Bishop NJ, Plotkin H, Chabot G, Lanoue G, Travers R. **Cyclic administration of pamidronate in children with severe osteogenesis imperfecta.** N Engl J Med 1998;339(14):947-52.
3. Barnes PJ. **Drug therapy: inhaled glucocorticoids for asthma.** N Engl J Med 1995;332(13):868-75
4. Gertz BJ, Holland SD, Kline WF, Matuszewski BK, Freeman A, Quan H, et al. **Studies of the oral bioavailability of alendronate.** Clin Pharmacol Ther 1995;58(3):288-98.

Assessor's Comment

The MAH included these studies as supportive documentation in the clinical trial package. The first 2 confirm an observed positive effect of oral and intravenous pamidronate treatment in paediatric patients with different types of paediatric osteoporosis and in paediatric OI patients. These studies confirm improvement in bone density. From a literature review, some studies demonstrate reduction in fracture rate and enhanced growth following treatment with nitrogen-containing bisphosphonates. This body of evidence should be strengthened by a larger controlled trial, as these 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 alendronate) is supported for the licensed indication of OI in children. It is noted that none of the studies are relevant to the paediatric use of alendronate in glucocorticoid-induced osteoporosis.

In 1997 Brumsen et al (1) reported their long term experience in treating paediatric patients with severe osteoporosis with nitrogen-containing bisphosphonates (pamidronate and olpadronate), focusing on issues of skeletal safety and efficacy. 12 patients were studied with variable diagnosis: 4 patients had OI, 1 patient had idiopathic juvenile osteoporosis, 5 patients were classified as idiopathic osteoporosis without metaphysical fractures, 1 had juvenile arthritis and 1 had a mitochondrial disorder with disabling myopathy; none of them had been treated with glucocorticoids in the past. The patients were put on pamidronate and olpadronate daily for long-term treatment lasting 2.2 to 8.2 years. There was a marked increase in BMD with treatment and this was more pronounced in patients who received treatment before puberty. There was no clear difference in response between patients with OI and those with idiopathic osteoporosis. When treatment was given before closure of the epiphyses was complete, characteristic sclerosis appeared at the metaphyses of long bone particularly around the knees and in the distal forearm, where growth activity is the larger; similar changes were seen in the vertebrae. Despite these radiological changes, skeletal maturation proceeded normally. Linear growth also proceeded normally during treatment. Patients treated before or in early puberty demonstrated

catch up growth, probably due to (partial) correction of vertebral deformities. Patients treated in late puberty did continue to grow but in the same percentile of the growth curves. Overall treatment was well tolerated. Flu like symptoms at the beginning of treatment were noticed in 8 patients. No patients developed symptomatic hypocalcaemia. It was therefore concluded that despite concerns on the effect of nitrogen-bisphosphonates on bone metabolism and growth, this study demonstrates that long-term continuous administration of oral pamidronate and olpadronate to children with severe osteoporosis “was devoid of any adverse effect on the growing skeleton”.

Assessor’s Comment

This study confirms the known positive effects of bisphosphonates treatment in children and adolescents with severe osteoporosis. However the limitations of this observational study do not allow clear assessment on the positive effects on growth and skeletal maturation claimed by the authors. The number of patients included is very small and there is significant heterogeneity among the diagnosis of the participants. The exact follow-up protocol is not mentioned in this paper, only the total duration of the treatment for each patient and therefore the timelines for measuring the positive effects on the efficacy parameters (BMD and growth) can not be assessed. As the duration of treatment was significant (up to 8 years), the lack of any unusual or severe adverse event offers some reassurance on the safety profile of the long term use of nitrogen-containing bisphosphonates in paediatric osteoporosis patients.

Glorieux et al (1998) reported the findings from an uncontrolled observational study involving 30 children (3-16 years old) with severe OI which were treated with IV pamidronate at 4-to-6 month intervals for 1.3 to 5 years. During treatment, alendronate significantly increased mean bone mineral density as well as mean Z-scores and there was no difference between prepubertal children and children undergoing puberty. Radiological evaluation demonstrated no new vertebral crush fractures and an increase in vertebral height. The characteristic sclerotic lines were evident under the growth plates. After each infusion cycle, there was a transient (2 to 4 weeks) decrease in serum calcium and serum phosphate but none of the children had symptomatic hypocalcaemia. Mobility improved in 16 children and all participants reported some relief of chronic musculoskeletal pain and fatigue. The mean incidence of radiologically confirmed fractures decreased by 1.7% per year ($p < 0.001$) and the authors concluded that treatment with pamidronate did not alter the rate of fracture healing, the growth rate or the appearance of growth plates.

Assessor’s Comment

The results of this study support the previously documented effects of IV pamidronate in children with OI. The anti-resorptive effects and favourable safety profile are consistent with those demonstrated in adult osteoporosis clinical trials using various doses and dosing regimens. Although the number of patients included in this study is significant, the lack of a control group limits the significance of the findings. The study is not powered to detect changes on fracture rates and it is known from the natural history of OI that the fracture rate decreases with time as the child grows. A fracture outcome study would have been the study of choice as the efficacy data presented here are based on changes in bone mineral density, which are surrogates for bone health rather than indicators of reduction in fracture events. In the assessor’s opinion the effect of the treatment on growth is inconclusive due to limitations of the study’s design.

The paper published in 1995 by Barnes (3) summarizes the known effects of glucocorticoids on bone metabolism and growth. Glucocorticoids reduce bone mass directly by inhibiting bone formation, and indirectly by inhibiting the secretion of androgen in the pituitary–gonadal and adrenal systems and by limiting calcium absorption in the intestines and calcium reabsorption in the renal tubules, thereby causing secondary hyperparathyroidism. Although oral glucocorticoid therapy is a well-known cause of osteoporosis and increased risk of vertebral and rib fractures,

but the author questions the effects of long-term treatment with inhaled glucocorticoids in association with an increased risk of fractures. There has been particular concern that inhaled glucocorticoids may cause stunting of growth. Asthma itself, like other chronic diseases, may result in poor growth and delay the onset of puberty. The delay of puberty, however, may allow children with asthma to grow for a longer period, so that their final height is normal. This influence of asthma on growth makes it difficult to assess the effects of inhaled glucocorticoids in cross-sectional studies.

Assessor's Comment

This is a rather old publication reviewing the effect of glucocorticoids on bone and growth. Regarding the long term use of inhaled corticosteroids, there is still some debate regarding the safety of long-term use of these agents, particularly in children. This concern mainly stems from the findings of short-term studies assessing the effects of inhaled corticosteroids on epiphyseal growth rate or the hypothalamic-pituitary-adrenal axis. The clinical relevance of these findings to long-term treatment is unknown although it is considered significant by many authors; some uncertainty exists regarding the predictive value of changes in cortisol levels and clinically relevant changes in growth or bone mineral density. Regarding the use of oral administration, decreased BMD has been demonstrated in various paediatric disorders that require glucocorticoids, and a recent population-based study reported increased fracture risk in children who require >4 courses of glucocorticoids (van Staa TP, Cooper C, Leufkens HG, Bishop N. Children and the risk of fractures caused by oral corticosteroids. *J Bone Miner Res.* 2003;18:913–918). However the prevention or the treatment of glucocorticoid-induced osteoporosis in children remains controversial and it has been concluded that “Following an understanding of the natural history of GC-induced osteoporosis in children, randomized, placebo-controlled prevention and intervention trials will be the next step toward the development of clinical practice guidelines.” (Ward 2005).

The final paper (4) by Gertz et al (1995) summarizes the clinical studies performed to examine the oral bioavailability of Alendronate as well as the effect of food, the timing of the meals and beverages other than water on the PK profile of the drug following oral administration. With the exception of one study of men, all subjects were post-menopausal women. In summary, except for a somewhat greater whole body (i.e. skeletal) retention, the disposition and oral absorption of alendronate are generally similar to those reported for other bisphosphonates. There is limited oral bioavailability (0.7% in fasting stage), which is sensitive to the timing of food intake. The authors concluded that “a practical dosing recommendation, derived from these findings and reflective of the long-term nature of therapy for a disease such as osteoporosis, is that patients take the drug with water after an overnight fast and at least 30 minutes before any other food or beverage.”

4. Overview of safety

The MAH has provided a very short overview of alendronate's safety profile in the paediatric population. It is mentioned that the experience with alendronate obtained from clinical studies in paediatric patients (age range from 4 to 18 years) has been reported in previous PSURs, including PSUR #19 (Protocol 172), #23 (Protocol 155), and #25 (Protocol 135). These PSURs are not provided by the MAH in this instance. It is however concluded that the safety results from these studies indicated alendronate to be generally well tolerated and overall to have a favourable safety profile consistent with the one observed in adult patients with osteoporosis. A cumulative paediatric data from spontaneous reports received in paediatric patients being treated with alendronate sodium from market introduction (16-Jul-1993) through 15-Jul-2007 was first presented in PSUR #28. Since then, periodic paediatric data have been presented in each PSUR. The MAH also reports that the review of the spontaneous reports received by the company in paediatric patients in alendronate treatment demonstrated a safety profile similar to

that observed in adults. The MAH concludes that will continue to monitor the reports received in all age groups paediatric patients receiving alendronate.

Assessor's Comment

The safety data provided by the MAH for this European work-sharing procedure under Article 45 are very limited as these have been previously reviewed in regularly submitted PSURs. The available information suggests that the adverse events experienced by children exposed to alendronate are similar to those experienced by the adult population. However, the total experience remains very small. In addition, review of the literature in the use of bisphosphonates in OI and other paediatric conditions of low bone density 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 alendronate. 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). Therefore, the long-term safety of alendronate in children cannot be assured at this stage.

5. Discussion on clinical aspects

Literature strongly suggests that long term administration of glucocorticoid (oral or inhaled) in childhood induced not only osteoporosis but also growth failure via direct action on bone and cartilage and indirectly via hormonal derangements. It has been reported that even if bone loss is small, the decrease in the Z score of BMD is large because bone mass increases during childhood in healthy children (Rabinovich 2004). Up to now, there has been no standard approach to the management and treatment of glucocorticoid-induced osteoporosis in children, although guidelines for its treatment in adults have been available in many countries. Based on these guidelines, bisphosphonates are recommended as first-line drugs for all patients who have undergone long-term treatment with glucocorticoids. Additional complexities in the assessment and management of growing children mean that evidence-based guidelines for this complex patient group have not been produced. Factors, which need to be taken into account, include defining osteoporosis in childhood and addressing the effects of chronic disease and glucocorticoid treatment on a number of parameters including the skeleton, growth, puberty, nutrition and vitamin D status (Brown and Zacharin 2005).

The use of bisphosphonates for glucocorticoid-induced osteoporosis in childhood is still not common. A literature review conducted by the rapporteur identified a number of studies investigating the efficacy of bisphosphonates for the treatment of childhood glucocorticoid-induced osteoporosis. In 2007 Inoue et al investigated the efficacy of intravenous alendronate for the treatment of glucocorticoid-induced osteoporosis in children with autoimmune diseases. Five children with autoimmune disease and osteoporosis were treated with 5 mg intravenous alendronate once every 3 months. After 1 and 2 years, they evaluated the changes in the Z score of the femoral neck BMD, serum bone alkaline phosphatase, and urinary deoxypyridinoline. Six patients with autoimmune disease and osteoporosis, for whom BMD could be observed over a 1-year period without alendronate treatment, were defined as controls. After 1 and 2 years of treatment, it was concluded that intravenous treatment significantly inhibited bone loss. It was also found that a high level of bone turnover before alendronate treatment was significantly related to the efficacy of alendronate for glucocorticoid-induced osteoporosis. The authors concluded that this finding suggests that maintained bone formation is sufficient for a recovery of BMD even under glucocorticoid treatment, and the best period for administering alendronate is thus considered to be during periods of high bone turnover. In a retrospective chart review, Steelman and Zeitler (2003) reported gains in BMD and fracture reduction with cyclic single-day intravenous pamidronate infusions in eight glucocorticoid-treated children over a noticeably short period of observation (6-month). In a preliminary study, Bianchi et al. (2000) showed a 15% increase in BMD over baseline in 38 glucocorticoid-treated patients with

connective tissue disease over 1 year who were treated with oral alendronate. There was no formal control group in this study, but children with milder forms of the same diseases not requiring glucocorticoid treatment showed a non-significant change in BMD from baseline over the same time period.

It is concluded that management of steroid-induced osteoporosis in children and adolescents is complex. Literature suggests that some interventions, possibly treatment with bisphosphonates might be needed in those at risk of failing to achieve optimal peak bone mass, such as childhood and adolescent corticosteroid users. Conducting prospective randomized interventional trials would provide the basis for management guidelines. From the data provided by the MAH in this European work-sharing procedure under Article 45, there is no robust evidence supporting the efficacy or safety of Alendronate in paediatric patients with glucocorticoid-induced osteoporosis.

V. MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION

➤ Overall conclusion

The presented data submitted in this article 45 European work-sharing procedure is insufficient to support a variation regarding the use of Alendronate sodium in the paediatric population with glucocorticoid-induced osteoporosis. In addition, the findings from the study indicating that the oral bioavailability of alendronate is slightly lower in glucocorticoid-treated paediatric patients compared with historical adult bioavailability data are considered to be inconclusive. As appropriate dosing recommendation does not exist for children, the inclusion of the PK findings in section 5.2 “Pharmacokinetic properties” could be potentially misleading for the prescribers and could be interpreted as a need for higher doses of alendronate in glucocorticoid-treated paediatric patients. Therefore the rapporteur is of the view that the information from study Protocol 155 should not be included in the SmPC/PIL of alendronate containing products.

It is recommended that all alendronate containing products across the EU should include the following statement in the SmPC:

4.2 Posology and method of administration

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

Regarding the previously included information in section 4.2 for paediatric patients with OI, the rapporteur concludes that the statement should be included in section 5.1 as proposed by the new SmPC guidelines and for consistency with other bisphosphonates already assessed through European work-sharing under article 45.

Therefore the rapporteur proposes that the statement currently found in section 4.2 should be moved to section 5.1 in the SmPC:

5.1 Pharmacodynamic properties

Paediatric patients: Alendronate sodium has been studied in a small number of patients with osteogenesis imperfecta under the age of 18 years. Results are insufficient to support the use of alendronate sodium in paediatric patients with osteogenesis imperfecta.

Regarding the information included in the PIL of alendronate containing products, the following statement should be included:

Children and adolescents

Alendronate should not be given to children and adolescents.

➤ **Recommendation**

The applicant is therefore requested to submit a Type IB C.I.3 variation to update sections 4.2 and 5.1 of the SmPCs and the appropriate section of the PILs of products containing Alendronate sodium in line with the above work-sharing recommendations

VI. LIST OF MEDICINAL PRODUCTS AND MARKETING AUTHORISATION HOLDERS INVOLVED

MAH: Merck Sharp & Dohme Limited

Medicinal products : Fosamax / Adronat / Dronal / Fosavance

MAHs : Abello SA, Sigma-TAU IFR SpA, Frosst Portuguesa - Produtos Farmacêuticos Lda, Tecnifar - Indústria Técnica Farmacêutica S.A, Istituto Gentili S.p.A, Neopharmed S.p.A