

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

NERIDRONIC ACID (NERIDRONATE)

NERIXIA

UK/W/006/pdWS/001

Rapporteur:	UK
Date of the Final report (Day 120):	9 January 2010
Date of finalisation of PAR:	19 October 2010

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	NERIXIA
INN (or common name) of the active substance(s):	Neridronic acid (Neridronate)
MAH:	See section VI
Currently approved Indication(s)	Osteogenesis Imperfecta Paget's disease
Pharmaco-therapeutic group (ATC Code):	Drugs affecting bone metabolism Bisphosphonate
Pharmaceutical form(s) and strength(s):	25mg and 100mg solution for injection or infusion IV or IM

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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. Sodium neridronate is an aminobisphosphonate, similar to alendronate and pamidronate. Studies have demonstrated that the intracellular target of Neridronate in osteoclasts is an enzyme involved in the conversion of mevalonate into geranylgeranylpyrophosphate. The result is that osteoclasts can no longer form vesicles or organize the ruffled border of bones. The final effect is apoptosis of osteoclasts and therefore inhibition of bone resorption by them. 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.

Neridronic acid (Neridronate) is used in the following indications:

- Osteogenesis Imperfecta
- Paget's disease

It is noted that the drug is only licensed in Italy for the indication of OI and no other bisphosphonate is currently licensed for OI in Europe.

The currently available pharmaceutical forms are:

- Nerixia 25mg solution for IM or IV injection
- Nerixia 100mg concentrate for solution for infusion for IV use.

No specific paediatric formulation is available.

The currently approved posology in the approved SmPC for OI is:

"4.2 Posology and method of administration

Osteogenesis Imperfecta:

From 25 mg to 100 mg IV, based on body weight, in one administration with slow infusion. Prior to administration dilute in 250-500 ml of physiological solution. The indicative posology is of 2 mg/kg body weight every 3 months.

In adults the total dosage can be fractioned in intramuscular dosages of 25 mg/die up to 4 consecutive days every 3 months."

The data package submitted by one MAH under article 45 of the Paediatric Regulation comprises 4 documents relevant to the paediatric use of Neridronate in OI. The MAH concludes that based on the clinical studies conducted in the paediatric population with OI and the review of the safety profile of Neridronic acid, the risk/benefit ratio appears favourable for the use of Nerixia in patients with OI , including children.

Based on the review of the presented paediatric data on pharmacokinetics, safety and efficacy, the rapporteur considered that:

"The SmPC of Neridronate should be updated with specific wording regarding use in the paediatric population for the licensed Osteogenesis Imperfecta indication listed in section 4.1. Similarly in section 4.2, comprehensive dosing recommendations should be available for the paediatric population. The MAH should review all available data and propose an update to the SmPC, justified by the available data."

Following circulation of the draft preliminary paediatric assessment report (Day 70 report), comments were received from member states who fully endorsed the conclusions and recommendations of the Rapporteur. Additional comments were received from Italy who has a particular interest in this procedure as they hold the only European licence of Neridronate. These comments were attached to the final preliminary PdAR (day 89) which was circulated to the MAH in June 2009.

A preliminary response for the MAH was received in July 2009 in which the company confirmed the ongoing review of the open label, non controlled 3 year phase of the NEROI clinical trial. The final report is expected to be available at the end of 2010 and is expected to provide additional efficacy and safety information on the long-term use of Neridronate in the paediatric OI population. This letter was communicated to Italy in August 2009. As a response to this information and comments from Italy, the rapporteur concluded that the current European work-sharing procedure under Article 45 for Neridronate should not be delayed as the new data should be submitted and reviewed under a separate regulatory procedure to the competence authorities as appropriate.

The final response from the MAH was received in October 2009, including:

- Response to the request to update Nerixia SmPC.
- The proposed SmPC wording relevant for paediatric use but without any further discussion.

RECOMMENDATION

Based on the review of the presented paediatric data the rapporteur considers that: For all products containing Neridronic acid across the EU, it is recommended that SmPCs contain the following statement:

4.1 **Therapeutic indications**

Adults

Osteogenesis imperfecta.

Paget's Disease

Children (less than 18 years of age)

Osteogenesis imperfecta.

4.2 **Posology and method of administration**

Osteogenesis Imperfecta

Children (less than 18 years of age)

The recommended dose is 2mg/kg body weight (maximum 100mg) by slow intravenous infusion (over at least 2 hours) every 3 months. Prior to administration the injection is diluted 250-500 ml 0.9% sodium chloride.

For all products containing Neridronic acid across the EU, it is recommended that PILs contain the following statement:

“What Neridronic acid is used for:

Neridronic acid can be used in adults to treat Paget's Disease and Osteogenesis imperfecta. In children less than 18 years Neridronic acid can be used to treat Osteogenesis imperfecta"

"Posology, method and time of administration.

Children

Osteogenesis Imperfecta

The recommended dose is 2mg/kg body weight (maximum 100mg) by slow intravenous infusion (over at least 2 hours) every 3 months. Prior to administration the injection is diluted in 250-500 ml 0.9% Sodium Chloride."

I. INTRODUCTION

On 20 March 2009, a MAH submitted the following 4 documents for Neridronic acid (Neridronate), in accordance with Article 45 of the Regulation (EC)No 1901/2006, as amended on medicinal products for paediatric use:

- The expert report on the clinical documentation related to osteogenesis imperfecta (OI) - 2001
- The 3 years ad interim analysis of the clinical trial NEROI-2001
- A clinical overview developed for the purposes of the current European work-sharing procedure
- The periodic safety update report (PSUR) for the period 4 April 2002 – 30 September 2006.

An extended list of literature references as well as the currently authorised SmPC have also been provided.

The MAH stated that the first 2 documents were originally submitted with the marketing authorization application in May 2001. The marketing authorization was granted by the Italian Health Authorities in April 2002 for the indication “Osteogenesis Imperfecta” in 2 formulations of 25mg and 100mg solution for injection or infusion for IM and IV administration. In 2006 the new indication “Paget’s disease” was approved for the 100 mg dosage form, but it is noted that this condition does not occur in the paediatric population and therefore it is not relevant to this overview.

The MAH concludes that based on the clinical studies conducted in the paediatric population with OI and the review of the safety profile of Neridronic acid, the risk/benefit ratio appears favourable for the use of Nerixia in patients with OI , including children.

II. SCIENTIFIC DISCUSSION

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

Neridronate is currently marketed in Italy in parenteral formulations (25mg and 100mg) for intravenous or intramuscular injection and for dilution as an intravenous infusion. The paediatric dose used is 2mg/kg every 3 months.

II.2 Non-clinical aspects

1. Introduction

Non-clinical studies have not been provided or summarized by the MAH on Neridronate. 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 Neridronic acid.

Some information is available at the currently approved SmPC in section 5.3. Following intravenous administration for 4 weeks the dosages up to 2.5 mg/kg/die in the rat and up to 20 mg/die in the dog was found to be well tolerated. Additional information on carcinogenicity is not provided as: *“Carcinogenicity tests were not carried out, given the absence of mutagenesis effects of the medicinal product, the chemical-physical characteristics of the product, and the evidence that other bisphosphonates, currently utilized in therapy, have not shown carcinogenicity risk.”*

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 documents submitted in the application for marketing authorisation, the effect of Neridronate in the developing skeleton does not appear to have been investigated by the MAH.

II.3 Clinical aspects

1. Introduction

The MAH has provided a clinical overview of the paediatric use of Neridronic acid in patients with OI. The majority of the data in the paediatric population in this overview is from the NEROI study, which will be assessed below. Further information from published studies in the literature is also summarized in this overview as supporting evidence for the efficacy of Neridronic acid and other bisphosphonates in the treatment of paediatric OI patients. Additionally the periodic safety update report (PSUR) for the period 4 April 2002 – 30 September 2006 is included as an overview of the drug's safety profile.

The originally submitted line-listing by the MAH included 2 additional recently published papers investigating the effects of Neridronic acid treatment in children with OI. These published studies were included in the assessment and they are summarized in section 6.

2. Clinical overview

The report is a very useful summary of the available data from the MAH and the published literature.

In respect of the paediatric population the report concludes that:

“Neridronate has been investigated in one of the larger clinical trials performed with aminobisphosphonates both in adult and paediatric patients affected by OI; cyclic infusions of neridronate given quarterly have been reported to increase the Bone mineral density (BMD), and this is associated with a lower risk of clinical fracture. The interim analysis has confirmed the efficacy of neridronate in the paediatric population affected by OI.” Additionally, the MAH states that *“On the basis of the safety data showed above, the risk/benefit ratio appears favourable for the use of Nerixia(Neridronate) in this kind of pathology and in the paediatric population.”*

3. Clinical studies

The NEROI study with Neridronate in OI patients (Children and adults) 2001

Open label not controlled 3-year study of the effect of infusion of Neridronate in patients with osteogenesis imperfecta.

➤ **Methods**

- Objective

The purpose of the study is to assess the efficacy of treatment of OI with neridronate, by means of clinical criteria (number of new fractures, pain, articular mobility), biological criteria (response of bone turnover markers), and in terms of bone mass (DXA type densitometry of the wrist, lumbar spine and femur; Quantitative Computerised Axial

Tomography of the wrist (pQCT) and radiography of the hand for radiometric assessments).

- Study design
Prospective open-label, uncontrolled study.
- Study population /Sample size
Given the particular characteristics of the disease that is being studied, no sample size has been calculated. The idea was, however, to recruit not less than 50 subjects with OI in all its forms. Initially the protocol included patients over the age of 9 years. At a later stage, through an amendment to the protocol, the minimum age was reduced to 6 years. Patients that have been treated with bisphosphonates in the last 12 months or calcitonin in the last 3 months were excluded for the trial.
- Treatments
In this study, the drug was always administered by intravenous route, at a dose of 2mg/kg, up to a maximum of 100 mg, dissolved in normal saline (approximately 10 mg/100 ml), with an infusion time of not less than two hours. The infusions were done at three-monthly intervals. The frequency of administration was reduced (every 6 months) if the levels of alkaline phosphatase (AP) were less than a third of the normal maximum amount for an adult subject (for example, less than 95 U/L where the normal adult value is <275 U/L).
- Outcomes/endpoints
Clinical efficacy
Previous fracture episodes and those which have occurred during the study were recorded. Any effect on spontaneous pain was also monitored, using an analog scale from 0 to 100, and any effect on articular mobility, according to a four-point scale.

Biochemical efficacy
The following tests were done under baseline conditions and every 3 months thereafter, during treatment:
 - Fasted urinary calcium/creatinine ratio
 - Urinary N-telopeptide
 - Free urinary deoxypyridolin
 - Urinary hydroxypyridolin
 - Total and bone alkaline phosphatase (with ELISA)
 - Osteocalcin (OC)
 - Serum Calcium, phosphorus, albumin
Bone composition efficacy
The following assessments were done under baseline conditions and every 6 months thereafter, during treatment:
 - Ultradistal and proximal densitometry of the radius (DXA)
 - Densitometry of the lumbar spine and of the femur (DXA)
 - Distal and proximal pQCT of the radiusFurthermore, each year, an anteroposterior X-ray was done of the hand in order to measure the cortical thicknesses and metacarpal index of all the patients on the study, after digitalisation of the image.

Tolerability assessment

The following parameters were assessed, at the time of recruitment and every 3 months:

- Full blood count
 - Liver function tests (GOT, GPT, GGT)
 - Serum Creatinine
 - Full urine test
- Statistical Methods
 The percent changes from the baseline of the BMD (bone mineral density), BMC (bone mineral content) and area of the vertebral column, of the femur and of the proximal radius, have been analysed by means of descriptive statistics. The mean values of the percent changes from the baseline have been compared with 0, using a one-sample t-test. For patients up to the age of 20, the Z-Score of the lumbar BMD has been calculated, and the mean values observed at the various visits have been compared with the baseline mean value, using the t test for paired data.
 Some parameters obtained by means of pQCT have also been analysed, using the same methodology as that for the densitometric parameters described above.
 In order to take account of multiple tests, Bonferroni's correction of the probability associated with each test has been applied.
 For each patient up to the age of 20, the frequency of fractures (number of fractures/year) observed during the treatment period, and the frequency of the fractures recorded in the two years prior to commencement of the trial have been calculated. The average values of the two frequencies have been compared by means of the t test for paired data. Furthermore, the proportions of the patients with fractures, observed before and during the treatment period, have been compared by means of the McNemar test.

➤ Results

- At March 2001, an interim analysis of 61 patients (25 males and 36 females) was performed. The paediatric population consisted of 10 males and 12 females (mean age: 12.0 ± 2.6 ; range: 7-17); typing of OI was I in 14 cases, III in 5 cases and IV in other 3 cases.
- Efficacy results
 By comparing the average number of fractures/year in the two years of treatment vs. the two years preceding the enrolment, a statistically significant reduction from 0.48 ± 0.46 to 0.23 ± 0.45 (-52%) was found ($p = 0.035$). The frequency of patients with fractures was 13 out 21 (one patient was excluded from analysis because of missing medical history) in the two years before the study, and 5 out 21 during the two-year treatment, with a statistically significant difference ($p = 0.039$).
 Bone densitometry showed a statistically significant increase in BMD of lumbar spine at 6, 12 and 18 months, while the increase at 24 months failed to reach the statistical significance because of the small sample size. A statistically significant increase in BMC and total area of lumbar spine was also observed. Similar results with a statistically significant difference vs. baseline were observed for BMD, BMC and area of femur and proximal radius.
 The average Z-Score of lumbar BMD showed a statistically significant ($p < 0.05$) improvement from -3.25 ± 1.74 at baseline, to -2.65 ± 1.88 at 6 months, -2.14 ± 1.66 at 12 months and -2.22 ± 1.97 at 18 months; again, the sample size at 24 months (four patients) was too small to perform a valid statistical analysis.
 The pQCT of proximal radius showed an increase in cortical area ranging +9.8% at 6 months to +28.7% at 24 months compared to baseline, as well as a less marked increase in the cortical density.

- Safety results

In addition to the bone fractures that have been already reported in Section 2.5.4 as criteria for efficacy, an acute phase reaction was observed in 13 out of 22 patients. The average duration of the acute phase reaction was 3.2 ± 1.8 days and no children needed to stop the medication.

Other two adverse events were observed in the study: one children experiencing trigeminal neuralgia and renal colic, and one patient with stomatitis and cutaneous eruption. The second case was considered as probably related to the treatment.

The values of all the haematology and blood chemistry tests, with the exception of creatinine, remained within the respective reference ranges. The mean value of serum creatinine was below normal at the baseline and remained below the normal at visits V3 (after 6 months) and V5 (after 12 months).

Assessor's Comment

Evidence from the NEROI suggests that intravenous neridronate increase BMD in children and adults with OI without further investigating the clinical significance of this to the patients. The number of patients is small and the follow up period is limited. Additionally the cohort is considered to be very heterogeneous as it appears to include mild as well as severe cases of OI. It is unclear whether either treatment decreases fractures; the number of post-treatment fractures is compared with historic data from 2 previous years and it is known from the natural history of OI that the fracture rate decreases with time as the child grows. In terms of the safety profile of neridronate, it appears to be well tolerated. The 2 cases of ADR are not presented in detail as they include events that are not currently included in the SmPC. However no similar ADRs have been identified in the data provided by the MAH in this review.

Prosecution of the NEROI study

The NEROI study has been continued after 2001 with some amendments to the protocol. More importantly, a 12-month “run-in” period with no treatment was introduced into the protocol in order to have a more accurate assessment of the incidence of fractures. Before 2001, the number of fractures occurring during the study was compared with a “historical” data related to the 24 months before the enrolment.

In other two consecutive amendments, the minimum age for enrolment has been progressively reduced to 3 years, earlier, and to 1 month, later. Thus, the paediatric population has been significantly enlarged.

These amendments and the consequential findings of the paediatric use of Neridronate were reflected in 2 published papers by the investigators' team.

Intravenous Neridronate in children with Osteogenesis Imperfecta: A randomized controlled study

Gatti et al, 2005

In 2005 Gatti et al have published a part of the results achieved in 64 pre-pubertal children, (boys 6–11 years, girls 6–9 years), with any type of OI and who were never treated with bisphosphonates. According to the amended protocol, they received either IV Neridronate (2 mg/kg every 3 months) or no treatment, with a ratio of 2:1. Control patients were given the same bisphosphonate therapy at the end of the first “run-in” year. Calcium and/or Vitamin D dietary intake was carefully monitored.

BMD and projected bone areas, as measured by DXA, at spine and hip, height, and peripheral fracture incidence, both prospective and retrospective, were the main outcomes of the study.

During the first year of observation, 45% of the patients of control group and 27% of the active group had at least one non-vertebral fracture but the difference was not statistically significant ($p=0.2$). The treated patients who fractured experienced most often a single fracture, and the overall number of fractures was significantly lower in the active than in the control group: 13 in 44 patients and 18 in 22 patients, respectively (RR = 0.36; 95% CI, 0.15–0.87; $p<0.05$).

At the end of the first year, spine and hip BMD rose by 3.5–5.7% in control patients and by 18–25% ($p < 0.001$ versus controls) in the active group, respectively. During the following 2 years, the treatment in all patients was associated with BMD increases of 10–25% per year. Height and the DXA-derived projected area of lumbar spine rose during the first year of observation significantly more in the active group than in the control group (<0.01 and <0.05 , respectively). Both height and spine projected area continued to rise in the treated patients toward levels found in healthy individuals.

Ten of the patients complained of flu-like symptoms, resembling a typical acute phase reaction 24–36 h after the first intravenous infusion, which lasted <36 h. An attenuated response was also noted by all of them after the second infusion. None of the patients complained of other side effects. Serum calcium and phosphate were within the normal range at all time-points before the neridronate infusions. Symptomatic hypocalcaemia was never reported.

Assessor's Comment

The results of this study support the previously documented effects of neridronate in children with OI. In the assessor's opinion the effect of the treatment on growth is inconclusive due to limitations of the study's design (i.e. 1 year duration of run-in period and lack of correlation with disease complications and functioning levels)

Early bisphosphonate treatment in infants with severe osteogenesis Imperfecta. Antoniazzi et al 2006

The objective of the study was to evaluate prospectively the efficacy of bisphosphonate treatment in infants with severe forms of OI.

10 children (4 males and 6 females), with a diagnosis of OI type III at the mean age of 33 days (range: 18-44 days) were enrolled in this study.

Five patients [group A] started treatment with neridronate (2 mg/kg IV for 2 consecutive days, every 3 months) at a mean age of 37 days (range 25-46 days), just after diagnosis. The other 5 patients [group B] were followed up for 6 months and started treatment at a mean age of 220 days (range 203-238 days). Patients were checked every 3 months until the age of 18 months. Ten children, matched for sex, age, and clinical severity of OI, whose charts were reviewed and collated, constituted an historical control group [group C].

The patients were reviewed for weight, length, and number of fractures every 3 months. Serum and urinary levels of calcium, phosphorus, creatinine (Cr), serum AP, 25-hydroxyvitamin D, insulin-like growth factor I (IGF-I), PTH and OC, urinary type I collagen N-terminal telopeptide (uNTX), and lateral radiography of vertebral column were conducted every 6 months.

The clinical results showed that in the first 6 months, patients in group A, grew significantly better in weight and length than those of groups B and C ($p<0.05$), and patients in group B grew better than those in group C, after the start of treatment, reaching a statistically significant difference versus the control group at 1.6 years of age ($p<0.05$).

Concerning the fracture rate, the incidence of radiologically confirmed fractures significantly decreased in group A in comparison to groups B and C (2.4 vs. 6.0 and 6.8 fractures/yr ; $p<0.05$) during the first 6 months of treatment. In the second 6 months both groups A and B had a significantly lower fracture rate in comparison to group C (2.0 and 2.8 vs. 5.4 fractures/yr ; $p<0.05$). No fractures sustained on treatment had clinical or radiographic impairment of healing

as assessed by routine radiologic study. No one child required intramedullary rod placement during the study period.

Laboratory data showed that the baseline OC and IGF-I levels were significantly lower than normal levels for age, whereas calcium phosphate ALP 25-OHD and PTH were in the normal range for age. Urinary uCa/uCr ratio and uNTX/uCr ratio were significantly higher than normal values for age. During neridronate therapy there were no significant changes in serum calcium, phosphate, and 25-OHD and a slight rise in ALP and PTH levels. Osteocalcin levels increased in group A from 2.5 ± 1.0 at the beginning to 5.4 ± 1.1 nmol/l after 12 months ($p < 0.05$ vs. group C). IGF-I levels increased in groups A and B after the start of treatment, but the increment was statistically significant only in group A ($p < 0.05$ vs. group C). uCa/uCr ratio and uNTX/uCr ratio showed a significant decline over time and uNTX/uCr ratio levels were significantly lower in treated compared with untreated patients ($p < 0.05$ vs. group C).

In 9 patients an acute phase reaction after the first infusion cycle was noted with short-term fever up to 38.5° C responsive to acetaminophen. During treatment, none of the patients showed urinary protein excretion, white blood cell count reduction, or respiratory distress syndrome. No infant missed a scheduled infusion because of difficulty with the protocol.

Assessor's Comment

The sample size is very small and the design of the study limits the significance of the findings. The follow up period is too short to provide robust evidence on the advantages of early treatment of infants with OI.

In the assessor's opinion, this is a very limited study that partly confirms findings from older children of the effects of neridronate treatment.

4. Discussion on clinical aspects

In the submitted studies, the very serious condition of paediatric OI is reviewed. In the recent years bisphosphonates have been the main drug class of clinical research into establishing safe and effective methods of treatment and prevention of long-term complications of the disease. The efficacy data from these studies reviewed here confirm the effect of neridronate, expected from other bisphosphonates on the skeleton. However the number of patients was overall very small, particularly in the younger age groups. Additionally the follow up periods of these studies are too limited in order to assess a likely positive long term effect of early treatment in the progress of the disease. In terms of safety, no major issues were noted with the use of neridronate in these studies. The acute phase reaction with myalgia and fever could represent a clinically significant problem, particularly in very young children if the first infusion cycles are to be administered outside a hospital environment.

Regarding the PD/PK profile of Neridronic acid, the MAH summarizes the findings from Registration study LCG 538/00. This was a single-centre, randomised, open, four-period cross-over study with the aim to determine the pharmacokinetic profile of Neridronic acid after IM and IV administration of 25 mg, and to evaluate the linearity of the kinetics after intravenous administration of 25, 50 and 100 mg of the drug to healthy adult volunteers. No PD or PK studies in the paediatric population have been provided and from the information provided it is not clear how the currently approved posology of 2mg/kg up to a maximum of 100mg has been established.

Assessor's Comment

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. Many, 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.

5. PSUR

The post marketing experience with Nerixia is summarized in the Periodic Safety Up-date Report (PSUR) submitted by the MAH, containing the safety data reported globally for the period since April 4, 2002 to September 30, 2006.

During this review period, an estimated 100,111 patients have been treated with Neridronate. These patients are thought to be mainly adults affected either by OI or by Paget's disease.

A total of 23 individual case safety reports (ICSR) including 72 adverse reactions fulfilled the criteria for inclusion in the main line listings. Four of these 23 ICSRs contained a total of 15 serious adverse reactions. All cases came from spontaneous sources. Most patients were adults or elderly, with only 1 patient reported to be 15 years.

The most commonly reported adverse drug reactions (ADR) were expected from the SmPC, i.e. pyrexia (11 events, corresponding to 15.3% of total ADRs), myalgia (9 events; 12.5%), musculoskeletal pain (3 events; 4.2%) and chills (3 events; 4.2%). Two or more of these events were often concomitant in the same patient, imputable to an acute phase response (increase in body temperature together with the presence of flu-like symptoms), a well-known reaction that could follow an intravenous or intramuscular administration of amino-bisphosphonates. For the intramuscular presentation other reported ADR were local symptoms, as pain and reactions at the injection site.

A summary with comments of the adolescent case was provided by the MAH:

“Case No. NE012002S – Code 43322 (Health Authority)

Myalgia, Pyrexia

Serious ICSR. A young boy (15-year-old) affected by osteogenesis imperfecta received an IV injection of neridronate at the dose of 100 mg (as Neridronic acid) on November 5, 2002. Next day the patient was hospitalized for a severe myalgia with fever that resolved after 24 hours until a complete recovery.

Comment (by the MAH): Myalgia and fever are typical reactions of the acute phase response, that could follow an intravenous or intramuscular administration of aminobisphosphonates. The mechanism of action is thought to be that aminobisphosphonates transiently stimulate the production of proinflammatory cytokines such as interleukin-1, interleukin-6, and tumor necrosis factor-alpha. So the reactions, expected for neridronate, are related to the treatment.”

No pregnancy reports with maternal exposure were received.

The MAH concluded that no new safety issues were identified from the current medical literature on neridronate.

Within the past 2 years, an increasing body of literature has suggested that bisphosphonates, especially zoledronic acid and pamidronate preparations, may be associated with osteonecrosis of the jaws. This is the reason why in Europe, recently, the Pharmacovigilance Working Party of EMEA initiated a study on adverse reactions affecting the bones in treatment with bisphosphonates. The study was intended to clarify whether degeneration of the jawbone (osteonecrosis) is an adverse reaction from treatment with bisphosphonates. Italian Health Authority was the Rapporteur for neridronate, so on June 2005 Abiogen Pharma was asked to submit an evaluation of the risk associated with neridronate treatment. The MAH's conclusions were that there is no evidence of a causal association between neridronate and osteonecrosis; nevertheless the MAH decided to support an introduction of a warning concerning the use of bisphosphonates and osteonecrosis of the jaw in the "precautions" section of the SPC in the interest of patient safety and physician awareness.

Assessor's Comment

The data provided in this safety review confirm that neridronate is generally well tolerated. No unexpected ADRs have been identified. The assessor agrees with the inclusion of a statement regarding the 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.

A 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 neridronate. 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).

6. Additional references

The following list of studies was originally submitted as under article 45 of the Paediatric Regulation by the MAH. These 2 published studies were not mentioned in the final submission or summarized by the MAH in the clinical overview report. However they have been included in the assessment and they are summarized below.

- **Reduction of plasma taurine level in children affected by Osteogenesis Imperfecta during bisphosphonate therapy** (2007). D'Eufemia P, Finocchiaro R, Zambrano A, Tetti M, Ferrucci V, Celli M. *Biomedicine & Pharmacotherapy* 61; 235-240
- **High levels of serum Prostaglandin E2 in children with Osteogenesis Imperfecta are reduced by Neridronate treatment** (2008). D'Eufemia P, Finocchiaro R, Celli M, Zambrano A, Tetti M, Villani C, Persiani P, Mari E, Zicari A. *Pediatric research* 63(2);203-206

Reduction of plasma taurine level in children affected by Osteogenesis Imperfecta during bisphosphonate therapy

D'Eufemia et al, 2007

The aim of the study is to investigate a possible interaction between pharmacological effects of bisphosphonates and amino acids (AAs) involved in bone tissue metabolism. The authors performed plasma and urine AA analysis in children affected by OI before and during treatment with bisphosphonates.

In the last decade a growing number of experimental and clinical studies indicates that several amino acids (AAs) are implicated in bone mineralization. Hydroxyproline represents a special AA abundant in collagen, where it plays a structural role. Arginine and lysine show a positive effect on human osteoblasts, which is related partly to the production of those factors required for matrix synthesis, and partly to the direct or mediated activation of cell proliferation. Taurine is localized in matrices of the bone and can regulate osteoblast metabolism with antiosteopenic effect.

Fourteen pre-pubertal children affected by different types of OI, aged from 2 to 11 years (mean 6.9 years) were enrolled in the study. None of the patients were previously treated with bisphosphonates. The treatment consisted of one infusion at a dose of 1 mg/Kg/body weight neridronate every 3 months. No adverse side-effects were noted apart from acute phase reaction during the first infusion cycle. Plasma and urine specimens for AA analysis were taken at baseline (T0) and three months after each infusion of four consecutive cycles (T1-T4). Bone mineral density (BMD) at lumbar spine was measured by DXA at baseline and after 6e12 months of treatment. The reference normal control group consisted of 20 healthy children matched for sex and age who underwent routinely haematological assessment. Control values have been compared with pre-treatment (T0) values of patients with OI.

Data were reported as mean±SEM. The within-subject changes in AAs and BMD in respect to the pre-treatment levels (T0) were tested by Student's t-test. Correlations were performed by linear regression analysis.

In the patient's group the plasma pre-treatment (T0) concentrations of AAs implicated in bone metabolism showed a significant increase of hydroxyproline in respect to the controls whereas basal urinary excretion showed no significant changes. A significant decrease in respect to the pre-treatment levels (T0) was observed after the fourth infusion for taurine. In addition, urinary excretion of this amino acid showed a significant decrease after the fourth infusion. No significant correlations were found between plasma level or urinary excretion of hydroxyproline, taurine, arginine and lysine in respect to bone mineral density.

The authors of the article concluded that it is likely to hypothesize that the decrease of plasma taurine found in this study could reflect the augmented bone requirements of this AA as a consequence of bone accrual induced by bisphosphonate treatment. Although the causes of this effect on taurine remain unclear, its biological implications should be further investigated to better understand the mechanism of bisphosphonates' action in OI and in other disorders of bone metabolism.

Assessor's Comment

This study is limited to a very small number of patients. It is noted that the dose used is lower than the one suggested in the SmPC (1mg/kg instead of 2mg/kg), without a clear indication for this dosing. The assessor agrees with the authors' conclusion that the finding of taurine reduction after treatment with neridronate should be further investigated in order to conclude on its clinical significance in the management of paediatric metabolic bone diseases.

High levels of serum Prostaglandin E2 in children with Osteogenesis Imperfecta are reduced by Neridronate treatment

D'Eufemia et al, 2008

The aim of the study was to evaluate the serum level of PGE2 in children affected by OI at basal time and during treatment with neridronate. Prostaglandins, especially prostaglandin E2 (PGE2), are known to be potent activators of bone remodelling and have been reported as having both anabolic and catabolic effect on bone. Furthermore, PGE2 can modulate type I and type III collagen production. Bisphosphonates are currently used in the treatment of several forms of OI. Their main effect is the reduction of bone turnover through decreasing bone re-absorption. In

addition, it has been recently reported that bisphosphonates modulate the release of proinflammatory mediators.

Sixteen prepubertal children affected by OI, aged from 2 to 11 y (median 6.9 years) were enrolled in the study. 11 children were diagnosed with mild form (type I) and 5 with severe forms of OI (type III/IV). None of the patients was previously treated with bisphosphonates and this study does not include patients who had experienced fractures, including vertebrae, in the previous 6 months. The treatment consisted of one infusion at a dose of 2 mg/Kg/body weight neridronate every 3 months. No adverse side-effects were noted apart from acute phase reaction within 24–48 h after first infusion cycle. Levels of serum PGE2 and biochemical parameters of bone metabolism (serum calcium, inorganic phosphorus, creatinine, total and bone alkaline phosphatase), and urinary creatinine, calcium, and c-terminal telopeptide of collagen-I (CTx) were assayed at baseline (T0) and immediately before the 3rd (T1) and 4th (T2) cycle of treatment (6 and 12 months after the start of treatment, respectively). Bone mineral density (BMD) at lumbar spine (L1–L4) was measured by DEXA at baseline (T0) and after 6 months (T1) and 12 months (T2) of treatment. The reference normal control group consisted of 16 healthy children matched for sex and age who underwent routine haematological assessment. Control values have been used to compare with pre-treatment (T0) values of patients.

Data were reported as mean±SD. The data do not appear to be normally distributed and may be log normal. It has been therefore applied the Mann-Whitney nonparametric test to compare the OI subjects with the controls and the Wilcoxon test to compare the values of PGE2, BMD, and biochemical parameters of bone metabolism between T0, T1, and T2. Correlations were performed by Spearman's rank correlation test. A result is considered statistically significant if $p < 0.05$.

At baseline the level of serum PGE2 of 11 patients affected by mild OI (type I) and the 5 patients affected by severe OI (type III/IV) showed values significantly higher in respect to the controls. No significant correlations were found at baseline between serum PGE2 levels, BMD, and biochemical parameters of bone metabolism, including bone apposition (bone alkaline phosphatase) and re-absorption (urinary CTx/creatinine) markers. After two cycles of neridronate treatment (T1), a significant reduction of serum PGE2 in respect to the baseline (T0) levels was observed both in mild and severe forms. Following the fourth infusion (T2), there was a further significant reduction of serum PGE2 levels. There were no statistically significant differences in serum PGE2 levels between mild and severe forms at baseline and during treatment. No significant correlation was found between percentage variation (T0–T2) of serum PGE2 level and percentage variation (T0–T2) of BMD or biochemical bone parameters.

The results of this study prove that serum PGE2 basal levels are increased in children with OI, a disease characterized by high bone turnover rate, in which there is no evidence of chronic proinflammatory activation. These results are an indication of the complex role of this cytokine in regulating bone remodelling. It is not clear why PGE2 are increased in children affected by OI. The results suggest that in patients with OI the increased basal serum PGE2 levels can be attributed to excessive PGE2 release, perhaps mediated by COX-2 activation induced by mechanical stress in bone tissue. Whether the role of PGE2 in the pathogenesis of OI has an importance comparable with that reported in inflammatory-mediated bone loss conditions is not known. The investigators correlated basal serum PGE2 levels and BMD and biochemical parameters of bone remodelling, but no statistically significant results were found. These could be partly related to the small size of the study and the heterogeneity of the disease. The authors concluded that in the present study very high basal serum PGE2 levels in OI children were observed, which were consequently lowered by neridronate treatment. These results could be important for the understanding of the role of metabolic factors in the pathogenesis of OI and the mechanism of action of bisphosphonates. This may have important implications for the management of bone loss in non-inflammatory diseases associated with proinflammatory activation.

Assessor's Comment

This is a very interesting study to evaluate the effects of bisphosphonates on PGE2 levels in patients with OI. However the findings from such a small number of patients should be interpreted with caution. The assessor agrees with the conclusion of the investigators that further research is needed in the pathogenesis of OI and other paediatric metabolic bone conditions.

III. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION ON DAY 89

The use of neridronate is essentially confined to Italy. The use of bisphosphonates in children with OI has become a common clinical practice, however there are some concerns on the safety of their use in the growing skeleton. It is therefore considered important that the MAH review the long term outcomes of the OI children that have been treated with Neridronate in Italy, as this might be an easily identifiable and accessed cohort. Assessment of the degree of disability should be reviewed in addition to the overall fracture incidence and other safety outcomes to give evidence on the overall effect of the treatment.

As a conclusion the presented data do not present any new evidence on the safety and efficacy for the use of Neridronic acid for the paediatric population with OI. However the SmPC should be updated with specific wording regarding the use in the paediatric population for the licensed Osteogenesis Imperfecta indication listed in section 4.1. Similarly in section 4.2, comprehensive dosing recommendations should be available for the paediatric population. The MAH should review all available data and propose an update to the SmPC. The proposal should be justified by supporting data from the MAH databases and relevant published data.

IV. MAH RESPONSE TO THE PRELIMINARY PDAR DAY 89

The MAH submitted a response to the Preliminary PdAR, dated 05/10/2009. In the cover letter the company concludes that, based on the existing data on the currently licensed indication of OI, a proposal for SmPC wording changes is appropriate for paediatric use in section 4.1 and 4.2. The MAH has also submitted suitable wording changes to be included in the PIL, reflecting the SmPC changes in the paediatric indications and posology. It is also noted that having already submitted an extended review of the available data on the initial submission on March 2009, the MAH does not present any further overview and "any new data emerging from the completion of the final report of the study foreseen by the end of 2010 will be submitted as a separate procedure as suggested".

In section 4.1 of the proposed SmPC the authorised indications have been split for adults and children by the MAH due to the fact that "... while OI can affect both adults and children, Paget's disease does not affect children. "

The proposed wording for section 4.1 is :

4.1 Therapeutic indications

Adults

Osteogenesis imperfecta.

Paget's Disease

Children

Osteogenesis imperfecta.

In section 4.2 of the proposed SmPC wording reflects the exclusive intravenous route of administration in children . the applicant also concludes that “the proposed variation also clarifies the fact that in children also dosages below 25 mg can be administrated”.

The proposed wording for section 4.2 is :

4.2 Posology and method of administration

Osteogenesis Imperfecta

Adults

From 25 mg to 100 mg IV, based on body weight, in one administration by slow infusion (at least 2 hours). Prior to administration dilute in 250-500 ml of physiological solution. The indicative posology is of 2 mg/kg body weight every 3 months. The total dosage can be fractioned in intramuscular dosages of 25 mg/die up to 4 consecutive days every 3 months.

Children

The indicative posology is of 2 mg/kg body weight up to 100 mg IV in one administration by slow infusion (at least 2 hours), every 3 months. Prior to administration dilute in 250-500 ml of physiological solution.

Paget’s Disease:

The most commonly recommended dosage is 100 mg/day intravenous, for 2 consecutive days, by slow infusion (at least 2 hours) by previous dilution in 250-500 ml of physiologic solution. Lower dosages can be sufficient for less severe forms of the disease. The chance to repeat the therapeutic cycle must be evaluated after at least 6 months, when the therapeutic effect on bone turnover (serum alkaline phosphatasemia) of the first cycle has completely been expressed.

Assessor’s Comment

The applicant in the response to Day 89 preliminary PdAR provides proposed wording changes to the SmPC and PIL without submitting any additional data reflecting of this decision. No additional information is provided to reflect the MAH’s response to the rapporteur’s overall conclusions. Specifically regarding the rapporteur comments on safety concerns as also raised by Italy, no additional information is provided. In the preliminary response dated 29/07/09 the MAH foresees some additional efficacy and safety information to be available in 2010 and confirms the intention to submit the final report at due course.

The proposed separation of the indications in section 4.1 for the adult and the paediatric population is acceptable and the rapporteur agrees with the applicant’s view that Paget’s disease is not relevant to children 0 to 18 years of age.

Regarding section 4.2 the applicant proposes a dosing regime without any explanation of the rational (PK data or otherwise). However the rapporteur notes that the proposed dose is the one utilised in the NEROI study that led to the initial licensing of Neridronate in children with OI and it is therefore considered acceptable. The rapporteur does not however agree with the MAH’s comment that this variation provides information on the usage of lower doses as only a maximum of 100mg is mentioned and no other restriction. The proposed wording for section 4.2 has been revised to better reflect the European SmPC guideline (See below in section V of this report).

V. MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION

Overall the proposed changes in the SmPC and PIL of Neridronate reflect the existing paediatric information available as submitted by the MAH during this European work-sharing procedure under Article 45. However as new evidence become available on the long term use of Neridronate in the paediatric OI population from the completion of the NEROI study, the 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.

SmPC wording Recommendation

Section 4.1: Acceptable as proposed by MAH:

4.3 Therapeutic indications

Adults

Osteogenesis imperfecta.

Paget's Disease

Children(less than 18 years of age)

Osteogenesis imperfecta.

Section 4.2 : Amendment to the proposed wording for the paediatric OI use

4.4 Posology and method of administration

Osteogenesis Imperfecta

Children (less than 18 years of age)

The recommended dose is 2mg/kg body weight (maximum 100mg) by slow intravenous infusion (over at least 2 hours) every 3 months. Prior to administration the injection is diluted in 250-500 ml 0.9% Sodium Chloride.

PIL Wording recommendation

“What Neridronic acid is used for:

Neridronic acid can be used in adults to treat Paget's Disease and Osteogenesis imperfecta. In children less then 18 years Neridronic acid can be used to treat Osteogenesis imperfecta”

“Posology, method and time of administration.

Children

Osteogenesis Imperfecta

The recommended dose is 2mg/kg body weight (maximum 100mg) by slow intravenous infusion (over at least 2 hours) every 3 months. Prior to administration the injection is diluted in 250-500 ml 0.9% Sodium Chloride.”

The applicant is requested to submit a Type 2 variation to update the SmPCs and PILs of products containing the active ingredient Neridronate in line with the above work-sharing recommendations within 60 days of this report.

VI. MEDICINAL PRODUCTS AND MARKETING AUTHORISATION HOLDERS INVOLVED

NERIXIA MAH: Abiogen Pharma SpA