SCIENTIFIC DISCUSSION

1. Introduction

Darbepoetin alfa (Aranesp®/Nespo®) was approved in the European Union in June 2001 via a centralised procedure. Its active substance is a modified form (ie. with 2 additional sialic acid-containing carbohydrate chains) of recombinant human erythropoietin (rHuEPO), produced in Chinese hamster ovary cells by recombinant DNA technology. It has a prolonged half-life and increased biologic activity relative to rHuEPO. The 2 additional N-glycosylation sites result from 5 amino acid substitutions in the erythropoietin peptide backbone. The additional sugar residues are molecularly indistinct from those on rHuEPO.

Darbepoetin alfa is currently indicated for use in:

- Treatment of anaemia associated with chronic renal failure (CRF) in adults and paediatric subjects ≥ 11 years of age
- Treatment of symptomatic anaemia in adult cancer patients with non-myeloid malignancies receiving chemotherapy

The company is requesting an amendment to the present indication in order to allow treatment to CRF paediatric subjects, in addition to adults, as follows:

- Treatment of anaemia associated with chronic renal failure in adults and paediatric ~~subjects ≥ 11 years of age~~patients.
- Treatment of symptomatic anaemia in adult cancer patients with non-myeloid malignancies receiving chemotherapy

As a consequence of the requested new indication, the MAH is also applying for major changes to sections 4.2 (posology) and 5.2 (Pharmacokynetic properties), and other changes in section 10 of the SPC.

2. Clinical aspects

Rationale for the proposed change
The scope of this variation is the expansion of the pediatric application to the use of darbepoetin alfa in paediatric chronic renal failure subjects ≤ 11 year of age.

The original marketing application for darbepoetin alfa included interim data from an open-label, single-dose, crossover, pharmacokinetic study (980212) in paediatric subjects with chronic kidney disease (CKD; a term used to represent the spectrum of kidney disease) who were between 3 and 16 years of age. Based on final data from study 980212, the use of darbepoetin alfa for the treatment of anemia in pediatric patients with CKD was subsequently approved for children ≥11 years.

In support of this variation application the MAH has submitted two pharmacokinetic studies (980212 and 200000126) and one efficacy study (200000100).

- *Pharmacokinetic Studies*

1. Study 980212

Study Design
An open-label, multicenter, 2-period, 2-treatment, randomised, cross-over study to determine the pharmacokinetics of darbepoetin alfa in 13 paediatric patients (between 1 and 16 years of age) with chronic renal failure on dialysis or not on dialysis or end-stage renal disease (ESRD). Five US centers recruited patients between 14 April 1999 to 19 November 1999.

Treatments
Each subject received 2 doses of darbepoetin alfa . The first dose of darbepoetin alfa (0.5 µg/kg) was administered intravenous (IV), followed 14 to 16 days later by subcutaneous (SC) injection (or vice versa determined by the randomisation sequence).

Objective
To determine the pharmacokinetics and safety of a single dose of darbepoetin alfa given either IV or SC in paediatric patients with CRF receiving dialysis or not.

Endpoints
Efficacy end points
The primary end point was the $t_{1/2,z}$ of darbepoetin alfa after IV and SC dosing.
The secondary endpoints were the followings:

- IV Dosing, C_0 (peak concentration at time zero), AUC 0-∞, MRT 0- ∞ (mean residence time to infinity), CL, V_0 (initial volume of distribution.
- SC Dosing: C_{max}, T_{max}, AUC (0-∞), MRT (0-∞), F (bioavailability), CL/F.
- Safety endpoints: Reporting of adverse events, NESP antibody formation and others.

Blood sampling and analytical methods
Blood for determination of darbepoetin plasma concentrations was drawn at baseline and at predefined time points up to 168 hrs post dose during each sequence. Timing for blood draws slightly changed and the number of blood draws reduced after the enrolment of the first 7 patients but the total duration of sampling remained unchanged. Serum samples for the detection of darbepoetin alfa antibodies were taken before the first dose of darbepoetin alfa, on study day 15 and at the end of the study. Two assays were used, a radioimmunoprecipitation (RIP) screening assay and a cell-based bioassay to detect antibodies that neutralize or inhibit the activity of darbepoetin alfa.

Drug concentrations were determined using a conventional solid-phase sandwich serum enzyme immunoassay.

Statistical methods
The primary PK analysis was performed using non-compartmental methods and baseline corrected serum concentrations of darbepoetin alfa ANOVA was performed on pooled data. In addition, if a significant treatment-by-period interaction was found, the analyses were performed using the first study period. All serum concentrations below the limit of quantification of the assay were considered zero. Actual sampling times were used for estimation of parameters.

Compartmental modelling was also performed as a secondary analysis.

Patient characteristics
Seven male and 6 female patients with a median age of 13 years were enrolled. Patients were distributed in subgroups of age (1-6 years: 1 patient each in the IV-SC group and in the SC-IV group (3 and 4 years of age), 7-11 years: 2 patients in each group, 12-16 years: 4 subjects in the IV-SC group and 3 patients in the SC-IV group).

The mean Hb concentration was 11.93 g/dl in the IV-SC group and 10.62 g/dl in the SC-IV group.
All patients had been receiving rHuEpo before enrolment into the study.

10 subjects were receiving dialysis (one of them peritoneal dialysis and 9 subjects hemodialysis) and the 3 remaining patients were not on dialysis.

PK results
Twelve out of the 13 patients enrolled received study medication. Of these, 10 IV profiles and 8 SC profiles could be extrapolated. No treatment-by-period interactions or period effects were observed, although the ability to detect these effects was limited by the small sample size. Mean Cmax was about 10 fold and AUC 2-fold higher after IV administration in comparison to SC administration. Mean $t_{1/2}$ was longer after SC application.

Safety
Adverse Events
Nine of the 12 subjects receiving study drug reported at least one AE, all of which were mild to moderate in severity. The most frequently-reported AE was injection site pain (4 subjects). Three subjects experienced 4 mild adverse events (3 events of injection site pain and 1 headache) that were considered treatment-related by the investigator.

SAE's
No deaths, SAEs or adverse events leading to withdrawal occurred during the study.

Laboratory findings
No Hb values above 13 g/dL were reported.

Inmunological
No anti-epoetin antibodies were detected in any subject.

3. Study 200000126

Study Design
An open-label, multicenter, single-arm, pharmacokinetic study of darbepoetin alfa administered by SC injection for the treatment of anemia in paediatric subjects with non-myeloid malignancies receiving multicycle chemotherapy. Subjects completing the primary 6-dose treatment phase could continue to receive darbepoetin alfa in a treatment-extension phase. Five US centers recruited patients between 13 April 2001 to 22 November 2002.

Objective
To assess the PK profile and the tolerability of SC administered darbepoetin alfa in paediatric patients with nonmyeloid malignancies who were receiving multicycle chemotherapy.

Treatments
Subjects were to receive 6 doses of darbepoetin alfa 2.25 μg/kg administered SC beginning on the first day of the next cycle of chemotherapy. After the first administration of darbepoetin alfa, blood samples were collected for the evaluation of the PK profile over a 10-day period. Subjects then received 5 additional doses once weekly with samples being collected on a weekly basis.

Subjects who completed the 6-dose (7-week) primary treatment phase could continue to receive darbepoetin alfa through the end of their planned course of chemotherapy in a treatment extension phase.
All subjects were to complete a 1-week follow-up period after the last dose of darbepoetin alfa. Dose adjustments were made in case of Hb values outside the age specific target range.

Subjects
Main inclusion criteria:

- Patients younger than 18 years of age with nonmyeloid malignancies
- anaemia (Hb ≤ 11 g/dl for subjects 0 to 11 years and 12,0 g/dl for subjects 12 to 17 years)
- minimum body weight of 15 kg
- at least 6 additional weeks of cyclic chemotherapy planned
- ECOG performance status of 0 to 2
- anemia predominantly due to the cancer or chemotherapy (i.e. serum folate ≥ 2.0 ng/ml, Vitamin B12 ≥ 200 pg/ml, no hemolysis, no GI bleeding)
- Adequate renal and liver function.

Treatment with rHuEPO within 4 weeks before enrolment or prior treatment with darbepoetin alfa were exclusion criteria.

Endpoints
Efficacy endpoints
Primary PK endpoints: CL/F, t ½,z, Tmax
Secondary PK endpoints: AUC (0-t), AUC (0-∞), Vz/F, Cmax
Efficacy endpoints: proportion of subjects 1) with RBC transfusions, 2) achieving Hb response (≥ 2.0 g/dL increase in the absence of RBC transfusion), 3) Hb response or Hb concentration ≥ 12.0 g/dL; weekly mean change in Hb from baseline.

Analytical methods
Serum samples for the detection of NESP antibodies were taken before the first dose of NESP, on study day 15 and at the end of the study. Two assays were used, a radioimmunoprecipitation (RIP) screening assay and a cell-based bioassay to detect antibodies that neutralize or inhibit the activity of NESP

Safety endpoints
AEs, concomitant medication, anti NESP antibodies, laboratory values, vital signs, RBC transfusions, Hb above allowed range.

Analytical methods
Drug concentrations were determined using an ELISA (Quantikine IVD human erythropoietin enzyme-linked immunosorbent assay, R&D Systems, Minneapolis, MN, USA) at MDS Pharma services (Montreal, Quebec, Canada).

Statistical methods
Enrolment was stratified by subject age (0 to 11 years and 12 to 17 years) to provide a more balanced representation of NESP PK in the paediatric population.

Patient characteristics
A total of 16 subjects were enrolled into the study, 12 male and 4 female patients (mean age of 11.8 years, range 5 to 18 years, 7 patients were age ≤ 11 years). Ewing´s sarcoma was the most common primary tumour type (N=4); 3 patients had rhabdomyosarcoma, 2 patients had Wilm´s tumour, Hodgkin disease or osteosarcoma respectively and 5 patients had pulmonary metastasis and no patient had liver metastasis.

All subjects had received prior chemotherapy. The mean number of prior cycles of chemotherapy was 9.2 (range: 3 to 23) and 5 patients had received prior radiotherapy. All subjects received chemotherapy during Study 200000126. The most frequently administered agents were cyclophosphamide, etoposide, and vincristine (75% for each agent)

The mean baseline Hb level was 9.41 g/dl (SD 1.17). The mean baseline endogenous erythropoietin concentration was 86.74 (SD 165.39 mU/ml). One subject had an extremely high baseline erythropoietin level of 695.7 mU/ml and was therefore excluded from analysis. Fifteen patients completed the study, one patient discontinued at week 3 (withdrawal of consent) and 10 patients participated in the extension phase.

PK Results
Single dose intensive PK profile
Fifteen subjects were included in the pharmacokinetic analysis. One subject was excluded because of a high baseline erythropoietin value. Extrapolated pharmacokinetic parameters ($t_{1/2,z}$, $AUC_{(0-\infty)}$, CL/F and V_z/F) were summarized for 11 of the 15 subjects. Of the 4 subjects not included in the summary statistics, 1 subject received a dose of darbepoetin alfa > 10% of the nominal dose, and for 3 subjects the terminal phase could not be reliably extrapolated because of the impact from chemotherapy.

After SC administration, absorption was slow, with the maximum concentrations (mean±SD 10.5±3 ng/mL) occurring at 24 to 143 hours (mean 71 hours) post dose. Darbepoetin alfa exhibited a long terminal half life (mean 49.4 h). Mean relative clearance was 1.87 mL/hr/kg. Concentrations had declined to near-baseline levels by 336 hours post dose.

Adverse Events
Fifteen of the 16 patients reported ≥1 AEs, most commonly fever (50%), granulocytopenia (38%), vomiting (38%), injection site pain (31%), and abdominal pain (31%). Six subjects reported AEs that were considered related to darbepoetin alfa by the investigator, mostly mild injection site pain and injection site erythema).

Adverse events of special interest
Three of the 6 AEs of historical interest for CKD subjects were also considered relevant for oncology subjects and analyzed separately for Study 20000126: hypertension, convulsions (seizures), and thrombotic events. No convulsions or thrombotic events were reported during this study. One subject had hypertension, which was mild in severity. This event was not considered related to darbepoetin alfa by the investigator and was not associated with an elevated or rapid increase in Hb concentration.

Serious adverse events and deaths
Nine subjects reported SAEs, most commonly fever (44%) and granulocytopenia (31%), which are consistent with those expected for subjects with cancer undergoing chemotherapy (Walsh et al, 2001).

One subject experienced moderate gastrointestinal haemorrhage and limb pain considered serious and related to darbepoetin alfa by the investigator but was not withdrawn from therapy. No patient died during the study.

Laboratory findings
Two subjects ≤ 11 years of age had a Hb excursion of > 13.0 g/dL during the study. One patient had a Hb concentration of 14.6 g/dL within 28 days after receiving a RBC transfusion. No clinical sequelae were reported for this subject. The other patient had a Hb concentration of 14.4 g/dL during the study. This subject experienced dehydration at the time of the excursion and returned to 10.2 g/dL one week later. Darbepoetin alfa was not withheld for either subject, which was a deviation from the protocol. None of the subjects ≥ 12 years of age had a Hb excursion.

No unexpected changes in haematological parameters were observed during the study. As expected for subjects receiving chemotherapy, individual laboratory AEs related to decreases in blood cell counts were reported during the study (e.g. granulocytopenia) None of these AEs were considered related to treatment.

Inmunological
No anti-epoetin antibodies were detected in any subject.

- ***Efficacy study***

4. Study 200000100

Study Design
Open-label, multicenter, randomised, non-inferiority study of NESP and recombinant human erythropoietin (rHuEPO) for the treatment of anemia in paediatric subjects with CKD or end-stage renal disease (ESRD) receiving dialysis. A 20-week dose titration period was followed by an 8–week evaluation period. Forty nine US centers recruited patients between (4 August 2000 to 23 July 2004).

Subjects
Inclusion criteria:
- Patients 1 to 18 years of age with chronic renal failure (GFR < 30 mL/min/1.73 m^2)
- clinically stable (as judged by the investigator)
- 2 Hb values, 1 during screening and 1 at baseline, within 9,5 and 12,5 ng/dl)
- stable therapy given by IV or SC route of administration for at least 8 weeks before randomisation (Stable was defined as ≤ 25% change in prescribed dose over 8 weeks, same route of administration and no more than 1 missed or withheld dose during each of the two 4-week periods before randomisation)

- TSAT (transferrin saturation) ≥ 20% at the time of randomisation
- serum albumin ≥ 3.0 g/dl

Main exclusion criteria: hypertension, severe hyperparathyroidism, inflammatory disease, malignancy, RBC transfusion within the past 8 weeks

Treatments
Patients were randomly assigned in a 2:1 ratio to receive either darbepoetin alfa once weekly (QW) (if previously receiving rHuEPO 2 or 3 times weekly) or once every other week (Q2W) (if previously receiving rHuEPO QW). Subjects randomised to continue rHuEPO therapy were to maintain their schedule and route of administration. The weekly starting dose of NESP was calculated based on a subject's rHuEPO dose for 2 weeks (dose conversion factor: 100 IU rHuEPO = 0.42 µg NESP).

Dose adjustments
Hb was measured weekly throughout the study. The dose of darbepoetin alfa or rHuEPO was adjusted in 25% increments/ decrements of the starting dose throughout the study to maintain subjects' haemoglobin concentration within 10.0 to 12.5 g/dl for up to 28 weeks. After a dose change, 2 further consecutive weekly Hb determinations had to be outside the target range before the dose could be changed again. If medically indicated, more frequent dose changes were possible. If Hb value was above 14 g/dl, study drug was withheld until the Hb concentration decreased below 12.5 g/dl. The dose of study drug was then reinitiated at 75% of the last weekly dose given before withholding.

Objectives
To demonstrate that darbepoetin alfa is comparable (non-inferior) to rHuEPO for treatment of anemia in pediatric subjects with CKD receiving and not receiving dialysis and to determine the safety and tolerability of darbepoetin alfa in this pediatric population.

Outcomes/endpoints
Primary: change in Hb level between the screening/baseline period and the evaluation period
Secondary:
- Average weekly dosage of darbepoetin alfa during the evaluation period
- Percentage of Hb values within the target range during evaluation period
- Safety and tolerability of darbepoetin alfa (adverse events, vital signs, laboratory parameters, red blood cell transfusions, dose adjustments, darbepoetin alfa antibody formation)

Analytical Methods

Blood samples were collected before the first dose and at the end-of-study visit for assessment of anti-darbepoetin alfa antibodies. Immunogenicity testing in the reference group was not foreseen in the protocol and only performed when clinically indicated.

Two validated assays were used. The first was Biacore 3000 (Biacore International, AB, Uppsala, Sweden) immunoassay to detect the presence of antibodies and to characterize the nature of antibody binding and antibody classes. Biacore positive samples (> 0.250 g/ml) were routed to a cell-based bioassay to detect neutralizing or inhibiting effects. If a sample was positive in both assays, a subject could then be defined as positive for the development of neutralizing antibodies (anti-darbepoetin alfa or anti-epoetin alfa antibodies).

Sample size
A sample size of 120 subjects (80 darbepoetin alfa, 40 rHuEPO) was estimated to be sufficient to provide approximately 80% power for demonstrating that darbepoetin alfa was non-inferior to rHuEPO, including a 35% drop out rate.

Statistical methodology
Randomization was stratified by age into one of three age groups (1 to 5, 6 to 11, and 12 to 18 years) and study center.

Definition of Non-inferiority: If the lower limit of the 95% CI for Hb change from baseline in the darbepoetin alfa group minus the change from baseline Hb in the rHuEPO group was greater -1.0 g/dl, darbepoetin alfa was considered non-inferior to rHuEPO.

The primary analysis employed an ANCOVA model with age group as covariate. For the secondary analysis an ANOVA was used.

The primary efficacy analysis was carried out using the per protocol (PP) analysis set. A secondary efficacy analysis was conducted using the modified intention to treat (mITT) analysis set (i.e. all subjects who received at least one dose of investigational product).
Exploratory analyses were performed on different subgroups (e.g. age groups, sex and disease status)
No interim analysis was planned or conducted.

Subject disposition
A total of 124 subjects were randomly assigned into the study, 82 to darbepoetin alfa and 42 to rHuEPO. One hundred and twenty three patients (99.2%) out of the 124 randomised patients received investigational product and 95 subjects (76.6%) completed the study. There was no obvious difference in discontinuation rates or reason for discontinuation between the treatment groups

Baseline data
There were 51 girls and 73 boys included in the study (mean age was 12.3 years -range 1 to 18 yrs-. In the 1 to 5, 6 to 11, and 12 to 18 year old patient groups, 10, 18 and 54 patients were allocated to darbepoetin alfa and 4, 10 and 28 subjects were allocated to rHuEPO, respectively.

Baseline mean Hb concentrations were 11.35 and 11.10 g/dl in the darbepoetin alfa and rHuEPO groups, respectively. The main cause of renal failure was glomerulonephritis or urologic. In the darbepoetin alfa group, the percentage of patients with glomerulonephritis was higher and the percentage of patients on dialysis lower and the mean duration of dialysis shorter compared to the rHuEPO group. Nevertheless, in both groups the majority of patients was already on dialysis.

Efficacy results
Of the 123 subjects randomly assigned and receiving treatment, a total of 86 subjects (69.4%) were evaluable for the primary efficacy analysis. More patients in the darbepoetin alfa group (72%) compared to the rHuEPO group (64.3%) were evaluable. The primary reason for exclusion was failure to complete the evaluation period or Hb measurements < 6 during evaluation period.
All 123 patients receiving at least one dose of investigational product were included in the secondary mITT analysis.

Treatment schedule for darbepoetin alfa was once weekly (QW) for 80% of patients and twice weekly (Q2W) for 20 % of patients. In the rHuEpo group, 60%, 15% and 25 % of patients received treatment 3 times a week, Q2W and QW, respectively.

Regarding the primary endpoint, there was a minor increase vs. a minor decrease in mean Hb from baseline to the evaluation period in the darbepoetin alfa vs. rHuEPO group, respectively. The lower limit of the 95% CI for the treatment difference was -0.45 g/dL indicating non-inferiority of darbepoetin alfa compared rHuEPO therapy according to the predefined criterion. Results were comparable in the mITT analysis (treatment difference 0.22 g/dL, 95% CI [0,47, 0,92]).

The percentage of Hb values were within the target range (10.0 to 12.5 g/dl) during evaluation period for 75% of patients in the darbepoetin alfa group and for 72.6 % of patients in the rHuEpo group. Results were comparable when using the mITT analysis set (74% and 76% respectively).

For the different age groups, 1-5, 6-11, and 12-18 year-old-group, the percentage of patients with Hb within the target range was 83%, 65% and 75% for the test group and 58%, 72% and 79% for the reference group respectively.

In terms of weekly dose of study drug during the evaluation period, the mean for Darbepoetin alfa dosage decreased slightly during the treatment period whereas the mean rHuEPO remained essentially unchanged. The mean weekly weight-adjusted doses at baseline and during the evaluation period, respectively, were 0.89 and 0.76 µg/kg in the darbepoetin alfa group and 194 and 180 U/kg/week in the rHuEpo group.

In the phase 3 study conducted in adults, the weekly weight-adjusted doses at baseline and during the evaluation period, respectively, were 0.85 and 0.72 µg/kg/week in the darbepoetin alfa group and 167 and 177 U/kg/week in the rHuEpo group. Red blood cell transfusions were required by 6% of patients of the darbepoetin alfa group and in 14% of patients of the rHuEpo group.

Safety Results
All patients receiving at least one dose of study drug were included in the safety analysis.

In the darbepoetin alfa group, 81 patients were treated for a mean duration of 23.9 weeks. Of those, 62 patients (76.5%) were on study drug for more than 24 weeks.

In the rHuEpo group, 42 patients were treated for a mean (range) duration of 24.8 weeks. Of those, 28 patients (66.7%) were on study drug for more than 24 weeks. For the safety analysis set, the weight corrected mean weekly dose was 0.78 µg/kg/week (0.1 to 3.8) for darbepoetin alfa and 183.82 (40.4 to 513.7 U/kg/week) for the reference product.

Adverse Events
Adverse events (AEs) occurred in 86% and 83% of the darbepoetin group and the rHuEpo group, respectively. There were no marked differences in the frequency and type of AEs between treatment groups. The most common AEs were fever (20% vs. 29%, respectively), headache (19% vs. 24%), upper respiratory infection (19% vs. 14%) and worsening hypertension (16% vs. 17%).

Adverse events of special interest
Six AEs of historical interest were analysed separately: hypertension, myocardial infarction, convulsions (seizures), vascular access thrombosis, transient ischemic attack, and cerebrovascular disorder. The incidence of hypertension and convulsions were similar between the treatment groups, while a higher percentage of subjects administered rHuEPO (10%) had vascular access thrombosis compared with darbepoetin alfa (5%) . No subjects in either group experienced myocardial infarction, transient ischemic attack, or cerebrovascular disorder during the study. When analyzed by subject exposure, the rate of hypertensive events was 35 events/100-subject years for both treatment groups.

Serious adverse events and deaths
Serious adverse events (SAEs) occurred in 40% and 48% of the darbepoetin and the rHuEpo group, respectively. The most common SAEs were fever (9% test vs. 7% reference), sepsis (9% vs. 0 %), access infection (6% vs. 2%), access complication (4% vs. 10%) and renal failure (3% vs. 7%).
In each group, two subjects had a SAE which was considered related to treatment.
Thrombosis of the vascular access and access stenosis occurred in 2 subjects of the darbepoetin alfa group and thrombosis of the vascular access and a positive measurement for non-neutralizing antibodies to rHuEpo occurred in 2 subjects of the rHuEpo group. One subject in the darbepoetin alfa group died due to renal failure.

Laboratory Findings- hemoglobin excursions
In the darbepoetin alfa group, 22 (27%) subjects had a Hb excursion ≥ 14.0 g/dl compared with 10 (24%) patients in the rHuEpoetin group. The median time to decrease to ≤ 12.5 g/dl was 3.1 (1.0 to 5.0) and 2.3 weeks (2.0 to 4.7 weeks) in the test and in the reference group respectively.

Immunological events
A total of 81 patients had antibody testing performed, 80 treated with darbepotin alfa and one patient treated with rHuEPO. Seventy-three (90%) and 70 (86%) of subjects in the darbepoetin alfa group, respectively, had baseline and end-of-study samples analyzed. Of these subjects, 7 (9.6%) tested positive at baseline (pre-existing antibodies) and 6 (8.6%) at the end of the study. Two previously

antibody negative patients developed binding**,** non-neutralizing antibodies during the study. All subjects tested in the bioassay were negative for neutralizing antibodies to darbepoetin alfa or epoetin alfa.

Discontinuation due to AE
Withdrawals from the study due to an AE occurred in 4 subjects of the darbepoetin alfa group and in none of the rHuEpo group. Three of these events leading to withdrawal were considered related to study medication: 2 subjects had injection site pain and 1 subject had moderate hypertension.

DISCUSSION

Efficacy
The current indication of Aranesp includes only adult cancer patients with non-myeloid malignancies receiving chemotherapy. The used dosage of 2.25 µg/kg per week in the present study is in accordance with that recommended for treatment of chemotherapy-induced anaemia in adult cancer patients.
Overall, the PK data submitted and the comparison of study results with those obtained in adult patients with CKD or chemotherapy induced anaemia suggest that the PK profile of darbepeotin alfa (single dose) is not substantially different between children and adults supporting a common starting dose as is the case for other epoetin containing products. The present results are generally in line with the ample experience obtained with other epoetin containing medicinal products demonstrating effective use in children with chronic renal failure and recommending the same posology for anaemia correction in children and adults. In addition, the numbers of young children included in paediatric studies using other rHuEPOs were not substantially higher compared to those of the present study. Chronic renal insufficiency and dialysis dependency is very rare in children making it difficult to perform large studies in this vulnerable population.

The results of the 200000100 study demonstrate non-inferior efficacy of darbepoetin alfa compared to rHhEPO with regard to the primary endpoint “change in Hb”. Although the pre-defined non-inferiority margin of -1 g/dL may be considered somewhat wide when used in a maintenance phase study in previously clinically stable patients, the actual lower limit of the 95% CI for the treatment difference of -0.45 g/dL is clearly acceptable. A total of 42 patients (26 of whom were included in the PP analysis) included in this study were in the age range (≤ 11 years) for which approval of darbepoetin therapy is sought. Most patients were older than 11 years, a patient population for which darbepoetin therapy is already licensed.
The results of study 200000100 also suggested that paediatric patients with chronic renal failure can be switched from rHuEPO to darbepoetin alfa by using the proposed conversion factor 100 IU rHuEPO = 0.42 µg NESP or by dividing the total weekly dose of rHuEPO by 240. The chosen dose conversion factor is supported by the fact that in the darbepoetin alfa group, on average, only a minor down-titration was necessary to maintain the Hb levels in the target range after the switch from rHuEPO. At present, the same posology is recommended for children ≥ 11 years of age and for adults, which is further supported by the results of the present study. However, the subgroup analysis suggests that the younger the child, the higher the maintenance dosage needed. Since the required epoetin dosage, if anything, is higher in younger than in older children/adolescents and, in addition, is titrated individually according to treatment response, this does not constitute a safety concern.

Safety
The safety profile of epoetin use is qualitatively similar in adults and children, and, based on results from clinical studies and post-marketing experience, AE frequency appears to be similar or lower in children than in adults. Although the number of paediatric patients investigated in the submitted studies is small and the duration of treatment short, the safety results are in line with the known safety profile of darbepoetin alfa and therefore do no elicit new safety concerns.

Because the pediatric clinical trial data submitted are considerably limited especially in children 1 to 6 years of age and therefore insufficient for comprehensive evaluation of safety issues of darbepoetin alfa in the paediatric population, the CHMP recommended that as part of a RMP, an appropriate pharmacovigilance plan should be implemented to closely monitor safety and efficacy of darbepoetin

alfa in this population. This pharmacovigilance plan should include standard pharmacovigilance procedures as well as a more proactive part to conduct appropriate pharmacovigilance in low used products. The pharmacovigilance plan should also address anti-darbepoetin antibodies as well as PRCA, risk factors for the appearance of hypertension and thromboembolic and cardiovascular ADRs in the pediatric population treated with darbepoetin alfa. The progress of the surveillance will be reported within regular PSURs and interim results provided annually. The MAH was also requested to submit a study protocol for an observational study to collect long-term safety data on the paediatric population receiving darbepoetin alfa. Data will be collected at regular time intervals including data of darbepoetin use, concomitant medication, indication of use and diseases, routine laboratory findings, adverse events, causes for discontinuation of darbepoetin alfa etc. The children and adolescents should be followed up until darbepoetin use is stopped. Progress of the surveillance will be reported within the regular PSURs and interim results should be provided annually. However the MAH must submit a proposal of study protocol.

A post-approval prospective surveillance registry is suggested to monitor all paediatric CRF patients receiving darbepoetin alfa or other epoetins in order to expand the safety database and to demonstrate long-term safety of darbepoetin alfa compared to other epoetins in this special population. The MAH should submit PSURs limited to the paediatric population at six-month intervals for two years after approval. The MAH was requested to submit a detailed protocol for a registry before approval of this variation. The CHMP in October 2006 requested additional clarification to the MAH on the following aspects:

- Although, no neutralizing antibodies were detected, the frequency of binding, non-neutralizing antibodies appears high, even knowing that the Biacore assay is highly sensitive for the detection of anti epoetin antibodies. In addition, interpretation of the 2 cases of newly developed anti-darbepoetin antibodies during the study is difficult, particularly because immunogenicity has not been routinely evaluated in the reference group.

- The submitted data are too limited to allow a comprehensive evaluation of safety issues of darbepoetin alfa in the paediatric population. Therefore, an appropriate pharmacovigilance plan should be implemented which should include standard pharmacovigilance procedures as well as a more proactive part to conduct appropriate pharmacovigilance in low used products. A post-approval prospective surveillance registry is suggested to monitor all paediatric CRF patients receiving darbepoetin alfa or other epoetins in order to expand the safety database and to demonstrate long-term safety of darbepoetin alfa compared to other epoetins in this special population. The MAH should submit PSURs limited to the paediatric population at six-month intervals for two years after approval. The MAH was requested to submit a detailed protocol for a registry before approval of this variation.

Based on the Posology and Method of Administration Section (4.2) of the Summary of Product characteristics for darbepoetin alfa, doses are adjusted by 25% if the Hb value is out of the target range. The CHMP agreed that some dose titration has to be allowed to counteract the usually occurring Hb fluctuations in patients with renal anaemia. Individual Hb concentrations in haemodialysis patients are subject to (substantial) fluctuation over time due to factors and concomitant disorders such as infections and GI bleedings.

An additional question regarding study 200000100 was the recommendation to switch from rHuEPO to darbepoetin alfa in children with CKD and the fact that the recommendation is not made for adults. The CHMP recommended to the MAH provide more data on this matter.

Further to a request from the CHMP, the MAH submitted answers on the issues highlighted by the CHMP in March. Regarding the first question, the MAH supports that, pharmacokinetic data available indicate that PK is similar in subjects < 6 years and those 7 to 16 years. Moreover, darbepoetin alfa PK in pediatric subjects (study 980212) is similar to that in adult CKD subjects (55 to 94 years; Study 960224). The MAH agreed that the available PK data in subjects < 6 years are scarce and to obtain additional data using sparse sampling and to perform population PK analysis. Following completion of

the population PK analysis and subsequent inter-population comparisons, the MAH will provide results and conclusions on these PK observations, and, if any, their likely clinical importance for this titrated drug. The CHMP agree with the MAH on this issue.

Due to the limited data currently available on long term safety associated with paediatric use of darbepoetin alfa in the CKD setting, the second issue requested to the MAH was to provide a proposal of registry study to collect long-term safety data on the paediatric population (up to age 16 years) with chronic kidney disease (CKD) receiving or not receiving dialysis receiving darbepoetin alfa I order to assess the usage pattern of darbepoetin alfa in this paediatric patient population, haemoglobin and selected related laboratory values over time.

In addition to the normal 3-yearly PSUR reporting cycle for the product, the MAH commit to providing paediatric PSUR reporting submissions to regulatory authorities every 6 months for the first 2 years following approval of this variation. Pharmacovigilance findings associated with the registry will be combined with those reported through normal post-marketing procedures.

Finally, the MAH was requested to perform a drug utilisation study to analyse the prevalence of use, doses administered, duration of use and the reasons for stopping or switching to another epoetin, the indications and the concomitant medication of darbepoetin use in the pediatric population. The MAH confirmed that the registry study 20070211 will provide information on route of administration and doses used as well as presence or development of contraindications, i.e. uncontrolled hypertension and hypersensitivity reactions but it will not address use of the product outside the approved indications in the pediatric population. The CHMP agrees with the MAH that the off-label use of darbepoetin alfa is of little significance in the pediatric population compared to the adult population. Therefore, the observational study 20070211 should be sufficient to survey drug utilization.

Risk Management Plan

The MAH submitted a risk management plan, which included a risk minimisation plan. The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information

Summary of the EU Risk Management Plan for Aranesp/Nespo (Darbepoetin alfa)

Safety Concern	Pharmacovigilance Plan	Risk Minimization Plan (All have routine risk minimization and communication activities)
Immunogenicity	Stimulated reporting with antibody testing; Routine pharmacovigilance with enhanced follow-up for PRCA cases; Systematic monitoring in ongoing studies	Risk of PRCA, guidance for workup in case of non-response, and recommendation to stop ESA therapy in case of PRCA are described in the "special warnings and precautions for use" section 4.4 of the SPC. PRCA is also listed in section 4.8. Hypersensitivity reactions are described in section 4.3 and 4.8 of the SPC.
Thromboembolic and cardiovascular events	Routine Pharmacovigilance; Systematically collected and analyzed in ongoing clinical studies	The potential for increased thromboembolic events is described in 4.4 "special warnings and precautions for use" section of the SPC, for cancer patients. Recommendations against exceeding specific hemoglobin concentrations appear for both cancer and chronic renal failure indications. There is additional information in section 4.8 "undesirable effects" section of the SPC. It includes information on risk of thrombosis of vascular access for chronic renal failure patients, and risk of

Safety Concern	Pharmacovigilance Plan	Risk Minimization Plan (All have routine risk minimization and communication activities)
		thromboembolic reactions for cancer patients.
Hypertension	Routine pharmacovigilance; Systematically collected and analyzed in ongoing clinical studies	Section 4.3 of the SPC contraindicate use in poorly controlled hypertension Section 4.4 Special warnings and precautions for use in chronic renal failure patients specify risk and give management guidelines. Hypertension is also listed in section 4.8 of the SPC, for chronic renal failure patients.
Convulsions	Routine pharmacovigilance; Systematically collected and analyzed in ongoing clinical studies	Section 4.4 -Special warnings and precautions for use in chronic renal failure patients notes observed occurrence and recommends use with caution in patients with epilepsy. Convulsion is also listed in section 4.8, for chronic renal failure patients.

Safety Concern	Pharmacovigilance Plan	Risk Minimization Plan (All have routine risk minimization and communication activities)
Tumour progression and/or decreased survival among patients with malignancies	Pharmacoviligance program with 4 studies ongoing and one completed and analyzed. Standard Pharmacovigilance; Systematic monitoring in ongoing clinical studies	The potential for tumour growth in cancer patients who receive darbepoetin alfa is described in section 4.4 special warnings and precautions section of the SPC. Indication is restricted to non-myeloid malignancies.
Lack of pharmacokinetic data on chronic renal failure patients 1-5 years of age	Studies targeting this specific concern	Based on study results, SPC to be updated with additional physician guidance on the PK profile of darbepoetin alfa used in children under 6 years
Lack of data for correction of anaemia in paediatric patients with chronic renal failure	Studies targeting this specific concern	Based on study results, SPC to be updated with additional physician guidelines on anemia correction in the pediatric CKD population
Lack of long-term safety of Darbepoetin alfa in pediatric patients with chronic renal failure	Routine pharmacovigilance; Monitoring ongoing studies including observation registry study	Based on study results any necessary long term safety concern will be reelected in the SPC.

Benefit/Risk evaluation

Overall, there is no doubt that darbepoetin alfa is efficacious in treating renal anaemia not only in adult and adolescent patients but also in younger children. However, pharmacokinetics of darbepoetin alfa may be different (lower AUC and Cmax and higher CL/F) especially in young children compared to adolescents and adults (showing that younger children with renal anaemia require higher epoetin maintenance doses than do older children or adults), the submitted PK data are extremely limited in children < 6 years of age and therefore CHMP requested more PK data in this age group. However, no safety issue arises from these considerations. The MAH agrees to provide further PK data from minimal sampling technique in this population.The benefit-risk ratio for the proposed extension of indication, i.e. use of darbepoetin alfa in children < 11 year of age with renal anaemia, is considered positive with the MAH's commitment to providing more PK data in patients < 6 years of age and to additional PhV activities.

5. CONCLUSION

On 19 July 2007 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics and Package Leaflet subject to the additional commitments undertaken (see below).

Follow-up measures undertaken by the Marketing Authorisation Holder

As requested by the CHMP, the MAH agreed to submit the follow-up measures as listed below and to submit any variation application which would be necessary in the light of compliance with these commitments:

Area[1]	Description	Due date[2]
Pharmacovigilance	<u>Long term registry study</u> Perform observational registry study to collect long-term safety data on the paediatric population with chronic renal failure receiving darbepoetin alfa and particularly addressing the following risks: -thromboembolic events -seizures -severe hypertension -cardiovascular events -pure red cell aplasia -hypersensitivity reactions Enrolment of 180 subjects (minimum of 30 subjects < 6 years of age). Pharmacovigilance findings from the registry will be included as part of a paediatric specific PSUR, which will be submitted every 6 months for the first 2 years following approval of the expanded paediatric indication for Aranesp in the CKD setting. Interim summary results from the registry & drug utilization will be submitted annually following study start.	Study start Q2 2008 Study completion 2013 First report Q2 2009
Pharmacovigilance	<u>Paediatric PSUR</u> Paediatric specific PSUR reporting submissions to regulatory authorities will be made every 6 months for the first 2 years following approval of the expanded paediatric indication for Aranesp in the CKD setting.	First submission Q2 2008
	<u>Pharmacokinetic in <6 years old</u> Population (single dose) PK data in at least 15 patients < 6 years with renal anaemia. This will investigated as part of US study 20050256. Results from PK sampling to be submitted once completed.	Q3 2011
Clinical	<u>Paediatric haemoglobin target</u> A rationale for the haemoglobin target concentration in children, possibly taking into account different age groups should be provided. If necessary, adoption of the target value may be included in a future variation.	Q1 2008

1. Areas: Quality, Non-clinical, Clinical, Pharmacovigilance
2. Due date for the follow-up measure or for the first interim report if a precise date cannot be committed to.