



European Medicines Agency
Evaluation of Medicines for Human Use

London, 3 July 2008
Doc. Ref No.: EMEA/478500/2008

**ASSESSMENT REPORT
FOR
NESPO**

**International non-proprietary name/Common name:
darbepoetin alfa**

Procedure No. EMEA/H/C/333/X/0043

Variation Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted
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1. Introduction

The Marketing Authorisation Holder for Nespo has submitted a line extension pursuant to Annex II of Commission Regulation (EC) 1085/2003 (variation regulation) in order to replace the existing manufacturing process with a more efficient high throughput (HT) process, for which a re-establishment of the master cell bank was necessary.

In accordance with the relevant guidelines, i.e. the Note for Guidance on Biotechnological/Biological Products subject to changes in their manufacturing process (CPMP/ICH/5721/03) an extensive comparability exercise for darbepoetin alfa manufactured by the HT process versus the currently licensed darbepoetin alfa manufactured by the roller bottle (RB) process was conducted to support that darbepoetin alfa HT is comparable to darbepoetin alfa RB with regard to quality, safety and efficacy.

2. Quality aspects

Introduction

The active substance of Nespo is darbepoetin alfa, a hyperglycosylated recombinant human erythropoietin (rh-EPO) analogue. Darbepoetin alfa is produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology.

Darbepoetin alfa is currently manufactured by a roller bottle (RB) process that uses recombinant CHO cells. The proposed changes to the production process for darbepoetin alfa will replace the current RB production technology with a more scalable mode of production in bioreactors; concurrently the applicant removed or replaced certain media components. The proposed changes to the production process include a re-established cell line and production in suspension cell culture associated with the HT process.

The Drug Product manufacturing process and the presentations remain unchanged.

Drug substance

Darbepoetin alfa has been manufactured in recombinant Chinese hamster ovary (CHO) cells that are cultivated adherently in roller bottles (RB). The Company has developed a more scalable process for which the MCB was re-established. This re-established MCB is optimised to the different cultivation conditions.

For the purpose of process validation, data from 3 consecutive commercial scale lots were used to assess key and critical performance parameters of the cell culture and purification process. Each of the three validation runs met all specified acceptance criteria for key and critical performance parameters.

The viral safety was well addressed in the dossier. Media used during culturing of the cells do not contain any material directly derived from animal or human origin. Comparability for the laboratory scale studies with the 15 kL process scale has been shown.

An extensive biochemical and biophysical characterisation programme for darbepoetin alfa drug substance derived from the HT process has been conducted on three batches at the 2 kL pilot scale and three batches at the 15 kL commercial scale.

Darbepoetin alfa drug substance from all three processes and scales showed comparable bioactivity in the bioassay.

Based on the characterisation data of darbepoetin alfa HT from the 2 kL and 15 kL processes it can be concluded that no significant differences were observed between the scales. Therefore darbepoetin alfa drug substance from the 2 kL scale, which was used in clinical studies, can be considered representative of darbepoetin alfa drug substance from the 15 kL scale.

The stability program was conducted to investigate the stability of darbepoetin alfa drug substance from the HT process in two different containers, the currently used container and a newly introduced container, at the recommended storage temperature of 5°C (2°-8°C), as well as at temperatures of 29°C (27-30°C) and 37°C (35-39°C). Assays and acceptance criteria used for the stability program are identical to those used for the licensed RB process with the addition of the appearance assay.

No difference resulted from storage of pilot scale 2 kL HT lots at 5°C for up to 24 months in the two container types thus the current commercial drug substance expiry period of 24 months is considered confirmed. The stability results of the 2 kL HT lots indicate that the stability profile is consistent and comparable with material from the RB process.

12 months of stability data are available for the HT 15 kL validation lots stored at recommended and accelerated conditions in the proposed polypropylene container. Results are consistent with those observed for HT 2 kL lots. Data obtained to date for the HT 15 kL lots at accelerated conditions exhibit comparable stability profiles for the HT 2kL and RB material.

- **Comparability Exercise for Drug Substance**

The overall comparability approach for darbepoetin alfa HT includes clinical comparability, analytical comparability, analytical methods comparability where methods were to be changed, process comparability and comparability of the drug product.

Analytical comparability was based on lot release testing, additional extended characterisation of the drug substance and stability testing.

In conclusion, the comparison of darbepoetin alfa drug substance from all processes by various high-level analytical techniques revealing a profound insight into the structural characteristics of the molecule and confirmed a high level of comparability between darbepoetin alfa drug substance from the currently licensed RB process and darbepoetin alfa from the 2 kL and 15 kL HT process.

Impurities

The applicant does not discriminate between product-related substances and product-related impurities and considers all variants (active and inactive) as product-related impurities.

Product-related impurities including higher and lower molecular weight species (HMWS and LMWS), darbepoetin alfa with oxidised methionine and other protein modifications were examined by the Applicant.

Generally, the process- and product related impurities in the drug substance from the RB and HT processes are considered comparable.

Drug Product

The composition or formulation of the drug product is identical to the currently licensed product. The drug product is currently presented as a liquid ready-to-use formulation either in a pre-filled syringe (PFS) or a vial.

The proposed shelf life specification is mainly identical to the shelf life specification presented at the initial submission. Changes introduced into the drug product specification enhance the quality assurance of the product and align with PhEur expectations.

12 months data are available to assess drug product stability of batches derived from 15 kL drug substance lots. All data gained so far were within the acceptance limits.

As these data are supplemented by 24 months of data generated on clinical drug product lots derived from drug substance 2 kL process, a shelf-life of 24 months for drug product is considered justified.

- **Comparability Exercise for Drug Product**

Studies were performed to demonstrate comparability between drug products containing drug substance derived from RB process, from HT 2kL process and from HT 15 KL process.

It was demonstrated that all release data of drug product lots of the proposed HT process met the acceptance criteria originally established for RB drug product, independently of whether the drug substance was derived from 2 kL or 15 kL process. This finding was also confirmed by additional testing of oxidised variants and aggregates.

Likewise, no significant differences were observed between degradation rates of drug product containing drug substance produced by HT 2kL or RB manufacturing processes in the first comparability stability study. In addition, in a second stability study, up to 12 months of stability data have been evaluated in order to compare drug product derived from RB, HT 2kL and HT 15 kL processes. No significant differences were observed at the recommended storage conditions.

3. Non-clinical aspects

Darbepoetin alfa (Nespo) is a hyperglycosylated analogue of recombinant human erythropoietin (r-HuEPO) and is an erythropoiesis-stimulating protein that supports the survival, growth, and differentiation of erythroid progenitor cells in the bone marrow. To support the change in the manufacturing process to a HT process the MAH conducted three preclinical studies to compare darbepoetin alfa manufactured by HT technology to that manufactured by the licensed RB process. These include a single-dose pharmacokinetics study in male beagle dogs (study 103100), a 4-week toxicity study in beagle dogs including pharmacokinetic and immunological measurements (study 103367), and an in vitro binding study on frozen sections of various human tissues (study 103528). All studies were performed in direct comparison of darbepoetin alfa RB and darbepoetin alfa HT.

Pharmacology

Pharmacodynamic data on the comparison between darbepoetin alfa HT and darbepoetin alfa RB can be retrieved from an in-vitro receptor binding study on human tissue sections and from the repeated-dose toxicology study in dogs. The latter study encompassed weekly measurements of relevant haematological parameters, which are the prime targets for epoetin treatment, in direct comparison between darbepoetin alfa HT and darbepoetin alfa RB. In this study the haematological parameters changed over time of treatment as expected (increase in red blood cell count, haemoglobin, haematocrit, reticulocytes and related parameters), and there were no meaningful differences between the two preparations tested so that pharmacodynamic comparability could be confirmed.

The in-vitro receptor binding study on slices of various human tissues was aimed at not only comparing binding to the epoetin target cells in the bone marrow but also to detecting potential off-target sites in other organs or tissues. However, no competition experiments were performed within this study to enable clear discrimination between specific and unspecific binding. Furthermore, the results of the study were difficult to assess because no photographs of the stained tissue sections were provided. The method was rather complex as antibodies were employed to detect bound epoetin (instead of using labelled epoetin) which makes interpretation more complicated. Nevertheless, the clear pharmacodynamic results of the repeated dose dog study are considered sufficient to demonstrate comparability at the pharmacodynamic level.

Pharmacokinetics

Classical ADME studies were not performed, and these are not considered necessary for a comparability exercise. The main pharmacokinetic parameters AUC and C_{\max} were determined after a single administration of both preparations in direct comparison and after repeated administration (three times a week for four weeks), also in direct comparison. This was done in one animal species, dog, and this is considered satisfactory. No meaningful changes were detected between the two preparations darbepoetin alfa HT and darbepoetin alfa RB; an around 25 % higher exposure (AUC) of darbepoetin alfa HT as compared to darbepoetin alfa RB after four weeks of application is not considered biologically relevant given the rather high inter-individual variation of AUC values. Therefore comparability can be assumed at the level of preclinical pharmacokinetics.

Toxicology

The standard toxicological parameters determined in the 4 wk repeated-dose dog study were in line with the erythropoetic effect of darbepoetin alfa, were considered secondary to increased haematopoiesis, and are well known from other epoetin preparations. No meaningful differences between darbepoetin alfa HT and darbepoetin alfa RB were observed and no unexpected toxicities occurred with either preparation. Therefore, comparability was shown at the level of general toxicity.

Antigenicity of both preparations was also tested in the repeated-dose study in each dog. Antibodies against darbepoetin alfa were detected immunologically in a biosensor after four weeks in the same number of animals treated with darbepoetin alfa HT and darbepoetin alfa RB arguing for a comparable immunogenic potential of both preparations. Nevertheless, when considering the amount of antibodies formed (given as $\mu\text{g/mL}$ by the biosensor procedure used) the animals treated with darbepoetin alfa RB had all over lower serum antibody concentrations (a few microgram per mL) than the animals treated with the darbepoetin alfa HT material.

Serum samples which tested positive for antibodies in the immunogenic assay were also screened for neutralising capacity in a cell culture based bioassay. In addition, an indirect indicator of the possible formation of neutralising antibodies was a marked decrease in reticulocytes in some of the treated dogs, although it was noted that in some cases the results of the bioassay did not fit the haematological observations (either the bioassay was positive whereas no decrease in reticulocytes was detected or, vice versa, there was a marked decrease in reticulocyte count but a negative bioassay). A possible explanation for this discrepancy would be that the drop in reticulocytes was due to iron deficiency in some animals.

All three preclinical studies (103100, 103367 and 103528) were performed according to GLP regulations except the steps in study 103528 undertaken to optimise the immunohistochemistry method used.

4. Clinical aspects

Pharmacokinetic study

One comparative PK study, study 20030247, has been submitted, which was a randomized, 2-way, open-label, crossover study to assess the comparability of the pharmacokinetics of darbepoetin alfa manufactured by HT versus RB processes following subcutaneous administration of darbepoetin alfa in healthy subjects. 48 healthy subjects, 32 women and 16 men were included into the study. Subjects received 2 single doses ($1 \mu\text{g/kg}$) of darbepoetin alfa manufactured using HT and RB technology, with 14 days of pharmacokinetic sampling in each study period. A 28-day washout period separated administrations.

The primary endpoint was the pharmacokinetic parameter AUC_{0-t} of darbepoetin alfa. The secondary endpoints were the additional pharmacokinetic parameters AUC_{0-∞}, C_{max}, t_{max}, apparent clearance (CL/F), mean residence time (MRT), and terminal half life (t_{1/2z}).

Furthermore, safety endpoints including subject incidence of adverse events and clinically significant changes in vital signs, physical exams, clinical laboratory tests, ECG's and the incidence of neutralizing seroreactivity. Two subjects discontinued participation in the study before the 2nd dose because of a positive drug screen when checking in for period 2. Both subjects received darbepoetin alfa manufactured using the HT process in period 1 and were not included in the PK analysis.

Forty-eight subjects had complete pharmacokinetic data for darbepoetin alfa manufactured by the HT process, and 46 subjects for the RB process. Forty-six subjects were included in the pharmacokinetic analysis for AUC_{0-t} and C_{max}.

The 90% CI for comparison of AUC_{0-t} for darbepoetin alfa manufactured using the HT and RB technologies was within the predefined acceptance criteria (80% to 125%). The 90% CI for the ratio of AUC_{0-∞} and C_{max} for the two manufacturing processes were also within the acceptance range. In addition, mean CL/F, MRT, and t_{1/2z} values, as well as median T_{max} values, were comparable for the HT and RB manufacturing methods of darbepoetin alfa.

AUC_{0-∞} values could not be reliably determined for 7 subjects for one or both treatments, since the portion of the estimated AUC_{0-∞} value determined by extrapolation exceeded 20% (reflecting uncertainty in the parameter estimate); therefore, 39 subjects were included in the pharmacokinetic analysis for AUC_{0-∞}. However, the point estimate (90% CI) when these 7 subjects were included in the analysis was still within the acceptance range (99.8; [97% to 102%]). Comparative PK data demonstrating comparable PK profiles were provided for SC use but not for IV use.

The issue of the need of a further PK study for the IV route of administration has been discussed by the CHMP. The CHMP was of the opinion that in this special case a further PK study for IV administration in addition to the already submitted SC study is not necessary because the results for the SC route of administration demonstrated equivalent PK profiles and the SC route of administration is more sensitive to possible changes concerning the darbepoetin alfa HT product's PK profile. Furthermore, additional subgroup analysis for SC and IV treated patients of the current efficacy and safety study have been provided with the MAH's response in order to support equivalent efficacy for both routes of administration.

Pharmacodynamic study

No PD study has been performed for this procedure. However, PD parameters are not critical, since phase III efficacy/safety studies have been provided.

Clinical efficacy

One clinical efficacy study (Study 20040104) has been provided to demonstrate comparability of efficacy for darbepoetin alfa produced by RB and HT process. The efficacy study is the only controlled trial which has been submitted for this line extension procedure and therefore considered as pivotal study for comparison of efficacy and safety.

Study 20040104

Study 20040104 aimed at studying the efficacy of darbepoetin alfa manufactured by HT bioreactor technology and darbepoetin alfa manufactured by RB technology for the treatment of anemia in patients with chronic kidney disease receiving haemodialysis. The study was designed and performed as a maintenance study.

Patients who were stable on treatment with darbepoetin alfa RB were randomised to receive either darbepoetin alfa RB or darbepoetin alfa HT for 28 weeks (20 weeks titration period and 8 weeks evaluation period).

446 patients with chronic kidney disease were randomized, 222 for darbepoetin alfa HT and 224 for darbepoetin alfa RB. Renal disease aetiology and baseline characteristics were comparable in the 2 treatment groups.

Subjects were treated for up to 28 weeks according to their randomised treatment assignment with either with darbepoetin alfa RB or HT. Patients received IV or SC application of darbepoetin alfa maintaining the same route of administration, dose and frequency (once weekly or once every other week) they had received before randomisation. Only 35 patients in the HT group and 37 patients in the RB group were treated with darbepoetin alfa as SC application. The results for both primary efficacy endpoints show comparable efficacy of darbepoetin alfa RB and darbepoetin alfa HT according to the predefined acceptance criteria:

362 subjects (81%; 183 HT, 179 RB) were included in the primary analysis set and 438 (99%; 217 HT, 221 RB) were included in the full analysis set. Mean (SD) baseline haemoglobin concentrations were 11.8 (0.80)g/dL and 11.8 (0.78) g/dL and mean (SD) baseline darbepoetin alfa doses were 0.49 (0.31) and 0.52 (0.48) µg/kg/week for the darbepoetin alfa HT and RB groups, respectively.

The first primary endpoint, the difference in mean change in haemoglobin concentration from baseline to the evaluation period between the darbepoetin alfa HT and RB groups was -0.19 g/dL (95% CI: -0.42, 0.03 g/dL). The 2-sided 95% CI was entirely within the protocol specified and acceptable equivalence margin (± 0.5 g/dL).

The second primary endpoint, the mean difference in log-transformed ratio of dose during the evaluation period to the baseline dose between darbepoetin alfa HT and RB was 0.06 (90% CI: -0.03, 0.16). The 2-sided 90% CI was within the protocol-specified equivalence margin of log (0.80) to log (1.25), or -0.223 to 0.223. Equivalence between darbepoetin alfa HT and RB regarding haemoglobin maintenance and dose was also demonstrated in a sensitivity analysis performed on the full analysis set.

Concerning the secondary endpoints, in the primary analysis set, mean (SD) change in haemoglobin concentrations from baseline during the treatment period ranged from -0.17 (1.12) to 0.16 (1.04) g/dL for darbepoetin alfa HT and from -0.00 (1.16) to 0.27 (1.09) g/dL for darbepoetin alfa RB. In addition, 70% of subjects in both treatment groups had haemoglobin concentrations within the target range during the evaluation period.

Median (range) baseline weekly dose was 30 (5 to 150) µg/week for both treatment groups in the primary analysis set. Median (range) weekly doses during the evaluation period were 25.00 (0 to 175.0) and 20.00 (0 to 143.8) µg/week for darbepoetin alfa HT and RB, respectively. Median change in dose from baseline was 0 µg/week at each time point for both treatment groups, except for one time point (-2.50 µg/week for darbepoetin alfa RB at week 28).

The mean change in dose from baseline decreased during the first 12 and 11 weeks to approximately -7 µg/week for darbepoetin alfa HT and RB, respectively, and then remained relatively stable for both treatment groups.

Taken together, the secondary and ancillary analyses support the conclusions from the primary analyses. Therefore, comparable efficacy between darbepoetin alfa RB and HT has been demonstrated according to the pre-defined criteria.

As for all efficacy parameters, the 95% confidence interval for treatment differences is required. The 90% confidence interval for the co-primary endpoint dose ratio which was presented with the original study documentation is not acceptable. The MAH has therefore provided additional results calculating the 95% CI for the difference in log-transformed ratio of dose during the evaluation period to the baseline dose. For the primary Hb-targeted efficacy parameter the 95% CI for the difference in weekly dose ratio is (-0.05 to 0.18) for the primary analysis set and (-0.05 to 0.19) for the full analysis set. The

2-sided 95% CI also lies within the predefined equivalence margin of log (0.80) to log (0.125) or - 0.223 to 0.223.

The chosen equivalence margins for darbepoetin alfa dose has been provided and justified by the MAH. The MAH drew upon criteria usually employed for bioequivalence (FDA Guidance for Industry, Statistical Approaches to Establishing Bioequivalence, 2001) to demonstrate equivalent efficacy.

In the efficacy study 20040204, IV administration was used for the majority of patients and, therefore, the conclusion of comparable efficacy for SC administered darbepoetin alfa HT and RB was requested to be further justified by the MAH and at least some supportive evidence for comparable efficacy for this route of administration was requested. The MAH subsequently submitted additional subgroup analysis for the SC and IV application for the primary endpoints haemoglobin level and dose. There were no meaningful treatment differences in these primary endpoints either for the IV or the SC route of administration. Although the number of patients who received SC darbepoetin alfa is small (only 35 patients in the HT group and 37 patients in the RB group were treated with SC administered darbepoetin alfa), the data further support equivalent efficacy of darbepoetin alfa manufactured by the HT and RB processes for the SC route of administration.

In addition, the MAH was requested to provide additional efficacy analyses from the safety trial (for description see below) which should be restricted to patients having received darbepoetin alfa RB before and darbepoetin alfa HT after the switch and preferably include intra-individual comparisons of Hb concentrations and darbepoetin alfa doses during the 4 weeks before with those during the period 8-12 weeks after the switch.

Information on route of administration for individual patients was not available from the safety study. Since it is current practice that non-dialysis and peritoneal dialysis CKD subjects receive darbepoetin alfa via subcutaneous (SC) injections and most haemodialysis CKD subjects receive darbepoetin alfa via intra-venous (IV) injections, the applicant used these patient groups as surrogates for route of administration. This approach is considered acceptable. The vast majority of patients were not on dialysis and received darbepoetin alfa via SC route of administration. The mean baseline haemoglobin level was comparable in all treatment groups. As expected, the mean darbepoetin alfa dosages differed between treatment groups (highest in patients on haemodialysis). There was no clinically relevant change in mean Hb at 8 to 12 weeks after the switch from darbepoetin alfa RB to darbepoetin alfa HT compared to baseline. The change in mean dose from baseline to weeks 8-12 was different among the treatment groups but, overall, the change in darbepoetin alfa dosage was not meaningful. These results further support the assumption of equivalent efficacy for the SC route of administration.

Taking together the finding of comparable PK profiles for SC use and the supportive efficacy data on SC use (surrogate “pre-dialysis and peritoneal dialysis patients” in the safety study), equivalent efficacy of darbepoetin alfa RB and darbepoetin alfa HT can be concluded for the SC route of administration.

Clinical safety

• PK Study

Twenty-three (48%) subjects reported at least 1 adverse event (11 [23%] HT, 17 [37%] RB). Five subjects reported at least 1 adverse event during both periods. The most common treatment-emergent adverse events were headache (5 [10%] subjects) and abdominal pain and dizziness (4 [8%] subjects for each event). No notable differences occurred in the incidence of adverse events for the two different manufacturing processes. No serious adverse events occurred during the PK study.

• Efficacy Study

Study 20040104

Comparative safety data for darbepoetin alfa HT and RB resulted from the current pivotal efficacy study 20040104. Safety data from the uncontrolled safety study are considered to be supportive only. Overall, the observed AE profile is consistent with the underlying disease and its severity.

In the comparative efficacy study 20040104 no relevant differences in frequency of overall and specific adverse events, including AEs of particular interest, were observed for darbepoetin alfa HT compared to darbepoetin alfa RB. The frequency of SAEs and death was similar in patients treated with darbepoetin alfa RB or HT, which was considered reassuring by the CHMP.

Of the 442 subjects included in the safety analysis set, 174 (79%) in the darbepoetin alfa HT group and 174 (78%) in the darbepoetin alfa RB group reported ≥ 1 adverse event during the study. The most common adverse events in both treatment groups were muscle spasms (13% HT, 9% RB) and hypotension (10% HT, 9% RB). Treatment-related adverse events were reported for 6 subjects (3%) in the darbepoetin alfa HT group and 8 (4%) in the darbepoetin alfa RB group.

The proportion of subjects experiencing serious adverse events was similar between the treatment groups (29% HT, 32% RB). Two [1%] subjects in the darbepoetin alfa HT group and 4 [2%] in the darbepoetin alfa RB group experienced serious adverse events, which were considered treatment-related by the investigator. Seven subjects (3%) in the darbepoetin alfa HT group and 4 (2%) in the darbepoetin alfa RB group were withdrawn from the study because of an adverse event, none of which were considered treatment-related by the investigator. Fourteen subjects (6%) in the darbepoetin alfa HT group and 15 (7%) in the darbepoetin alfa RB group died during the study. Three fatal adverse events, 1 (sudden death) in the darbepoetin alfa HT group and 2 (thrombosis and cerebral circulatory failure) in the darbepoetin alfa RB group, were considered treatment-related by the investigator.

No differences between both treatment groups were seen concerning Hb excursions. Twenty percent and 22% of subjects in the darbepoetin alfa HT and RB groups, respectively, had ≥ 1 haemoglobin excursion (> 14.0 g/dL) during the study. Haemoglobin concentrations decreased and remained ≤ 13.0 g/dL for most of these subjects (95% HT, 90% RB). The median time required for haemoglobin to return to ≤ 13.0 g/dL was 3 and 4 weeks for the darbepoetin alfa HT and RB groups, respectively.

One non-comparative safety trial, study 20040180, has been performed with darbepoetin alfa HT. Furthermore, safety data from the PK study and the efficacy study have been provided.

For safety comparison data were pooled from two previous studies of darbepoetin alfa RB in non-dialysis subjects (Studies 20010212 and 20030153) and three previous studies of darbepoetin alfa RB in dialysis subjects (Studies 970200, 980117, and 980140) to draw comparisons with the safety profile of darbepoetin alfa HT.

Study 20040180

Study 20040180 is an Open-label, Single-Arm Study to Assess the Safety of Darbepoetin Alfa Manufactured by HT Technology in Subjects with Chronic Kidney Disease.

This open-label, multicentre trial evaluated the safety of darbepoetin alfa administered to subjects who either were receiving dialysis or not receiving dialysis. All subjects were receiving therapy with either darbepoetin alfa or rHuEPO at the time of enrolment. Darbepoetin alfa was to be administered for up to 52 weeks followed by an End-of-Study visit. The study concluded with a post-treatment assessment after the last dose of darbepoetin alfa, at approximately week 53.

The primary objective was to determine whether darbepoetin alfa manufactured by the current RB process and darbepoetin alfa manufactured by the HT process have a comparable safety profile. The secondary objective was to characterize laboratory parameters in subjects with CKD and the seroreactivity of darbepoetin alfa with the HT manufacturing process.

One thousand one hundred and twenty seven patients with CKD were enrolled, 560 subjects requiring and 567 subjects not receiving dialysis, 603 men (54%) and 524 women (46%).

Of the 560 subjects in the non-dialysis group, 554 (99%) received ≥ 1 dose of darbepoetin alfa HT. Seventy-nine percent of these subjects completed dosing with darbepoetin alfa and 119 (21%) withdrew from the study.

Of the 567 subjects in the dialysis group, 452 (99%) receiving haemodialysis and 110 (98%) receiving peritoneal dialysis received ≥ 1 dose of investigational product. Seventy-one percent of subjects receiving haemodialysis and 60% of peritoneal dialysis subjects completed all planned doses of darbepoetin alfa HT. 133 (29%) withdrew from the study.

Non-dialysis group

Adverse events occurred in 464 (84%) subjects in the non-dialysis group. The most common adverse events in this group were hypertension (25%) and peripheral oedema (10%). Hypertension (3%) and injection site pain (2%) were the most common treatment related adverse events. Serious adverse events occurred in 182 (33%) non-dialysis subjects. Chronic renal failure was the most common serious adverse event (6%) in this group of subjects. Treatment related serious adverse events occurred in 2 non-dialysis subjects (1 subject had a deep vein thrombosis and the other, worsening hypertension) and in each instance, resulted in their withdrawal from the study. Seventeen (3%) subjects were withdrawn from the study due to adverse events; 3 subjects had an adverse event that was considered to be related to investigational product by the investigator. These adverse events occurred in 1 subject each and were deep vein thrombosis, worsening hypertension, and rash. Twenty-one (4%) subjects in the non-dialysis group died during the study; the most common fatal adverse events were myocardial infarction (4 subjects), or acute myocardial infarction (2 subjects), and respiratory failure (3 subjects), and coronary artery disease (2 subjects). None of the deaths were considered to be treatment related by the investigator. The proportion of subjects with ≥ 1 haemoglobin excursion was 16%. The median time for haemoglobin values to return to ≤ 13.0 g/dL was 6 weeks.

Dialysis Group

Adverse events occurred in 522 (89%) subjects in the dialysis group. The most common adverse events in this group were hypertension (22%), nausea (13%) and diarrhoea (12%). Hypertension (3%), injection site pain (3%), and arteriovenous fistula thrombosis in haemodialysis subjects only (1%) were the most common treatment related adverse events. Serious adverse events occurred in 249 (43%) dialysis subjects. Congestive cardiac failure was the most common serious adverse event (4%) in dialysis subjects. One of these subjects had a treatment related serious adverse event (hypersensitivity) and was withdrawn from the study. Eighteen (3%) subjects in the dialysis group were withdrawn from the study due to adverse events; 3 subjects had an adverse event that was considered to be related to investigational product by the investigator (hypersensitivity, hypertension, and increased appetite). Forty-five (8%) subjects in the dialysis group died during this study; the most common fatal adverse events were chronic renal failure (7 subjects), and acute myocardial infarction, congestive cardiac failure, coronary artery disease, myocardial infarction, and sudden death in 3 subjects each. None of the deaths were considered to be treatment related by the investigator. The proportion of subjects with ≥ 1 haemoglobin excursion was 27%. The median time for haemoglobin values to return to ≤ 13.0 g/dL was 4 weeks.

Historical Trials

The non-dialysis studies 2002012 and 20030153 were included 97 and 150 patients respectively. 86 (89%) and 129 (86%) of patients completed the trials respectively.

The dialysis studies 970200, 980117 and 980140 were performed with 344, 169 and 703 patients respectively and 246 (72%), 141 (83%) and 528 (75%) patients who completed the studies respectively. The majority of patients had hypertension in their medical history and/or diabetes.

Comparison with historical data is difficult due to differences in study design and target Hb as well as possible differences in patient population and improved patient management over time. Therefore, the results from the comparison with historical trials or based on pooled data can be considered as supportive data only. Nevertheless, no new safety signal emerged from this comparison.

The MAH has presented the main study characteristics for the five historical safety studies. The CHMP agrees that despite some differences in the study design and study population, due to the fact that all studies were maintenance studies with a comparable achieved mean Hb level and only minor changes in mean Hb during all of these trials, the safety data of the historical studies can be used for comparison with the safety results of the current studies.

Exposure to the study drug was different among the studies. In the patients not on dialysis, mean duration of exposure was 47 weeks for darbepoetin alfa HT and 29 weeks for darbepoetin alfa RB. Therefore, exposure-adjusted subject incidences of AEs were calculated which is considered acceptable for maintenance studies. Hb target levels were different in all but one study compared to the current safety study.

In the non-dialysis group, all patients on darbepoetin alfa RB received the drug once monthly, whereas patients on darbepoetin alfa HT received the drug preferably once every two weeks. It is unclear whether this difference may affect the frequency of some AEs.

To account for differences in treatment duration between the current and comparator studies, the exposure-adjusted subject incidence of adverse events was used to compare the adverse event profiles. Consistent with the expected co-morbidities in the CKD population, adverse events were common across treatment groups for non-dialysis and dialysis subjects. Adverse event incidences in non-dialysis subjects were 2.5 and 3.6 per patient-year for darbepoetin alfa HT and RB, respectively (the subject incidence was 84% and 83%, respectively). Adverse event incidences in dialysis subjects receiving darbepoetin alfa HT and RB were 4.0 and 6.5 per patient-year, respectively (the respective subject incidence was 89% and 95%). Treatment-related adverse events for darbepoetin alfa HT were similar to, or lower than, darbepoetin alfa RB for both non-dialysis and dialysis groups. In non-dialysis subjects, the incidence of fatal adverse events was 0.043 and 0.036 per patient-year for darbepoetin alfa HT and RB, respectively (the subject incidences were 4% and 2%, respectively). For dialysis subjects, the respective incidences of fatal adverse events were 0.095 and 0.105 per patient year (the respective subject incidence was 8% and 9%). Serious adverse events for darbepoetin alfa HT were lower than darbepoetin alfa RB for both non-dialysis and dialysis groups. In non-dialysis subjects, the incidence of serious adverse events was 0.431 and 0.558 per patient year for darbepoetin alfa HT and RB, respectively (the subject incidences were 33% and 28%, respectively). For dialysis subjects the respective incidences were 0.678 and 0.761 per patient year (the respective subject incidences were 43% and 48%, respectively). The incidences of serious adverse events considered related to darbepoetin alfa HT and RB were 0.004 and 0.007 per patient year, respectively, in the non-dialysis groups and 0.002 and 0.055 per patient year, respectively, in the dialysis group. The respective subject incidences for darbepoetin alfa HT and RB for the non-dialysis group was 0% and 0%, and for the dialysis group, 0% and 5%.

The MAH has provided additional data concerning the number of withdrawals in the historical studies and their relation to study medication. A comparison of withdrawals due to adverse events of the historical and current studies did not reveal any meaningful differences in frequencies and the reasons for study discontinuation reflect the disease characteristics of this study population.

The MAH has further presented additional listings of deaths for all historical trials. The proportion and causes of deaths in the current studies are comparable to the proportion of those reported from historical studies.

Immunogenicity data

Seroreactivity analysis has been performed for all current studies, the PK, the efficacy and the safety study. During the efficacy study 20040104, the majority of patients were treated with IV administered darbepoetin alfa. The IV route of administration is considered less immunogenic than the SC route of

administration. Therefore, no valid conclusion on the immunogenicity of SC administered darbepoetin alfa can be drawn from this study.

Immunogenicity data have not been analysed according to route of administration (SC or IV) in either the efficacy or the safety study. It is not clear, how many patients were treated by SC and IV administration and which patients developed non-neutralizing antibodies. Therefore, additional analyses of immunogenicity data separately for each route of administration for the current efficacy and safety study have been requested.

The MAH has submitted the requested immunogenicity data separately for SC and IV route of administration for the efficacy study (20040104). As for the safety study (20040180) the route of administration for individual patients had not been documented for the surrogates “not on dialysis and peritoneal dialysis” for SC use and on the other hand “on dialysis” for IV use have been used as this reflects current clinical practice. This approach is considered acceptable.

No neutralizing antibodies were detected in the PK, efficacy or safety study. No significant differences in antibody incidence have been observed between the SC and IV route of administration or between darbepoetin alfa manufactured by the HT and RB processes. The results suggest that darbepoetin alfa manufactured by the HT process is no more immunogenic than that manufactured by the currently licensed RB process.

PK Study

No subject developed anti-darbepoetin alfa antibodies in this study. Three subjects had pre-existing non-neutralizing antibodies that reacted to either darbepoetin alfa or epoetin alfa.

Efficacy Study

Pre- and post-treatment antibody assay results were available for 84% and 83% of subjects in the darbepoetin alfa HT and RB groups, respectively. All subjects tested in the bioassay were negative for neutralizing antibodies to darbepoetin alfa or epoetin alfa.

Three hundred seventy-two subjects (189 HT, 183 RB) were tested for antibodies during the study. Twelve (5%) and 16 (7%) of subjects from the darbepoetin alfa HT and RB groups, respectively, were positive for binding, non-neutralizing antibodies. Six (3%) and 10 (5%) subjects tested in the darbepoetin alfa HT and RB groups, respectively, were positive for low-level, binding, non-neutralizing antibodies before and after receiving treatment. The antibody concentrations for these subjects did not change significantly throughout the treatment period. Five (2%) and 6 (3%) subjects tested in the darbepoetin alfa HT and RB groups, respectively, developed low levels of binding, non-neutralizing antibodies to darbepoetin alfa and/or epoetin alfa during the study. One subject was missing a baseline sample and was positive for binding, non-neutralizing antibodies to darbepoetin alfa and epoetin alfa after receiving darbepoetin alfa. An examination of adverse events reported during this study revealed no reports of pure red cell aplasia and no difference in the immunogenic potential of darbepoetin alfa HT compared with darbepoetin alfa RB.

Safety Studies

Study 20040180

Non dialysis group

The prevalence of binding antibodies at baseline for the non-dialysis groups was 8%. After treatment with darbepoetin alfa HT, 5% of subjects developed binding antibodies. All subjects tested in the bioassay were negative for neutralizing antibodies.

Dialysis group

The prevalence of binding antibodies at baseline for the haemodialysis and peritoneal dialysis groups was 5% and 12%, respectively. After treatment with darbepoetin alfa HT, 5% of subjects in the haemodialysis group and 3% of subjects in the peritoneal dialysis group developed binding antibodies. All subjects tested in the bioassay were negative for neutralizing antibodies.

Historical trials

In the current and comparator studies, all samples tested in the bioassay were negative for neutralizing antibodies. In addition, an examination of adverse events reported during the current study revealed no reports of pure red cell aplasia and no trends indicative of an increase in the immunogenic potential of darbepoetin alfa HT compared with darbepoetin alfa RB.

5. Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the MAH fulfils the legislative requirements. The MAH has submitted additional data to show equivalent efficacy for HT and RB darbepoetin alfa for the SC route of administration. The results for efficacy (haemoglobin and dose) obtained from the safety study are in line with the results obtained for the efficacy study and, together with the comparable PK profiles for SC use, support equivalent efficacy for the SC route of administration. Equivalent efficacy for darbepoetin alfa from the RB and HT processes had already been proven for the IV route of administration.

The safety profile for darbepoetin alfa manufactured by the HT process is no different to that manufactured by the previously licensed RB process. The MAH has provided further analyses using historical data in order to compare the safety of darbepoetin alfa manufactured by the HT process with previously licensed RB process. Although there are some differences in the study design of the historical studies, all studies were maintenance studies with similar achieved Hb levels and can therefore be considered suitable for comparison of safety. The safety results of the historical trials are comparable to the results obtained from the two current studies (safety 20040180 and efficacy 20040104). No neutralizing antibodies were found in the efficacy or safety study. Furthermore, the immunogenicity data of the two current studies show a comparable number of newly detected non-neutralizing antibodies for SC and IV use and for darbepoetin alfa HT compared to darbepoetin alfa RB.

From the safety point of view, all questions raised by the CHMP concerning the pharmacovigilance system and the risk management plan are sufficiently resolved. The MAH has provided a pharmacovigilance plan including details for the proactive surveillance in order to detect possible anti-erythropoietin antibody associated PRCA.

In addition to the demonstrated analytical, nonclinical and clinical comparability, to further delineate the safety profiles related to darbepoetin alfa from the RB and HT processes, the Rapporteur required the applicant to commit to a one-time transition from RB-derived product to HT-derived product within a narrow specified timeframe. In response, the applicant satisfactorily described the transition plan.

Risk Management Plan

The MAA submitted a risk management plan.

Table 1. Summary of All Proposed Pharmacovigilance and Risk Minimization Measures

Safety Concern	Risk Assessment and Minimization Activities			
	Routine Risk Minimization and Communication	Post-marketing Safety Surveillance	Safety Monitoring in Ongoing and Future Clinical Studies	Studies Targeting Specific Concerns
<i>Important Identified Risks</i>				
Immunogenicity	X	X	X	
Thromboembolic and cardiovascular events	X	X	X	
Tumour progression and/or survival	X	X	X	X ^a
<i>Important Potential Risks</i>				
Lack or loss of response	X	X	X	
Product quality complaints associated with adverse events	X	X	X	
<i>Important Missing (or Limited) Information</i>				
Pregnant women	X	X		
Lactating women	X	X		
Paediatric patients	X	X	X	X
Geriatric patients	X	X	X	
Non-white patients	X	X	X	
Patients with hepatic, cardiac, or pulmonary impairment	X	X	X	
Patients with other indications	X	X	X	X ^a
<i>Milestone of Risk Assessment and Minimization Activity</i>	Update of prescribing information and IB	PSUR	CSRs; IB; periodic reports to regulatory agencies	CSRs; IB; DMB recommendations; periodic reports to regulatory agencies

^a Included in separate RMP for tumour progression and survival in the oncology setting; not specific to darbepoetin alfa HT. CSR = clinical study report; DMB = data monitoring board; IB = Investigator Brochure; PSUR = Periodic Safety Update Report

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

6. Overall conclusions, risk/benefit assessment and recommendation

Quality

In general, the process change from a roller bottle process to a high throughput (HT) process has been adequately documented. From the quality point of view comparability of the drug substance and drug product derived from the HT process is confirmed.

Clinical

Comparable PK profiles for the darbepoetin alfa HT drug substance and the previously licensed darbepoetin alfa RB drug substance have been demonstrated for the SC route of administration. No further PK study for IV administration is necessary as the SC route of administration is more sensitive to possible changes concerning the darbepoetin alfa HT product's PK profile.

Comparable efficacy between darbepoetin alfa RB and HT has been demonstrated in the current efficacy study, the only comparative study submitted for this application. The MAH has demonstrated equivalent efficacy also for the 95% confidence interval for the primary endpoint dose ratio which is required for all efficacy endpoints. Therefore, equivalent efficacy is considered to be sufficiently demonstrated for darbepoetin alfa HT and RB.

In the efficacy study patients mainly received darbepoetin alfa by IV route of administration. The MAH has submitted additional subgroup analysis concerning the efficacy study for the SC and IV application for the primary endpoints haemoglobin level and dose. There were no meaningful treatment differences in the primary endpoints either for the IV or the SC route of administration. Although the number of patients who received darbepoetin alfa SC is small, these data further support the assumption of comparable efficacy of SC use of darbepoetin alfa HT and RB.

As the current efficacy study included mainly patients receiving darbepoetin alfa by IV route of administration, further supportive efficacy data from the current safety study were requested from the MAH. The additional efficacy data presented by the MAH further support the assumption of equivalent efficacy for the SC route of administration.

No new safety concerns arose from the efficacy study and the safety profile of darbepoetin alfa HT is comparable to darbepoetin alfa RB. The results from the single arm safety study and from historical trials support these findings. The MAH has presented the main study characteristics for the five historical safety studies which were all maintenance studies. The CHMP agreed that despite some differences in the study design and study population, as all studies were maintenance studies with comparable achieved Hb levels and only minor changes in mean Hb during these studies, the safety data of the historical studies can be used for comparison with the safety results of the current studies.

Darbepoetin alfa RB is considered to have a low immunogenic potential. The proposed change in the manufacturing process, however, may theoretically lead to a product (darbepoetin alfa HT) with increased immunogenicity. Since the SC route is more immunogenic than the IV route of administration, the MAH was requested to present antibody data separately for SC and IV route of administration. The MAH has submitted the requested additional immunogenicity data. There were no neutralizing antibodies detected in the current efficacy or safety study. No significant differences in antibody incidence have been observed between the SC and IV route of administration or between darbepoetin alfa manufactured by the HT and RB processes. The results suggest that darbepoetin alfa manufactured by the HT process is no more immunogenic than that manufactured by the current RB process. The MAH has provided further details for the proactive surveillance in order to detect possible anti-erythropoietin antibody associated PRCA.

Risk-benefit assessment

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that routine pharmacovigilance was adequate to monitor the safety of the product in addition to the proposed risk management measures described in table 13. The benefit-risk profile is considered to be positive. The CHMP recommends approval of this line extension.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus decision that the risk-benefit balance of Nespo in the treatment of symptomatic anaemia associated with chronic renal failure (CRF) in adults and paediatric patients and in the treatment of

symptomatic anaemia in adult cancer patients with non-myeloid malignancies receiving chemotherapy was favourable and therefore recommended the granting of the extension to the marketing authorisation.

Medicinal product no longer authorised