This module reflects the initial scientific discussion and scientific discussion on procedures, which have been finalised before 1 March 2002. For scientific information on procedures after this date please refer to module 8B.

1. Introduction

Epoetin delta is a recombinant human erythropoietin produced by an ATCC continuous human cell line using gene activation technology. It is indicated in “Treatment of anaemia in patients with chronic renal failure. It may be used in patients on dialysis and patients not under dialysis”.

2. Chemical, pharmaceutical and biological aspects

Dynepo is a ready to use aqueous solution for injection, available in glass vials or in glass pre-filled syringes with fixed needle.

Composition

The products are composed of Epoetin delta and excipients commonly used in this type of product: sodium phosphate monobasic monohydrate, sodium phosphate dibasic heptahydrate, polysorbate 20 (antiadsorbent), sodium chloride (osmotic agent) and water for injections.

The finished product is presented either in vials (2000, 3000, 4000 and 10000 IU/ml for a delivery volume of 1 ml) or in pre-filled syringes (1000, 2000, 3000, 4000 and 10000 IU for a delivery volume of 0,5, 0,5, 0,3, 0,4 and 0,5 ml respectively).

Active substance

The active substance of Dynepo, epoetin delta, is human erythropoietin prepared using gene activation technology from the culture of a continuous human cell line. Epoetin delta has the same amino acid sequence and glycosylation pattern as human erythropoietin. The use of the continuous human cell line has been satisfactorily addressed.

The applicant has provided a detailed description of the inserted DNA sequences and the cell line development. The master cell bank and working cell bank, prepared from a selected clone, were adequately tested for viability, sterility, mycoplasma and viruses.

Fermentation

Epoetin delta is produced by a fermentation process that is comprised of cell expansion of the working cell bank, inoculation of cell culture vessels and cell growth in a large scale fermentor. At the end of the fermentation phase, the cells are harvested and the supernatant is further processed.

Purification

Purification is accomplished by a sequence of chromatographic and filtration steps, including a viral filtration. The purification process has been developed to remove process- and product related impurities.

The company has validated the fermentation and purification process, and has set appropriate in-process controls. Information has been provided for all fermentation media, reagents and solvents used. Satisfactory information has been submitted to demonstrate both TSE compliance and viral safety.
Characterisation

Biochemical characterisation has been performed to investigate the primary structure as well as post-translational modifications by a range of methods (amino acid composition and N-terminal sequencing; peptide mapping by reverse phase chromatography following trypsin or Glu-C digestion; native and denaturing IEF; MALDI-TOF-MS (molecular mass); SDS PAGE after glycosidase digestion; Circular Dichroism, oligosaccharide profiling and charge analysis; purity by RP-HPLC and by SDS-PAGE; \textit{in vitro} activity by a commercial ELISA kit and \textit{in vivo} potency determination using the exhypoxic polycythaemic mouse assay.

The purification process has been designed to remove isoforms with low potency. The low residual levels and size of DNA in the active substance are not considered a risk.

Acceptable method validation data and reports have been provided. Manufacturing process validation has been performed on an acceptable number of batches demonstrating consistent production of the active substance. Satisfactory information has been provided on the critical steps of the manufacturing and delivery processes (culture, purification, characterisation and transportation).

Appropriate specifications have been set for analysis of the active substance at release and at the end of the shelf-life.

Other ingredients

All excipients in the product (sodium phosphate monobasic, monohydrate; sodium phosphate dibasic, heptahydrate; polysorbate 20 (of vegetable origin); sodium chloride; water for injections) comply with the appropriate specifications and monographs of the current Ph. Eur.

Satisfactory control specifications and certificates are provided for the packaging materials.

Product development and finished product

Buffer is prepared in a compounding vessel and filtered through a 0.22 \textmu m filter. To this a pre-defined amount of active substance is added. Buffer solution is added to reach the target batch weight for the active substance. The formulated bulk is sterilised through two in-line 0.22 \textmu m filters and aseptically filled in vials or pre-filled syringes. The manufacturing process for the finished products has been validated and is controlled by in-process controls. Specifications have been set for testing the formulated bulk prior to filtration.

The finished products (vials and pre-filled syringes) are tested according to agreed release specifications. Identification, bioassay and impurities by RP-HPLC testing are identical to those tests performed for purified bulk active substance, all of which have been validated. Monomer content is determined by SEC. This method is stability indicating, and can detect increase in aggregates following stressed storage conditions. The exhypoxic mouse bioassay is used to determine potency. The release specifications for potency are 80-125 \% of stated potency (of 178,000 U/mg). Fiducial limits for potency not less than 64 \% and not more than 156 \% will be met (p=0.95). The bioassay has been validated for accuracy, specificity, linearity, repeatability, intermediate precision and between laboratory reproducibility. The minor deviations from the bioassay described in the Ph.Eur. monograph are considered acceptable.

Stability of the product

Real time stability data support the shelf life and storage conditions as described in the product information.
3. Toxico-pharmacological aspects

Pharmacodynamics

In vivo studies

The pharmacodynamics of epoetin delta was investigated in rats and dogs during 1-month studies by either intravenous (iv) or subcutaneous (sc) administration.

The administration of epoetin delta, 3 times weekly, to both rats and dogs was demonstrated to increase erythropoiesis within 7 days and resulted in a dose-dependent increase in haematocrit (HCT), haemoglobin (HGB), reticulocyte- and red blood cell (RBC) production. Where iron sources were adequate, there was no associated fall in mean cell volume (MCV), mean cell haemoglobin (MCH) or mean cell haemoglobin concentration (MCHC). Epoetin delta was shown to be effective by both routes proposed for clinical administration. Pharmacological responses increased for at least 3 to 4 weeks after initiation of administration and declined toward normal values following cessation of exposure. There was a tendency for efficacy to fall with time, which may be associated with the formation of neutralising antibodies or development of tolerance. The production of antibodies in pre-clinical models would not however be unexpected with the introduction of a human protein into a non-human system. However, it is noteworthy that during the clinical trials, there was no impact of tolerance and no indication of development of neutralising antibodies to epoetin delta based on the clinical response (see clinical part). In a chronic dog toxicology study, erythropoietic stimulation persisted throughout the 6-month treatment period. For similar doses, sc administration was associated with equal or greater erythropoietic effects compared to iv injection. Epoetin delta was shown to be comparable to epoetin alfa in both rats and dogs.

General pharmacodynamics

The pharmacodynamic effects of epoetin delta appear to be consistent with the known pharmacological actions of erythropoietin. A battery of safety pharmacology studies also revealed effects consistent with the known properties of erythropoietin.

Safety pharmacology studies in the mouse, rat, guinea-pig and dog, together with studies using isolated rabbit Purkinje fibres was performed with epoetin delta.

No effects on the central nervous or respiratory systems, or on the resting membrane potential or action potential characteristics of isolated rabbit Purkinje fibres were detected. The administration of epoetin delta to conscious, transducer-implanted dogs resulted in minor ECG changes at 1240 U/kg, which was the highest concentration tested and approximately 10 times the anticipated clinical dose. In addition, changes in blood pressure and heart rate were also observed, although these were considered to be secondary to either the effects on blood viscosity induced by the elevated HCT or to an increase in total peripheral resistance. Both of these effects have been postulated as possible mechanisms responsible for the development of hypertension in patients treated with recombinant hamster/human erythropoietin.

Pharmacokinetics

The pharmacokinetics of epoetin delta was evaluated in the rat and dog following repeated s.c. or i.v. injection over periods of one to 6 months by measuring serum concentrations of erythropoietin.

Following i.v. Administration the initial dose exposure in rats, as indicated by AUC (0-24h), was generally linear. In dogs, however, disproportionate increases in exposure were observed. The magnitude of the difference was less pronounced at lower doses. The bioavailability of epoetin delta following s.c. Administration was approximately 50% in both the rat and the dog, compared to an equivalent i.v. dose. There were no significant gender differences with either species.
The t½ of s.c. doses was between 18 and 20 h, compared to between 7 and 12 h following i.v. injection, which suggests that slight accumulation of drug would be expected after administration 3 times weekly, although no clinically significant accumulation would be anticipated. Moreover, exposure decreased over the course of one-month, however, which compensates for and prevents accumulation and no accumulation of erythropoietin was thus observed in animals given epoetin delta 3-times a week. ELISA does not distinguish between endogenous and administered EPO and falling AUC over time may thus suggest increased clearance, reduced endogenous production or both. However, the observed decrease in exposure over time following repeated intravenous administration did not have an impact on the clinical efficacy (see Clinical aspects). Furthermore, studies conducted with epoetin delta and epoetin alfa have shown that the pharmacokinetic profiles are similar.

No studies on distribution, metabolism and excretion were performed, which is acceptable given the similarity of epoetin delta to naturally occurring human erythropoietin. The metabolism and excretion of epoetin delta is expected to be similar to that of the endogenous material.

No pharmacokinetic studies were performed with pregnant animals and this has been appropriately reflected in the SPC.

Toxicology

Single dose toxicity

Single dose toxicity of epoetin delta was studied following i.v. administration of 0-62,000 U/kg in rats and 0-31,000 U/kg in dogs. All animals survived to termination and there were no unusual clinical signs or gross pathological findings.

Repeat dose toxicity

Studies of up to one and 3 months duration were performed in the rat and up to 6 months duration in the dog.

Increased mortality and histopathological changes in kidney, heart, and gastrointestinal tract were observed after 3 months of i.v. dosing in the rat. These effects are likely to have limited clinical relevance since they were related to chronic blood hyperviscosity, vascular stasis, thromboses, increased peripheral resistance and hypertension as reported in the literature. Hypoxia-induced liver damage secondary to anaemia probably also contributed to the increased mortality. This have been reported in a variety of studies in which human erythropoietin was administered to rodents and is likely related to the formation of neutralising anti-epoetin delta antibodies which cross reacted with endogenous rat erythropoietin. Such an immune-mediated response to a non-self protein in rats is unlikely to have clinical relevance.

The effect of repeated i.v. administration of epoetin delta in the dog also included a comparison with epoetin alfa. Red colouration of skin, eyes, and gums were a common clinical feature noted in these studies. There were a number of unscheduled deaths for both compounds and the cause of death in many of these could not be conclusively determined from microscopic examinations but was likely related to the effects of polycythaemia on tissue perfusion.

Both epoetin delta and epoetin alfa produced dose-dependent and reversible interrelated effects associated with the known pharmacology of erythropoietin. These effects included erythropoietic stimulation, evidence of iron deficiency, reduced glucose levels and bone marrow hypercellularity occasionally progressing to myelofibrosis at doses and concentrations above those projected for clinical use. Myelofibrosis is an expected response following prolonged overstimulation of erythropoiesis as observed in rats and dogs with other erythropoietins. In addition, supraphysiological increases in red cell mass led to increased turnover of red cell components, and chronic blood hyperviscosity and vascular stasis. Changes in numerous serum chemistry values were also observed, but were likely due to the hyperstimulation of erythropoiesis and increased red cell metabolic demands, and hence, are most likely of little clinical relevance. The morphological findings in the spleen, kidney, liver and bone marrow are considered to be degenerative manifestations associated
with tissue hypoxia secondary to polycythemia and most of these changes appeared to resolve during the respective recovery periods.

Findings for both epoetin delta and epoetin alfa were similar and neither EP compound produced any systemic effects unrelated to erythropoietic stimulation.

**Immunotoxicity**

Formation of anti-epoetin delta antibodies occurred in rats treated by either i.v. or s.c. administration and is considered to have contributed to the development of anaemia, hypoxia-induced liver damage and decreased survival in rats. Antibody formation was observed in a few dogs treated with epoetin delta for one month by either route of administration, but did not appear to induce any signs of toxicity and no antibody formation was detected in dogs treated for 3 or 6 months by iv administration.

**Genotoxicity**

Epoetin delta was found to be non-mutagenic and non-clastogenic when tested in a standard battery of *in vivo* and *in vitro* assays.

**Carcinogenicity**

No *in vivo* carcinogenicity studies have been performed with epoetin delta since it is considered similar to a human protein and it is non-genotoxic in a standard battery of tests.

One *in vitro* cell proliferation assay was performed and was designed to compare the *in vitro* effects of epoetin delta and epoetin alfa on the growth of 6 different cell lines. Results of this study suggested that epoetin delta will act only on its intended target cells and will produce similar effects as normal human erythropoietin.

**Reproduction Toxicity**

In a rat fertility study, epoetin delta was well tolerated, producing a slight reduction of body weight gain and slight to moderate effects on semen at all dose-levels. These effects were not considered to be toxicologically significant as no adverse effects on either mating or fertility indices occurred and there were no histological changes observed in the testes. Similar effects on sperm parameters and spermatozoids in rats were also observed with the comparator product epoetin alfa.

Epoetin delta, when administered daily by i.v. injection to pregnant female rats at doses of up to 1500 U/kg produced no signs of maternal toxicity. A slight reduction of foetal body weight and delayed ossification of numerous bone structures were, however, observed. There was no dose relationship. These skeletal anomalies were not accompanied by morphological alterations and are not considered to be teratogenic effects. Similar effects were also observed in a rabbit teratogenicity study. These findings were also observed in animals treated with epoetin alfa, which is suggestive that they are class-related effects rather than compound specific.

In a pre- and post-natal development study using daily i.v. doses of up to 1500 U/kg from gestation day 6, through lactation and weaning, treatment-related pharmacological effects were observed on the F₀ females and their offspring. Secondary effects on the physical development of animals of the F₁ generation were also observed. These effects were generally slight or moderate and did not impair normal development of the F₀ generation up to and including the production of the F₂ generation. Similar effects have been observed in previous reproductive toxicity studies with recombinant hamster/human erythropoietin.

**Local Tolerance**

Epoetin delta as a ready-prepared aqueous solution, was injected as single i.v., intra-arterial, paravenous, s.c. or intramuscular doses to groups of female albino New Zealand White rabbits. The
injections were well tolerated, with no macroscopic or microscopic evidence of increased irritation compared to controls for all routes of administration.

Epoetin delta was also tested for pyrogenicity in male rabbits and no rectal temperature rises of more than 0.6°C above predose temperatures were observed over 3 hours following an i.v. administration. Therefore, epoetin delta is considered to be non-pyrogenic.

**Ecotoxicity/Environmental Risk Assessment**

No formal risk assessment has been conducted, however, epoetin delta is very similar to naturally occurring human erythropoietin. As already stated, it would be expected that the metabolism and excretion would be similar to that of the endogenous material and hence, no potentially harmful effects to the environment are expected.

**Product interactions**

Interaction studies have not been performed, but it was considered acceptable to address this issue in the clinical part. Any evidence of product interactions will be reported post-authorisation.

**Discussion on toxico-pharmacological aspects**

Overall pharmacokinetic and pharmacodynamic studies provided adequate evidence for efficacy of epoetin delta and consistent effects associated with the known pharmacology of erythropoietin were produced. The efficacy of epoetin delta was demonstrated in rats and dogs in a series of multidose studies and was shown to be equivalent to epoetin alfa. The pharmacokinetics of the compounds are also similar. The kinetics of epoetin delta are not linear, nor are they stable with time. However, the observation of a decrease in exposure following repeated intravenous administration, both pre-clinically and clinically, did not have an impact on the clinical efficacy (see Part IV: Clinical aspects).

The pharmacodynamic effects of epoetin delta appear to be consistent with the known pharmacological actions of erythropoietin. The increase in blood pressure and decrease in heart rate observed in the safety pharmacology study are considered to be secondary to the effects of elevated HCT on blood viscosity, or an epoetin delta-mediated increase in total peripheral resistance. Both of these hypotheses have been suggested as mechanisms responsible for the development of hypertension in patients treated with recombinant epoetin alfa.

The toxicological findings produced by epoetin delta are similar to those of epoetin alfa and includes no systemic effects unrelated to erythropoietic stimulation. No untoward findings were seen in reproduction or genotoxicity studies.

Of minor concern, however, are the adverse effects on sperm morphology and motility and the reduced survival and ossification seen in F1 pups. In this case, the relationship to epoetin delta pharmacology is less clear. However, as there were no effects on fertility and mating, no histological changes were observed and similar effects were seen with epoetin alfa, it is likely that this finding is of no toxicological significance. Further, these effects were seen at doses far in excess of the clinical dose and are not considered to be toxicologically significant.

One *in vitro* cell proliferation assay was performed, which indicated that epoetin delta only caused increases in proliferation in cells known to respond to erythropoietin or suspected of having erythropoietin receptors. In addition, positive effects of epoetin delta were always similar to those seen with epoetin alfa. Furthermore, the level and size of any residual host cell DNA in the finished product are such that there is no significant safety risk to patients.

4. **Clinical aspects**

Erythropoietin is an essential growth factor required for production of red blood cells. The stimulus for erythropoietin production is believed to be the oxygen content of blood delivered to the renal peritubular interstitial cells. When the peritubular renal cells are functioning correctly, individuals
with low blood haemoglobin (HGB) concentrations will produce increased quantities of erythropoietin, resulting in increased red blood cell production. Chronic renal failure (CRF) is characterised by a progressive loss of kidney function resulting from inherited disorders or conditions such as diabetes mellitus or hypertension. Anaemia of CRF is a chronic condition where failure of the diseased kidney to produce sufficient quantities of erythropoietin is the predominant pathophysiological mechanism.

Over the past fifteen years it has been shown that genetically engineered erythropoietin administered to anaemic CRF patients resulted in clinically significant increases in HGB. Epoetin alfa has been given to treat CRF anaemia in patients on dialysis as well as in those not yet receiving dialysis.

Epoetin delta is a glycoprotein containing 165 amino acids with two disulfide bonds and four sites of carbohydrate attachment. Epoetin delta consists of human erythropoietin produced by genetic engineering in a continuous human cell line and can be given intravenously (i.v.) or subcutaneously (s.c.).

For Epoetin delta it is recommended to adjust the dose individually to maintain the target haemoglobin in the range 10 to 12 g/dl. A starting dose is recommended of 50 IU/kg three times a week if given intravenously or twice a week if given subcutaneously.

All clinical trials were performed according to Good Clinical Practice (GCP) standards and agreed international ethical principles such as the Declaration of Helsinki and the ICH E6 ICH GCP guideline.

Clinical pharmacology

Pharmacodynamics

The pharmacodynamic effects of epoetin delta were examined in two 4-week clinical pharmacology studies. One randomised, double-blind, placebo-controlled, single followed by multiple dose, escalating study in twenty-one healthy male subjects. One randomised, double-blind, parallel group, epoetin alfa-controlled, single followed by multi-dose study in forty subjects (60% women) with chronic renal failure requiring haemodialysis who had been receiving epoetin alfa for at least 90 days with resulting HGB values between 10 to 12 g/dl. The patients started with an haemoglobin between 10 and 12, but epoetin alfa was withdrawn until the haemoglobin fell by 20% or to 9 g/dL whichever was lower. Increases in four main parameters were used to define the pharmacodynamic response: haemoglobin (primary parameter) and haematocrit, reticulocytes count and total erythrocyte count (RBC) (secondary parameters). Epoetin delta was administered i.v. as a single dose, followed by three times weekly over a dose range of 15-100 U/kg in healthy subjects and 50 or 100 U/kg in chronic renal failure subjects.

In healthy subjects epoetin delta had a non-linear dose-related effect on the pharmacodynamic parameters studied with increased HGB slope with increased dose (p=0.0001). The 15 IU/kg dose was close to the no-effect dose while 40U/kg and 100U/kg doses were distinguishable from placebo. Over a four week period the increase in haematocrit was 0.12 and 0.18 %/day with 40 and 100 IU/kg, which is comparable to results for epoetin alfa for the same two doses.

In CRF patients HGB started to increase with time for the four treatment groups from study day 10. Results were comparable between epoetin delta and epoetin alfa for the two doses evaluated and were not statistically differentiated at the 0.10 level. Both treatments displayed a trend of dose and concentration related increases in the pharmacodynamic parameters used to evaluate the activity of epoetin delta although not statistically significant. To detect an overall dose effect (i.e. between 50 and 100U/kg, p<0.05) it was necessary to get an average of results for both epoetin delta and epoetin alfa.

Based upon these preliminary data, clinical activity can be expected based on a starting dose of 50 U/kg, three times weekly within 1-2 weeks of initiating therapy. The magnitude and onset of the response will be comparable to that of epoetin alfa.
**Pharmacokinetics**

The pharmacokinetic properties of epoetin delta were examined in both healthy subjects (dose range 15 U/kg to 100 U/kg) and subjects with chronic renal failure (dose range 50 U/kg to 300 U/kg) following both i.v. and s.c. administration. The pharmacokinetics of i.v. epoetin delta in patients with CRF were similar to epoetin alfa. Following i.v. doses, volume of distribution approximates total blood volume and ranges from 0.063 to 0.097 l/kg. The elimination half-life ranges from 4.7 to 13.2 hours in subjects with chronic renal failure and from 2.2 (15U/kg) to 6.3 (100U/kg) in healthy subjects (approximately 50% shorter). Measurable concentrations of epoetin delta are maintained in the serum for at least 24 hours following doses ranging from 50 U/kg to 300 U/kg. Clearance showed a general inverse relationship with dose in healthy individuals but not in patients with CRF. Exposure to epoetin delta increases proportionately in subjects with chronic renal failure following i.v. administration of 50 U/kg to 300 U/kg. No accumulation of epoetin delta was observed after repeated i.v. administration three times weekly in either healthy subjects or patients with CRF. Instead subchronic dosing three times weekly for four weeks resulted in a 30-40% decrease in exposure and half-life for both epoetin delta and epoetin alfa.

Peak serum concentrations for s.c. administered epoetin delta occur between 8 and 36 hours following injection. The half-life of epoetin delta following s.c. administration is prolonged compared to i.v. administration and ranges from 27 to 33 hours in subjects with chronic renal failure. The bioavailability of s.c. administered epoetin delta is between 26% (150 U/kg) and 36% (300 U/kg).

The pharmacokinetics of single dose and multidose epoetin delta are comparable which is consistent with the lack of observed accumulation following chronic administration. The pharmacokinetic results are consistent with the known pharmacokinetics of erythropoietin and confirm the differences between subcutaneous and intravenous dosing.

**Interaction studies**

No formal pharmacokinetic interaction studies have been performed, which may be acceptable given the known pharmacology of erythropoietin and this is referred to in the SPC. Since epoetin delta is a protein, it is not expected to bind to other proteins and metabolic degradation is expected to follow the pathways of endogenous erythropoietin.

**Special groups**

Pharmacokinetics in children, elderly and in hepatic insufficiency populations have not been established with epoetin delta, which has been appropriately reflected in the SPC. However, a significant proportion of the efficacy trial population was over 65 years of age. In addition, a subgroup analysis of safety and efficacy for each of 3 populations (non-elderly, < 65 yr, elderly 65-75 yr. and extreme elderly, >75 yr) indicates that clinically relevant pharmacokinetic differences are unlikely. In view of the large number of geriatric subjects treated in the clinical studies (496/1308), sufficient information has been generated to allow for a precise assessment of dose, safety and efficacy without an additional study.

**Clinical efficacy**

Clinical experience with epoetin delta was obtained from two phase II controlled studies, one phase III study with a controlled period (double-blind) and an uncontrolled period (open-label), and one phase III uncontrolled (open-label) study. A total of 1308 chronic renal failure subjects with anaemia or a history of anaemia were treated with epoetin delta and 221 subjects were treated with the active comparator, epoetin alfa. There were 677 subjects who received epoetin delta during controlled studies. The treatment regimens were consistent with clinical practice and European Best Practice Guidelines for the Management of Anaemia in patients with CRF and all patient were monitored for need of iron supplementation. A summary description of these studies is provided below:
Studies providing clinical experience data

<table>
<thead>
<tr>
<th>Study</th>
<th>Duration (Phase)</th>
<th>Design</th>
<th>Dialysis type</th>
<th>Route</th>
<th>Dose(s) (U/kg)</th>
<th>No. of subjects</th>
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<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Epoetin delta</td>
<td>Epoetin alfa</td>
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<tr>
<td>Anemic subjects not previously exposed to epoetin alfa</td>
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<tr>
<td>A2002</td>
<td>12 weeks</td>
<td>Controlled; R,</td>
<td>Haemo</td>
<td>i.v.</td>
<td>epoetin delta: 15, 50, 150, 300 [a] epoetin alfa: 50 [a]</td>
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<tr>
<td></td>
<td>(Phase II)</td>
<td>DB, PG, DR</td>
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<td></td>
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<tr>
<td>A2004</td>
<td>12 weeks</td>
<td>Controlled; R,</td>
<td>Pre</td>
<td>s.c.</td>
<td>epoetin delta: 15, 50, 100, 200 [a] epoetin alfa: 50 [a]</td>
<td>64</td>
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<tr>
<td></td>
<td>(Phase II)</td>
<td>DB, PG, DR</td>
<td></td>
<td></td>
<td></td>
<td>16</td>
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<tr>
<td>Subjects previously controlled with epoetin alfa</td>
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<tr>
<td>A3001</td>
<td>24 weeks</td>
<td>Controlled; R,</td>
<td>Haemo</td>
<td>i.v.</td>
<td>Same as prestudy epoetin alfa dose, then titrated based on HGB</td>
<td>552</td>
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<tr>
<td></td>
<td>(Phase III)</td>
<td>DB</td>
<td></td>
<td></td>
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<td>191</td>
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<tr>
<td></td>
<td>weeks 25 to 52</td>
<td>Uncontrolled;</td>
<td>Haemo</td>
<td>i.v.</td>
<td>Same dose as week 24, then titrated based on HGB</td>
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<td></td>
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<td>A3002</td>
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<td>Uncontrolled;</td>
<td>Haemo</td>
<td>s.c.</td>
<td>Same dose as prestudy, then titrated based on HGB</td>
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<td>(Phase III)</td>
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<td>Peritoneal s.c.</td>
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<td></td>
<td></td>
<td>Pre</td>
<td>s.c.</td>
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</tr>
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</table>

R = randomised; DB = double-blind; PG = parallel group; DR = dose-response; OL = open-label; haemo = haemodialysis; pre = predialysis; i.v. = intravenous; s.c. = subcutaneous; HGB = haemoglobin; NA = not applicable

[a] After achieving HGB level \( \geq 11.5 \text{ g/dl} \) for two consecutive weeks or \( \geq 13 \text{ g/dl} \) once, dose was titrated based on HGB.

[b] The epoetin alfa subjects used a non-US formulation containing a phosphate buffer.

**Dose-response studies and main clinical studies**

**Dose response studies**

Studies A2002 (i.v.) and A2004 (s.c.) were dose-response studies of haemodialysis subjects in A2002, predialysis subjects in A2004 never previously treated with epoetin alfa (base haemoglobin below 10g/dL). The primary efficacy endpoint was ‘Total Success’ defined as the achievement of both ‘Correction Success’ (a haemoglobin level of \( \geq 11.5 \text{ g/dl} \) for two consecutive weeks or 13 g/dl once) and ‘Maintenance Success’ (maintenance of haemoglobin levels \( \geq 10.5 \text{ g/dl} \) after 12 weeks of therapy). In contrast to standard medical practice, this study design did not allow the subjects’ dose to be increased above that to which they were initially randomised.

In both studies, there were statistically significant differences (\( p = 0.0002 \) in study A2002 and \( p = 0.0001 \) in study A2004) in the percentages of subjects with the primary endpoint ‘Total Success’ (Correction and Maintenance Success) in the pooled two highest epoetin delta dose groups (150 and 300 IU/kg; 55.6% in study A2002 and 100 and 200 IU/kg; 85.2% in study A2004) compared to the 15 IU/kg group (4.5% in study A2002 and 13% in study A2004). Furthermore, the ‘Total Success’ rate showed a statistically significant increasing trend in dose-effect (\( p = 0.0001 \) using Jonckheere-Terpstra test) across the epoetin delta dose groups. There was no significant difference in ‘Total Success’ between the epoetin delta and epoetin alfa 50U/kg dose groups in either study.
‘Total Success’ in dose finding studies - ITT population

<table>
<thead>
<tr>
<th>Study</th>
<th>No. with Total success/No. treated (%)</th>
<th>Epoetin delta</th>
<th>epoetin alfa</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td>15 IU/kg</td>
<td>50 IU/kg</td>
</tr>
<tr>
<td>A2002</td>
<td></td>
<td>1/22 (4.5%)</td>
<td>3/14 (21.4%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15 IU/kg</td>
<td>50 IU/kg</td>
</tr>
<tr>
<td>A2004</td>
<td></td>
<td>3/23 (13.0%)</td>
<td>6/15 (40.0%)</td>
</tr>
</tbody>
</table>

Response to epoetin delta was consistent across both studies with the rate of increase in haemoglobin showing a statistically significant increasing trend with increasing dose of epoetin delta. Anaemic chronic renal failure subjects not previously treated with epoetin alfa responded to epoetin delta with a median rate of haemoglobin and haematocrit rise as shown below:

<table>
<thead>
<tr>
<th>Starting epoetin delta dose</th>
<th>Type of dialysis</th>
<th>Median haemoglobin increase</th>
<th>Median haematocrit increase</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>g/dl per day</td>
<td>g/dl per 4 weeks</td>
</tr>
<tr>
<td>A2002: 3x weekly i.v. haemodialysis</td>
<td></td>
<td>15 U/kg</td>
<td>0.013</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50 U/kg</td>
<td>0.031</td>
</tr>
<tr>
<td></td>
<td></td>
<td>150 U/kg</td>
<td>0.076</td>
</tr>
<tr>
<td></td>
<td></td>
<td>300 U/kg</td>
<td>0.070</td>
</tr>
<tr>
<td>A2004: 2x weekly s.c. predialysis</td>
<td></td>
<td>15 U/kg</td>
<td>0.017</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50 U/kg</td>
<td>0.032</td>
</tr>
<tr>
<td></td>
<td></td>
<td>100 U/kg</td>
<td>0.072</td>
</tr>
<tr>
<td></td>
<td></td>
<td>200 U/kg</td>
<td>0.090</td>
</tr>
</tbody>
</table>

In both studies, the rate of change in haemoglobin showed a statistically significant dose-response effect (p=0.0001) with increasing dose of epoetin delta. The rate of change for haemoglobin and haematocrit was comparable in the epoetin delta and Epogen 50U/kg dose groups.

**Long-term efficacy**

Study A3001 was a controlled study of 743 anaemic chronic renal failure subjects undergoing haemodialysis previously treated with i.v. epoetin, 552 were randomised to epoetin delta and 191 to epoetin alfa. All patients included had haemoglobin values of 10-12 g/dl on two consecutive weeks before randomisation. The dose of epoetin delta was identical to the dose of epoetin alfa at study entry and could be adjusted every fourth week to maintain the haemoglobin level at 10-12 g/dl.

The primary efficacy endpoint for study A3001 was the difference in average HGB levels between epoetin delta and epoetin alfa after 12, 16, 20 and 24 weeks’ treatment. Study A3001 was designed to show that this difference was within the clinically acceptable predefined range of −1 to 1 g/dl, i.e. efficacy of epoetin delta was to be concluded if the 90% confidence interval (CI) was within this interval.

Secondary efficacy endpoints included average HGB and HCT, percentage of HGB measurements above 10g/dl, percentage of HCT measurements above 30% and average treatment dose after 12, 16, 20 and 24 weeks treatment.

The secondary objective was to assess the long-term safety of epoetin delta.

The efficacy results were nearly identical for the two treatments as shown in the table below:
Long-term efficacy in study A3001

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unit</th>
<th>Epoetin delta</th>
<th>Epoetin alfa</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemoglobin</td>
<td>g/dl</td>
<td>11.57</td>
<td>11.56</td>
</tr>
<tr>
<td>Diff. epo delta – epo alfa (90% CI)</td>
<td></td>
<td>0.01 (−0.13; 0.15)</td>
<td></td>
</tr>
<tr>
<td><strong>Secondary</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haematocrit</td>
<td>%</td>
<td>36.8</td>
<td>36.6</td>
</tr>
<tr>
<td>Average dose[a]</td>
<td>U/kg</td>
<td>64</td>
<td>63</td>
</tr>
</tbody>
</table>

Average dose required to maintain haemoglobin in the target range of 10 to 12 g/dL when administered i.v. three times weekly over weeks 12 to 24.

The percentage of subject’s haemoglobin and haematocrit measurements that were above 10 g/dL and 30% respectively, for weeks 12, 16, 20 and 24 were, for haemoglobin: 89.0% epoetin delta vs. 90.5% epoetin alfa and for haematocrit: 95.7% epoetin delta vs. 93.9% epoetin alfa.

Inadequate responses were retrospectively analysed and defined as having a blood transfusion, having a haemoglobin level of < 8.5 g/dL on at least one occasion, or if a dose of epoetin (alfa or delta) of ≥450 IU/kg/week had been required to produce the expected increase in haemoglobin concentration. 27% of the epoetin delta patients and 23% of the epoetin alfa patients had at least one criteria for inadequate response and in 5% of the epoetin delta patients and 6% of the epoetin alfa patients no cause of the inadequate response could be found, but the possibility of anti-erythropoietin antibodies were excluded in all patients apart from two in each group who were not tested.

Study A3001 had an open-label, uncontrolled continuation phase. Epoetin delta was administered three times weekly during weeks 25 to 52, after 24 weeks of double-blind treatment with either epoetin delta or epoetin alfa, i.e. the subjects on epoetin delta continued their treatment while those on epoetin alfa were switched to epoetin delta. Epoetin delta (approximately 60 U/kg average dose given three times weekly) was effective at maintaining haemoglobin levels within the target range of 10 to 12 g/dL after exposure up to 52 weeks. The mean average haemoglobin after treatment with epoetin delta to week 52 was 11.31 g/dL and was similar to that for epoetin alfa during the first 24 weeks.

A3002 was an open-label study in chronic renal failure subjects previously treated with s.c. epoetin alfa, and included a total of 478 subjects: haemodialysis, peritoneal dialysis, or predialysis. Of the 478 treated subjects 365 (76.4%) completed at least 24 weeks of treatment and 113 (23.6%) were withdrawn prior to completing 24 weeks. Efficacy parameters were based on weekly evaluation of haematological parameters (HGB, HCT, RBC count and RET) and included average HGB and HCT, percentage of HGB measurements above 10 g/dL, percentage of HCT measurements above 30% as well as dose of epoetin delta after 12, 16, 20 and 24 weeks treatment.

Epoetin delta was effective at maintaining haemoglobin levels within the target range of 10 to 12 g/dL when administered s.c. once, twice or three times weekly up to 52 weeks as shown in the table below for the modified intent-to-treat population (N = 411):

<table>
<thead>
<tr>
<th>Variable</th>
<th>1 x weekly (N=101)</th>
<th>2 x weekly (N=152)</th>
<th>3 x weekly (N=158)</th>
<th>Total (N=411)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Average haemoglobin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>11.47 (1.13)</td>
<td>11.31 (1.10)</td>
<td>11.20 (1.09)</td>
<td>11.13 (1.11)</td>
</tr>
<tr>
<td><strong>Average haematocrit</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>36.9 (3.5)</td>
<td>36.3 (3.7)</td>
<td>36.2 (3.8)</td>
<td>36.4 (3.7)</td>
</tr>
<tr>
<td><strong>Average weekly dose</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>66.2 (58.3)</td>
<td>76.2 (58.3)</td>
<td>103.9 (88.0)</td>
<td>84.4 (72.8)</td>
</tr>
</tbody>
</table>
The main conclusion is that the results with s.c. administration of epoetin delta in this trial appear to be similar to those for i.v. administration in trial A3001. The median s.c. weekly dose at weeks 12-24 was some 45% of the weekly i.v. dose given.

**Clinical studies in special populations**

No trials have been conducted in special populations.

**Patient safety**

**Patient exposure**

In controlled and uncontrolled studies, 1308 subjects were exposed to epoetin delta. Of these, 861 were exposed for at least 24 weeks and 146 were exposed for 52 weeks. Epoetin delta was studied in double-blind, active controlled trials (677 subjects with epoetin delta and 221 with active control [epoetin alfa]) in subjects with chronic renal failure receiving varying dose amounts either by i.v. or s.c. injection. Total exposure to epoetin delta was 756 patient-years (248 controlled and 508 uncontrolled) and for epoetin alfa was 84 patient-years.

**Adverse events and serious adverse events/deaths**

The adverse event profile in controlled studies was comparable between epoetin delta and epoetin alfa for all subjects and in all subgroups evaluated including demographics (age, sex, race), duration of haemodialysis and concurrent illness (hypertension, diabetes). The two dose response studies (A2002 and A2004) using i.v. doses ranging from 15 to 300 U/kg three times weekly and s.c. doses ranging from 15 to 200 U/kg two times weekly showed no dose related adverse events. Most of the adverse events reported in clinical trials with epoetin delta were related to chronic renal failure, concomitant diseases, or concomitant treatment and were not necessarily attributable to epoetin delta therapy.

The following table provides the treatment emergent adverse events (TEAEs) reported in 10% or more of subjects receiving epoetin delta during the double-blind phase of active controlled trials in chronic renal failure subjects:

<table>
<thead>
<tr>
<th>Most Frequent (&gt;10%) Treatment Emergent Adverse Events in Controlled Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEAEs</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Subjects with events</td>
</tr>
<tr>
<td>Hypotension</td>
</tr>
<tr>
<td>Muscle cramps</td>
</tr>
<tr>
<td>Upper respiratory infection</td>
</tr>
<tr>
<td>Headache</td>
</tr>
<tr>
<td>Infection</td>
</tr>
<tr>
<td>Thrombosis</td>
</tr>
<tr>
<td>Diarrhea</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Dizziness</td>
</tr>
<tr>
<td>Malaise</td>
</tr>
</tbody>
</table>

In both controlled and uncontrolled clinical studies (total exposure of 756 patient-years), the most frequent adverse events per 100 patient-years of exposure were: hypotension (45.4), muscle cramps (38.4), upper respiratory infection (38.2), headache (37.3), infection (32.9), thrombosis (26.3), and hypertension (25.0).
Serious adverse events:

Controlled studies: 205/677 (30.3%) epoetin delta subjects and 59/221 (26.7%) epoetin alfa subjects reported serious TEAEs. The most frequent serious TEAEs for epoetin delta vs. epoetin alfa were infections (3.7% vs. 2.3%), sepsis (3.1% vs. 1.8%), “non-specified” infection (3.0% vs. 1.4%) and thrombosis (2.7% vs. 2.7%). Uncontrolled studies: 376/1061 (35.4%) epoetin delta subjects reported serious TEAEs. The most frequent serious TEAEs were thrombosis (3.5%), sepsis (3.3%) and myocardial infarction (2.9%).

Cluster events:

The overall incidence of TEAEs categorized by cluster, in controlled studies was similar between the epoetin delta (40.6%) and epoetin alfa (38.9%) treatment groups.

<table>
<thead>
<tr>
<th>TEAE</th>
<th>Controlled (a)</th>
<th>Uncontrolled (b)</th>
<th>Total (c)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>epoetin delta</td>
<td>epoetin alfa</td>
<td></td>
</tr>
<tr>
<td>Subjects with cluster</td>
<td>N=677</td>
<td>N=221</td>
<td></td>
</tr>
<tr>
<td></td>
<td>275 (40.6%)</td>
<td>86 (38.9%)</td>
<td>416 (39.2%)</td>
</tr>
<tr>
<td>or seizure-related TEAEs</td>
<td></td>
<td></td>
<td>598 (45%)</td>
</tr>
</tbody>
</table>

TEAEs by cluster:

<table>
<thead>
<tr>
<th>TEAE</th>
<th>Controlled (a)</th>
<th>Uncontrolled (b)</th>
<th>Total (c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arteriosclerosis:</td>
<td>84 (12.4%)</td>
<td>20 (9.0%)</td>
<td>220 (16.8%)</td>
</tr>
<tr>
<td>Symptomatic IHD:</td>
<td>47 (6.9%)</td>
<td>8 (3.6%)</td>
<td>131 (10.0%)</td>
</tr>
<tr>
<td>CVD:</td>
<td>10 (1.5%)</td>
<td>1 (0.5%)</td>
<td>38 (2.9%)</td>
</tr>
<tr>
<td>CHF:</td>
<td>25 (3.7%)</td>
<td>11 (5.0%)</td>
<td>82 (6.3%)</td>
</tr>
<tr>
<td>PVD:</td>
<td>31 (4.6%)</td>
<td>15 (5.9%)</td>
<td>80 (6.1%)</td>
</tr>
<tr>
<td>Venous Thromboembolism:</td>
<td>4 (0.6%)</td>
<td>0 (0%)</td>
<td>13 (1.0%)</td>
</tr>
<tr>
<td>Hypertension:</td>
<td>80 (11.8%)</td>
<td>22 (10.0%)</td>
<td>190 (14.5%)</td>
</tr>
<tr>
<td>Access-related events:</td>
<td>132 (19.5%)</td>
<td>48 (21.7%)</td>
<td>281 (21.5%)</td>
</tr>
<tr>
<td>Seizure-related events:</td>
<td>4 (0.6%)</td>
<td>2 (0.9%)</td>
<td>8 (0.6%)</td>
</tr>
</tbody>
</table>

IHD = any form of ischaemic heart disease a Studies A2002 and 2004 and double blind phase of A3001
CVD= any form of cerebrovascular disease b Open-label phase of A3001 and study A3002
CHF= any type of cardiac failure c Total= number of TEAEs reported in epoetin delta subjects from controlled and uncontrolled studies
PVD= peripheral vascular disease
Arteriosclerosis-related events include IHD, CVD and PVD clusters

The majority of cluster TEAEs were either access-related (19.5% epoetin delta vs. 21.7% epoetin alfa, mostly clotted dialysis access), or hypertension events (11.8% epoetin delta vs. 10.0% epoetin alfa). Although 90% of the subjects had hypertension at baseline, only approximately 10% experienced hypertension cluster events in both treatment groups; 4.3% of patients not having a history of hypertension experienced hypertension TEAEs. Here were also more ‘possibly related hypertension’ events in the epoetin delta group (3.2%) than in the epoetin alfa group (1.4%) but serial blood pressure measurements did not support any difference. All cluster TEAEs occurred at comparable rates between the 2 treatment groups with the exception of TEAEs in the symptomatic IHD category which appeared to be reported at a higher frequency in the epoetin delta treatment group (47/677, 6.9%) compared to the epoetin alfa group (8/221, 3.6%).

Arteriosclerosis-IHD, PVD, CVD, CHF: the difference observed between treatments in symptomatic IHD cluster TEAEs was mainly due to an increased frequency of angina pectoris (33/677, 4.9% epoetin delta vs. 4/221, 1.8% epoetin alfa) and to a lesser extent myocardial infarction (9/677, 1.3% epoetin delta vs. 1/221, 0.5% epoetin alfa). A logistic regression analysis taking baseline risk factors
into account showed a trend to a higher frequency with epoetin delta, but the difference between event rates for epoetin delta and epoetin alfa was not statistically significant (p=0.0716). A time-to-event analysis showed a similar result (p=0.0578). This higher frequency of symptomatic IHD events in the epoetin delta group was not confirmed by respectively higher frequencies of other serious and non-serious vascular events like PVD (4.6% for epoetin delta vs. 5.9% for epoetin alfa), CVD (1.5% vs. 0.5%), and CHF (3.7% vs. 5.0%) or venous thrombotic (0.6% vs. 0.8%) TEAE clusters. However, when taking into account arteriosclerotic TEAEs (by combining symptomatic IHD, CVD, and PVD cluster events), there was still a greater percentage events for epoetin delta (12.4% epoetin delta and 9.0% epoetin alfa). This is probably not clinically relevant since the previous history of IHD was high (approximately 40%) in both treatment groups. The previous history was the most important contributing factor for the occurrence of symptomatic IHD, as shown in the logistic regression analysis. There was also a lower use of concomitant “cardioprotective” drugs in the epoetin delta group compared to the epoetin alfa group. In order to evaluate the apparent slight increase in ischaemic heart disease among epoetin delta patients compared to epoetin alfa patients, the applicant has made appropriate commitments in order to follow up all cardiovascular events closely during the post-marketing phase.

**Hypertension:** The incidence of hypertension adverse events was similar in subjects receiving epoetin delta (12%) and subjects receiving epoetin alfa (10%) from controlled studies. Hypertensive encephalopathy and hypertension seizures have each been observed in a single subject with chronic renal failure treated with epoetin delta. The rate of hypertension adverse events in epoetin delta subjects from controlled trials (up to 6 months) was 32 cases per 100 patient-years while the rate in epoetin delta-treated subjects from the longer duration uncontrolled trials (> 6 months to 1 year) was 24 cases per 100 patient-years; the lower incidence of hypertension events in uncontrolled trials may suggest that the risk of hypertension does not increase over time. The onset of hypertension adverse events was similar between epoetin delta and epoetin alfa subjects with approximately 50-60% of these cases reported during the first 90 days of therapy.

**Seizure-related events (convulsions):** In controlled trials 4/677 (0.6%) subjects treated with epoetin delta experienced convulsions during controlled trials whereas 2/221 (0.9%) subjects receiving epoetin alfa experienced convulsions, with a frequency per 100 patient-years for epoetin delta of 1.6 and for epoetin alfa of 2.4. All convulsions occurred in subjects undergoing haemodialysis who had a history of hypertension; 4 events occurred during or immediately following a dialysis session and 1 event was associated with a hypertensive crisis.

In controlled and uncontrolled trials, the convulsion rate for epoetin delta-treated subjects was 1.1 per 100 patient-years. The majority (6 of 8 epoetin delta treated subjects) of these convulsions occurred after the first 3 months of treatment. Four of the 9 subjects (one had convulsion under epoetin alfa and then again after switching to epoetin delta in study A3002) who experienced convulsions also had a history of convulsions.

**Hypersensitivity reactions:** In controlled studies, the overall incidence of hypersensitivity reaction TEAEs (both systemic and local) was similar between the epoetin delta (21.6%) and epoetin alfa (18.6%) groups. During uncontrolled studies, the incidences of individual hypersensitivity reaction TEAEs were similar to the frequencies reported during controlled studies.

In controlled clinical trials, 3/677 (0.4%) epoetin delta treated subjects and 1/221 (0.5%) epoetin alfa treated subjects reported serious systemic hypersensitivity reactions, one of which was regarded as possibly related to treatment with epoetin delta (angioedema). However, this case was not considered a new safety signal because it represented an isolated occurrence with alternative explanations. No antibodies to epoetin delta were detected in any subjects tested in the clinical trials.

**Renal failure related TEAEs:** In controlled studies involving predialysis subjects (A2004), renal failure-related TEAEs were reported in 9.4% (6/64) of epoetin delta subjects versus no cases (0/16) in epoetin alfa subjects (Fisher’s exact test: p=0.340). During the uncontrolled studies involving predialysis subjects (A3002), 13.9% (5/36) of subjects experienced renal failure related TEAEs. In two subjects, the investigator as possibly related to study medication assessed the renal failure-related...
TEAEs. Worsening of renal failure may occur for many reasons in predialysis patients. This complication appeared not to be dose related in study A2004 and some of these subjects recovered despite continued treatment with epoetin delta.

**Anti-erythropoietin antibodies:** There were no positive on-treatment assessments for anti-erythropoietin antibody in the 15 healthy subjects (A1001) or 39 CRF subjects (A2003) exposed to epoetin delta in clinical pharmacology studies. Similarly, there were no positive on-treatment assessments in the 1235 evaluable subjects exposed to epoetin delta or in the 203 subjects exposed to epoetin during uncontrolled studies. There were no cases of pure red cell aplasia in subjects treated with epoetin delta. The Company has made appropriate commitments to monitor the incidence of antibodies to epoetin delta and investigate the potential neutralising effect of any anti-‘epoetin delta’ antibodies detected during the post-authorisation phase.

**Malignant and benign tumours:** A total of 3/677 (0.4%) epoetin delta subjects and 2/221 (0.9%) epoetin alfa subjects from controlled studies, and 11/1061 (1.0%) epoetin delta subjects from uncontrolled studies reported serious TEAEs that involved cancer. The investigator assessed the relationship of these events to study medication. The overall frequency of death per 100 patient-years of exposure to epoetin delta in controlled and uncontrolled studies was 7.0 compared to 6.0 deaths per 100 patient years for epoetin alfa.

**Adverse events resulting in clinical intervention:** In controlled clinical trials, the incidence of adverse events resulting in discontinuation of treatment was very small in subjects treated with epoetin delta and epoetin alfa (13/677, 2% and 7/221, 3%, respectively). In uncontrolled trials, the incidence was 1.7%. Adverse events resulting in temporary interruption of treatment occurred in 5/677 subjects (1%) treated with epoetin delta compared to 4/221 subjects (2%) treated with epoetin alfa. The occurrence of adverse events resulting in dose reduction was very low in subjects treated with epoetin delta and with epoetin alfa (5/677, 1%; 1/221, 1%, respectively). The occurrence of adverse events treated with counteractive medications was high, as expected in chronic renal failure subjects, but similar in subjects treated with epoetin delta and with epoetin alfa (549/677, 81%; 178/221, 81%, respectively).

**Local injection site reactions:** Subcutaneous injection of epoetin delta was well tolerated. In controlled Study A2004, no local injection site reactions were reported. In uncontrolled Study A3002, few local s.c. injection site reactions were reported: injection site haemorrhage (11/478 subjects, 2%), injection site pain (7/478, 1%), pruritus and allergic reaction (1/478, 0.2% each). The majority of these events were mild to moderate in intensity; all events were transient, and resolved while continuing treatment.

**Deaths:** In controlled trials, the frequencies of deaths occurring during treatment were comparable between subjects treated with epoetin delta (12/677, 1.8%) and with epoetin alfa (5/221, 2.3%). The frequency for occurrence of death based on the survival analysis was also comparable (4.1% for epoetin delta and 4.8 for epoetin alfa). The overall frequency of death per 100 patient-years of exposure to epoetin delta in controlled and uncontrolled studies was 7.0 compared to 6.0 deaths per 100 patient years for epoetin alfa.

**Laboratory findings**

There were modest increases in creatinine, calcium and uric acid, without any statistically significant differences between the two treatment groups. There was no increase in phosphorus, potassium or platelets. Most ferritin levels at baseline were above normal ranges in the two treatment groups. Most subjects were receiving iron supplementation as required by the study protocols.

There was no evidence from the vital signs or ECG data that epoetin delta had any increased risk compared to epoetin alfa.

**Safety in special populations**

**Pregnancy and Lactation:** No pregnancies are reported and this may reflect the high average age of trial patients and the impaired fertility associated with chronic renal failure. This has been appropriately addressed in the SPC.
**Paediatric patients:** An open label, paediatric study is ongoing for epoetin delta in chronic renal failure and will be submitted post-authorisation.

**Discussion on Clinical aspects**

**Discussion on Clinical Efficacy**

Erythropoietins prepared from different sources are thought to be similar in terms of their pharmacodynamic and pharmacokinetic properties.

Two phase II studies have shown definitive evidence of a clear dose response relationship and a similar effect at 50 IU/kg between epoetin alfa and epoetin delta when administered by the i.v. or s.c. routes. Epoetin delta was effective in correcting anaemia in predialysis and haemodialysis subjects who were never previously exposed to epoetin alfa. Based on the results from these studies a starting dose of 50 IU/kg is supported.

In the pivotal phase III study 26% of the study population had an inadequate response to therapy with both epoetin alfa and epoetin delta. The withdrawal rate mainly due to RBC transfusion was approximately 20% in both epoetin delta and epoetin alfa groups. There was obviously considerable overlap between the ‘inadequate response’ and ‘withdrawal groups’.

The weekly dose of epoetin delta was comparable in the <65 years, 65 to 75 years and >75 years age groups in studies A3001 and A3002 in either the intravenous or subcutaneous studies.

Subgroup analysis for age, sex, baseline pathology, dialysis type in all studies did not show unexpected differences between the treatment groups for either efficacy or safety in any of the subgroups.

The main efficacy trial showed near identical mean haemoglobin responses in a large number of patients to near identical mean doses of epoetin alfa (63 IU/kg) and epoetin delta (64 IU/kg) over a six-month period. It was further shown that epoetin delta is effective in maintaining HGB values above 11 g/dl when given by i.v. administration 3 x weekly to haemodialysis subjects who had previously received epoetin alfa over a period of 24 weeks. The median i.v. dose of epoetin delta necessary to maintain HGB levels between 10 and 12 g/dl in haemodialysis subjects was 46.0 IU/kg 3 times weekly during weeks 12 to 24 and 31 IU/kg twice a week following s.c. administration. The total weekly dose given subcutaneously appears just under half of the weekly dose required intravenously.

Efficacy of epoetin delta appears proven, sustained and comparable to epoetin alfa.

**Discussion on Clinical Safety**

Overall, epoetin delta seems to be well tolerated by both i.v. or s.c. routes. There were no significantly different adverse events compared to epoetin alfa. The higher incidence of angina as an adverse event with epoetin delta is noted but this may be a chance finding given the high background incidence of ischaemic heart disease in these patients. In order to evaluate the apparent slight increase in ischaemic heart disease among epoetin delta patients compared to epoetin alfa patients, the applicant has made appropriate commitments to follow up all cardiovascular events closely during the post-marketing phase.

The absence of antibody formation to epoetin delta is encouraging, although limited as no positive controls were tested. The applicant postulates that the formation of antibodies to existing erythropoietin products may be secondary to non-human glycosylation of the product, a step absent from the humanised production of epoetin delta. The applicant has made appropriate commitments to monitor the incidence of antibodies to epoetin delta and investigate the potential neutralising effect of any anti-‘epoetin delta’ antibodies detected during the post-authorisation phase.
In the controlled study involving predialysis subjects (A2004), renal failure-related TEAEs were reported in 9.4% (6/64) of epoetin delta subjects versus no cases (0/16) in epoetin alfa subjects. During the uncontrolled studies involving predialysis subjects (A3002), 13.9% (5/36) of subjects experienced renal failure related TEAEs. In 2 subjects, the investigator assessed the renal failure-related TEAEs as possibly related to study medication. This is unlikely to reflect a difference in the two treatments given the very small numbers and as the incidence of events in the comparison of epoetin delta with epoetin alfa treatment were relatively similar, and there was the inverse relationship between dose and renal failure-related TEAEs. There were no cases of pure red cell aplasia in subjects treated with epoetin delta.

Clinical safety still relies in part upon adequate pharmaceutical quality control and of the known pharmacology of erythropoietin. Overall the death rates are comparable between epoetin delta and epoetin alfa.

5. Overall conclusions and benefit/risk assessment

Quality

The active substance of Dynepo is epoetin delta, a human recombinant erythropoietin produced in a human continuous cell line via the gene activation technology. The use and benefits of a human oncogenic cell line have adequately discussed. The risks from residual DNA and potential host cell protein have also been addressed satisfactorily.

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Viral safety and batch-to-batch consistency has been documented and the relevant test will be performed according to the agreed specifications. Appropriate quality commitments have been set.

Preclinical pharmacology and toxicology

Overall, pharmacokinetic and pharmacodynamic studies provided adequate evidence in support of the efficacy and safety of epoetin delta. Consistent effects associated with the known pharmacology of erythropoietin were produced.

There does not appear to be any target organ toxicity associated with epoetin delta administration. Observed pathology can be related to exaggerated pharmacological activity. Of some concern are the adverse effects on sperm morphology and motility and the reduced survival and ossification seen in F1 pups. In this case the relationship to epoetin delta pharmacology is less clear. However, as the effects were not massive, there were no effects on fertility and mating and similar effects were seen with epoetin alfa, it is likely that this finding is of no toxicological significance. Furthermore, these effects were seen at doses far in excess of the clinical dose.

Efficacy

The pharmacodynamic and pharmacokinetic results are consistent with the known pharmacology of erythropoietin and confirm the differences between subcutaneous and intravenous dosing. Pharmacokinetics in hepatic failure and children has not been studied something which has been adequately reflected in the SPC.

Initial studies appear to provide adequate justification of the dose chosen for the main efficacy trials. The main controlled, blinded efficacy trial provides adequate evidence that epoetin delta is effective in maintaining adequate levels of haemoglobin and haematocrit in patients with chronic renal failure. The open label trial gave similar results with subcutaneous dosing. The results from clinical studies thus support the use of epoetin delta in the approved indication ‘treatment of anaemia in patients with chronic renal failure. It may be used in patients on dialysis and in patients not on dialysis.’ The dose ranging studies showed a clear dose response for both i.v. and s.c. administered epoetin delta and the
clinical data from the two pivotal clinical studies have shown that the recommended dose is effective and safe.

**Safety**

Overall epoetin delta seems to have been well tolerated by either i.v. or s.c. routes. There were no significantly different adverse events compared to epoetin alfa. No anti-erythropoietin antibodies were detected. Nevertheless, the applicant has made appropriate commitments to monitor the incidence of antibodies to epoetin delta and investigate the potential neutralising effect of any anti-‘epoetin delta’ antibodies detected during the post-authorisation phase.

The high background of events in the chronic renal failure population may confuse the identification of treatment related adverse events. Some reassurance is provided by the inverse relationship between renal failure-related TEAEs and dose and by the relatively similar incidence of events in the comparison of epoetin delta with epoetin alfa treatment but even here the confidence intervals are wide.

In order to evaluate the apparent slight increase in ischaemic heart disease among epoetin delta patients compared to epoetin alfa patients, the applicant has made appropriate commitments to follow up all cardiovascular events closely during the post-marketing phase.

Overall the death rates are comparable between epoetin delta and epoetin alfa.

**Benefit/risk assessment**

Based on the CPMP review of data on quality, safety and efficacy, the CPMP considered that the benefit/risk profile of Dynepo in the treatment of treatment of anaemia in patients with chronic renal failure (in patients on dialysis and patients not under dialysis) was favourable and therefore recommended the granting of the marketing authorisation.