SCIENTIFIC DISCUSSION

1. Introduction

Human erythropoietin is a glycoprotein which is produced primarily in the kidneys and promotes red blood cell production by stimulating the division and differentiation of committed progenitors in the bone marrow. Erythropoietin for clinical use is produced by recombinant DNA technology using mammalian cells as expression system. All epoetins in clinical use have a similar amino acid sequence as endogenous erythropoietin but differ in the glycosylation pattern. Glycosylation influences pharmacokinetics and may influence efficacy and safety, particularly immunogenicity.

Epoetin-containing medicinal products are currently indicated for several conditions such as anaemia in patients with chronic renal failure, chemotherapy-induced anaemia in cancer patients and for increasing the yield of autologous blood from patients in a pre-donation programme. The mechanism of action of epoetin is the same in all currently approved indications but the doses required to achieve the desired response may vary considerably and are the highest in the oncology indications.

HX575, the medicinal product applied for, has been developed as a biosimilar product to the reference product Eprex/Erypo (epoetin alfa, Janssen-Cilag GmbH). The active substance for both products, is an epoetin of identical primary structure as the endogenous human erythropoietin and is produced in Chinese Hamster Ovary (CHO) cells.

As required for a Similar Biological Medicinal Product application, the dossier contains a full quality Module 3 and reduced non-clinical and clinical Modules 4 and 5.

Principally, epoetin can be administered as an intravenous (IV) solution or as subcutaneous (SC) injection. Eprex/Erypo (containing epoetin alfa), the reference medicinal product chosen for the comparability exercise in this application, has been contraindicated for SC use in patients with chronic renal failure in the EU member states since December 2002, due to the increased frequency of anti-erythropoietin antibody-induced pure red cell aplasia (PRCA). It is assumed, although not finally proven, that the increased immunogenicity resulted from leachables released from the uncoated rubber stopper used for Eprex/Erypo. Following the start of the procedure, after demonstrating a substantial decrease in the frequency of PRCA, the SC use in patients with renal anaemia has been reinstated (24 May 2006) for epoetin alfa, together with the introduction of coated rubber stoppers and additional pharmacovigilance measures. HX575 drug product was developed with a Teflon coated rubber stopper in order to prevent leachables which may migrate from the primary packaging into the drug product.

During its temporary contraindication (subcutaneous in chronic renal failure patients), Eprex/Erypo could not be used as comparator in respective clinical trials to demonstrate comparability of HX575 versus Eprex/Erypo in the affected population.

The applicant claims all the indications approved for the reference product, with the exception of the indication for increasing the yield of autologous blood from patients in a predonation programme.

2. Quality aspects

Drug Substance

Manufacture
The drug substance is manufactured and released by Rentschler Biotechnologie GmbH, Germany. After a series of sub cultivations, the cells are seeded into the production fermenter. The production is based on a repeated batch fermentation, whereby the individual harvests are collected at daily intervals and each harvest is stored frozen until further processing.

The drug substance is recovered from the fermentation broth by a conventional protein purification process comprising orthogonal chromatography steps and a viral filtration step. The manufacturing

steps are monitored by a number of process controls (like acceptance criteria, action limits, informative values, and operational parameters).

The Master Cell Bank (MCB) and Working cell banks (WCB) were both established without the use of materials of human or animal origin and all subsequent steps in further manufacturing are performed without reagent of animal origin. Insulin provided in the cell medium is produced by *S.cerevisiae.* Characterisation of both cell banks in terms of genetic stability and viral safety is satisfactorily achieved by analysis of genotypic and phenotypic tests as well as virus testing.

Characterisation

HX575 drug substance was extensively characterised using orthogonal "state-of-the-art" methods. The set of analytical methods is appropriately designed and covers the analysis of the primary structure, higher order structures, post-translational modifications and Bioassays.

The characterisation of the protein structure is considered satisfactory. The primary structure and correct formation of disulfide bonds in accordance with the BRP reference standard was mainly confirmed by peptide mapping using different proteases in conjunction with subsequent MALDI-TOF analysis of isolated peptides and could cover 99% of the sequence. Full sequence confirmation was achieved by additional sequencing of selected peptides. Investigations on secondary and tertiary structure are also considered to adequately reflect correct folding of the molecules and batch to batch consistency. With respect to the glycan part the methodology applied for characterisation is also considered satisfactory. Structural analysis of N-glycans and O-glycans comprised monosaccharide analysis, sialic acids characterisation and sequence analysis of N-glycans and O-glycans on a qualitative and quantitative basis. Additionally, site specific glycan analysis has been performed.

High mannose-6-phosphate (HM6P) glycans, have been detected in batches used in clinical studies. These phosphorylated high mannose-type glycan structures were found to be located exclusively on glycosylation site Asn-24 as demonstrated by site specific analysis of glycan structures. It should be noted that HM6P glycan structures are naturally occurring glycan structures on lysosomal hydrolases and have also been detected on non-lysosomal proteins in low amounts. Receptor binding studies showed that HM6P-structures on EPO have a weak binding affinity to the mannose-6-phosphate receptor in contrast to classical mannose-6-phosphate-binding proteins such as lysosomal hydrolases and thus subsequent internalisation under physiological conditions is not expected.

Specification

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

Stability

The claimed shelf-life of the active substance is supported by batch data.

Comparability Exercise for Active Substance

The selected reference product for the comparability exercise was Erypo/Eprex (Janssen-Cilag GmbH). For comparison of the two drug substances the same set of tests and analytical procedures were mainly applied as in the characterisation part.

In accordance with the Guideline on Similar Biological Medicinal Products containing Biotechnology-derived Proteins as Active Substance: Quality Issues (EMEA/CHMP/BWP/ 49348/2005), the applicant isolated active substance from the reference medicinal product in order to perform the comparative analysis at the active substance level for some tests. Isolation was performed by immunoaffinity chromatography.

It was demonstrated that the isolated active substance used in the comparability exercise is representative of the active substance present in the reference medicinal product.

The analysis of the protein part did not reveal any significant difference with the reference product. Differences were observed at the glycosylation level. Phosphorylated high mannose type structures in HX575 were detected at higher levels than in Eprex/Erypo. However, they are considered to be

common glycoforms of recombinant erythropoietins and their presence is described in the literature for other recombinant cytokines and a large variety of non-lysosomal proteins from human plasma. The level of HM6P observed in HX575 did not impact on the efficacy or safety of the drug product. In addition, neuraminic acid differences were observed. However, HX575 drug substance showed lower values of N-glycolyl-neuraminic acid and diacetylated neuraminic acids as compared to Eprex/Erypo.

Comparison of the total molecules with respect to molecular size and aggregation state, binding affinity, biological activity *in vitro* and *in vivo* did not reveal any remarkable differences.

Viral safety

With regard to safety evaluation of adventitious agents multiple levels of control have been established throughout the HX575 drug substance manufacturing process to minimize the risk of contamination of the drug product with adventitious viruses. Cell banks have been extensively tested. A risk assessment with regard to TSE according to the "Note for guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMEA/410/01 Rev.2)" has been done.

Drug Product

The drug product is provided as a liquid ready-to-use solution in a single-dose pre-filled syringe. Epoetin alfa is formulated in a phosphate buffer with glycine and polysorbate 80 at concentrations of 2,000 IU/ml (1,000 IU and 2,000 IU in 0.5 ml and 1.0 ml respectively) and 10,000 IU/ml (3,000 IU, 4,000 IU, 5,000 IU, 6,000 IU, 8,000 IU and 10,000 IU in 0.3, 0.4, 0.5, 0.6, 0.8, 1.0 ml respectively).

Product development and manufacture

The drug product follows the same qualitative and quantitative composition as the reference product Eprex/Erypo. The formulations of both concentrations 16.8 µg/ml and 84 µg/ml are composed of phosphate-buffer, water for injections, polysorbate 80, glycine and sodium chloride, resulting in a different ratio between EPO and the excipients depending on the concentration.

The manufacturing process is a conventional process beginning with the dissolution of polysorbate 80 and other excipients. The solutions are mixed and drug substance bulk solution is added. After mixing, the DS formulated bulk undergoes a double filtration at 0.22 µm into storage bags and is aseptically filled in the syringes thereafter. The validation of the currently used manufacturing process is satisfactory.

Batch analysis

The batches selected for the batch analysis were considered to be acceptable.

Product Specification

Drug product release and stability specifications include tests for identity, purity, content, pharmaceutical tests and microbiological tests.

Stability of the Product

The applicant claims a 24-months shelf-life for the drug product when stored at 2-8°C. A 3 days hold time ≤25°C is also claimed for transportation and before administration of the product.

Comparability Exercise for Drug Product

Large numbers of HX575 and Eprex/Erypo drug product batches with approximately the same age at time of analysis were used for the comparability exercise.

Peptide maps show some differences in the region corresponding to fragments including the O-linked glycan due to a higher sialylation. For presentations at low concentration (i.e. 2000 IU/ml) and at equivalent age, HX575 drug products tends to have lower content of the oxidized variant, significantly fewer amounts of sub-visible particles and lower content of silicone oil than Erypo/Eprex. In summary, the comparability exercise performed at the drug product level shows that HX575 drug product is generally within the variability of Eprex/Erypo for the parameters tested.

3. Non-clinical aspects

Introduction

The biological activity of HX575 final drug product, determined *in vitro* and *in vivo*, was compared to the reference product Eprex/Erypo (Janssen-Cilag, Germany). Five non-clinical studies were submitted by the applicant in order to demonstrate the comparability of HX575 to the reference product Eprex/Erypo and to demonstrate the safety and local tolerability of HX575. These studies were undertaken in mice (pharmacopoeial test), dogs and rabbits.

Pharmacology

In vitro studies (ELISA, Plasmon resonance spectroscopy) indicated that there are no remarkable conformational or modification differences interfering with antibody binding between the different HX575 drug product batches in comparison to the reference product Eprex/Erypo.

A human erythroleukemic cell line was used for the characterization of the proliferation response after stimulation with erythropoietin standard. The human erythroleukemic cell line was used for the characterization of the proliferation response after stimulation with epoetin alfa or the BRP 95/548 erythropoietin standard. Conformational changes or modifications of the test item can influence the receptor binding and/or signal transmission properties and thus alter the response in the in vitro bioassay. Therefore, the cell based *in vitro* bioassay was chosen to characterize receptor binding and signal transmission of HX575, comparator and standard. The dose-response curves of consistency batches were compared with the dose response curves of the BRP 95/548 erythropoietin standard. The same comparison was done between Erypo and the BRP 95/548 erythropoietin standard. No differences became obvious between the HX575 or Erypo preparations and the BRP standard. The dose response curves of both test items are similar.

A 5-day study in dogs was performed, which focused on reticulocytes pharmacodynamic-pharmacokinetic. After three to four days of epoetin alfa injection a clear rise in reticulocytes was observed, which is reversible upon cessation of treatment. Although the quality and size of the biological effect is similar across groups exposed to epoetin alfa without meeting stringent criteria of pharmacokinetic bioequivalence, there was no remarkable difference between the HX575 batches (drug product) and the reference product Eprex/Erypo.

Pharmacokinetics

A study was performed in the dog, aiming to compare the bioavailability of two different batches of HX575 drug product to the reference product Eprex/Erypo, following daily intravenous injection over 5 days. In this study, female dogs were divided into 3 groups and were dosed according to a cross-over scheme. Three different epoetin preparations were tested, namely two batches of HX575 and one comparator batch Erypo. After a drug-free interval of 16 days each group was switched to another batch. Additional female dogs remained untreated and served as a negative control. Thereby each batch of epoetin, including the comparator, was applied to different dogs, and the resulting PK and PD data were treated as x-fold determinations. The following parameters were determined: Pharmacokinetics, haematology (erythrocyte and reticulocyte count, haematocrit, haemoglobin), antibodies against epoetin). In this study, exposures produced by a single iv administration of both test batches were lower than exposure produced by a single iv Eprex/Erypo administration. However, in comparison to the reference Eprex/Erypo, Test 1 (HX575 drug product 10,000 IU/ml) fulfilled conventional bioequivalence acceptance criteria for bioavailability whereas test 2 (HX575 drug product 10,000 IU/ml) did not. The difference in exposure could partly be attributed to the study design itself and potential differences of sensitivity of the ELISA assay for HX575 and Eprex/Erypo, and differences were not regarded to be relevant with respect to the conclusion of the toxicological assessment of the 13-week study performed in the dog. No data were provided regarding bioavailability following sub-cutaneous administration.

Toxicology

No own single dose toxicity studies were submitted by the applicant. According to literature data, the highest epoetin alfa dose tested was > 40-times the highest human dose administered clinically today (600 IU/kg). No lethality occurred.

A 13-week toxicity study was performed in the dog with HX575 drug product or comparator following intravenous administration, in accordance with the EMEA scientific advice. Each group of animals consisting of males and females was dosed IV daily for 13 weeks with either HX575 or with the comparator preparation. Males and females of each group were sacrificed and examined at the end of dosing (week 13), the remaining males and females were allowed to recover for five weeks, i.e. were sacrificed after 18 weeks.

The following parameters were obtained: toxicokinetics, clinical signs, mortality, body weight, food and water consumption, ECG, blood pressure, haematology, biochemistry (blood and urine), ophthalmology, organ weights, histopathology, local tolerance and anti-epoetin antibodies. This study thereby covered not only aspects of toxicity but also provided information on pharmacodynamics (frequent determination of relevant haematological parameters), safety pharmacology (ECG and blood pressure), immunogenicity (antibody formation) and toxicokinetics. For pharmacodynamics assessment the AUC values and the maximal concentrations (Cmax) of the relevant haematological parameters (reticulocyte count, reticulocytes as percentage of erythrocytes, haemoglobin content, haematocrit and erythrocyte count) were also determined for statistical analysis.

This study revealed no signs of overt toxicity. All changes observed were attributed to direct and adaptive responses of the organism to the massive erythropoietic impulse, especially in the high-dose groups. These responses included congestion of inner organs, in particular the spleen, liver and kidneys, changes in blood cellularity, rise in haematocrit and an increase in spleen, liver and kidney weights. A marked haematopoietic activation of the bone marrow was observed in dogs, even in the low-dose group. There was no difference in the safety profile with respect to pharmacodynamic effects or toxicity between HX575 drug product and Eprex/Erypo.

Anti-epoetin antibodies were detected in a few animals (2-3 per epoetin group) by an ELISA, the validation of which was considered acceptable. However, the number of animals affected was too low to allow meaningful conclusions on differences in immunogenicity between HX575 and Eprex/Erypo.

For pharmacodynamics assessment, the AUC values and the maximal concentrations (C_{max}) of the relevant haematological parameters (reticulocyte count, reticulocytes as percentage of erythrocytes, haemoglobin content, haematocrit and erythrocyte count) were determined for statistical analysis. For haemoglobin and haematocrit 100 IU/kg HX575 had the same effect as 500 IU/kg HX575 or Erypo so that for these two parameters the maximum response was obviously already reached at 100 IU/kg. In consequence, differences in potency of HX575 and Erypo, the latter tested at 500 IU/kg only, would not become evident from these parameters. For erythro- and reticulocyte count a clear dose-response-relationship was observed with 100 IU/kg being less effective than 500 IU/kg. There was some biological fluctuation but no systematic difference between 500 IU/kg HX575 and 500 IU/kg Erypo as quantified by calculating erythrocyte count AUC and C_{max}. Concerning reticulocyte count, C_{max} (i.e. maximal reticulocyte number was slightly lower (0.41 vs. 0.45 10^{12} per L) with HX575 than with Erypo, but AUC was virtually identical.

Blood biochemistry: No major differences between the effects of HX575 and Erypo was found with the exception of a marked LDH increase at test week (TW) 13 in males dosed with HX575. Organ weights: No meaningful differences were observed between HX575 and Erypo. Histopathology: All changes observed can be attributed to the direct pharmacodynamic effect of epoetin or reflect adaptive responses of the organism to the massive erythropoietic impulse given by epoetin especially in the high-dose groups. These responses included congestion of spleen, liver and kidneys, changes in blood cellularity, huge rise in haematocrit and increase in spleen, liver and kidney weights (see above). A marked haematopoietic activation of the bone marrow was observed already in the low-dose group. There were no meaningful differences between the animals treated with HX575 and the animals treated with Erypo.

Among several repeat-dose toxicity studies taken from the literature and performed in rats and dogs during up to 13 weeks, no specific targets of toxicity other than effects related to the pharmacodynamics of epoetin or to the immune challenge were identified. However, persistent stimulation by 500 I.U./kg BW/day in dogs resulted in bone marrow fibrosis. Following recovery, fibrosis was less than observed at the end of treatment. According to these literature data, subcutaneous application of epoetin alfa was at least as well tolerated as the intravenous administration.

The analysis of literature data revealed that the administration of rh-epoetin to dogs, rats, mice or monkeys caused the formation of antibodies. The titres of the responding animals were generally low and the response appeared dose-dependent. Where examined, the withdrawal of epoetin exposure was accompanied by a decrease of the antibody response.

Local tolerance was tested in two studies in the rabbit following a single intravenous, intramuscular, intra-arterial, intra-venous and subcutaneous injection administration. Results indicated that the epoetin injection solution HX575 revealed a good local tolerability in rabbits at all tested routes of administration. In the 13-week intravenous dog study HX575 was also locally well tolerated.

Regarding the potential systemic toxicity, no non-clinical study was performed using the subcutaneous route, whereas it was intended that HX575 would be used by the subcutaneous as well as intravenous routes of administration. The risks associated with subcutaneous routes are: 1) systemic toxicity, 2) specific local toxicity and 3) increased antigenic potential compared to intravenous route. Regarding systemic toxicity, it is considered that the intravenous route of administration covers the exposure and associated risk following subcutaneous administration. Local tolerance has been studied in the rabbit

Ecotoxicity/environmental risk assessment

No environmental risk assessment was required. In accordance with the guideline on the environmental risk assessment of medicinal products for /human use (EMEA/CHMP/SWP/4447/00), proteins are unlikely to result in significant risk to the environment.

Discussion on non-clinical aspects

The expected pharmacodynamic effect was shown in vitro as growth response of erythroleukemic cells and in vivo in normocythaemic mice measuring the reticulocyte response. The comparator Erypo was included in each case. The CHMP concluded that primary pharmacodynamic studies showed similarity between the HX575 and the reference product Eprex/Erypo.

Secondary pharmacodynamics, safety pharmacology and pharmacodynamic drug interactions studies were not submitted and this is acceptable for this application for marketing authorisation of a biosimilar product.

Within the PK section of the PK/PD study in dog, the time course of epoetin plasma levels after dosing was determined, and the common PK parameters were determined. These were in rather good agreement between HX575 and the comparator Erypo. Distribution, metabolism and excretion were not studied as this is not required according to the relevant European guideline on biosimilarity.

According to the guideline EMEA/CHMP/94526/2005, no genotoxicity, carcinogenicity nor reproductive toxicity studies are required for biosimilar products. Literature data indicated that epoetin alfa failed to induce bacterial gene mutations, chromosomal aberration in cultured mammalian cells, or micronuclei in mice. Epoetin alfa is not considered to have mutagenic potential. Literature data also indicated that epoetin alfa was not teratogenic in the rat at intravenous doses from 20 to 2,000 U/kg.

The antigenic risk is linked to the route, to the frequency of administration and to the presence of immunological adjuvants in the formulation. At the clinical level, this risk has been reduced for the reference product Eprex/Erypo by modifying the composition of the final product; particularly, the rubber stoppers of the prefilled syringes were changed. As this is an application for a biosimilar product with a reference product now authorised for intravenous and subcutaneous route and taking into account that the formulation of the new drug product HX575 is similar to that of the reference product Eprex/Erypo, it is considered that the potential immunological adjuvants (stopper leachables)

as reported with the reference medicinal product have been excluded from the final product and that antigenicity risk linked to subcutaneous administration of HX575 is sufficiently reduced. No additional non-clinical study is considered relevant on this topic. Antigenic potential was addressed at the clinical level.

4. Clinical aspects

Introduction

The applicant has submitted five pharmacology studies performed in healthy male volunteers investigating PK and PD of HX575 after single dose as well as multiple dose administration intravenous (IV) and subcutaneous (SC). Four of these studies were comparative in nature using either Erypo (epoetin alfa) or NeoRecormon (epoetin beta) as comparator. In addition, one confirmative phase 3 trial comparing efficacy and safety of IV administered HX575 and Erypo in patients with renal anaemia, and one exploratory study assessing efficacy and safety of HX575 in the treatment of chemotherapy associated anaemia were submitted. In the latter study, an Erypo group was included as a measure of internal validity.

GCP

The applicant has provided a statement that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC. During the assessment there was no indication for non-compliance.

Pharmacokinetics

The Applicant has provided results from the following five pharmacokinetic/pharmacodynamic studies performed in healthy volunteers and investigating single or multiple 100 IU/kg (3 times per week, t.i.w.) doses.

Table 2: Pharmacokinetic/pharmacodynamic studies with HX575 in healthy volunteers

Study	N	Route	Reference	PK Parameters
INJ-4	6	SC/IV	Eprex/Erypo	$AUC_{0\text{-last}}$, C_{max} after 100 µg/kg single dose of HX575 and Eprex/Erypo; pilot study
INJ-5	76	IV	Eprex/Erypo	AUC_{τ} of epoetin following a 4-week exposure (100 µg/kg t.i.w.); pivotal study.
INJ-6	72	s.c.	NeoRecormon	AUC_{τ} of epoetin following a 4-week exposure (100 µg/kg t.i.w.); characterization of PK
INJ-7	6	s.c.	-	AUC_{τ} of epoetin following a 4-week exposure (100 µg/kg t.i.w.); supportive data for PK
INJ-12	74	s.c.	Eprex/Erypo	AUC_{τ} of epoetin following a 4-week s.c. exposure (100 µg/kg t.i.w.); pivotal study. This study was requested by the CHMP

The assays employed for determination of epoetin plasma concentrations in these studies are considered qualified for the intended purpose.

The *Guidance on similar biological medicinal products containing recombinant erythropoietins* (EMEA/CHMP/94526/2005) states that "the selected dose should be in the sensitive part of the dose-response curve". Although the use of a dose of 100 IU/kg body weight (t.i.w.) has not been justified by the applicant, it is nevertheless acceptable since a dose proportional increase in serum epoetin has been demonstrated for IV epoetin doses beyond this dose (A. Markham *et al.* Drug evaluation, 1995). In addition, this 100IU/kg dose is a medium dose used for treatment in an epoetin sensitive target population, i.e. in patients with renal anaemia.

No equivalence margin had been pre-defined in any of these studies and the post hoc acceptance range (80-125%) has been derived from the *Note for guidance on the investigation of bioavailability and bioequivalence* (CPMP/EWP/QWP/1401/98) which has been established for chemically derived medicinal products. It is not clear whether this acceptance range can also be applied to biotechnology-derived medicinal products such as epoetin. Since clinical trials are required to demonstrate comparable efficacy and safety of a "biosimilar" medicinal product with the chosen reference product, this issue is not critical.

Study 2003-08–INJ 5 is considered the pivotal PK study for IV use. This was a two-centre, open, randomised, parallel group, repeated dose study. Multiple intravenous doses of 100 IU/kg body weight three times a week (t.i.w.) of either Test (HX575) or Reference (Erypo) for a total of 4 weeks were given to 80 healthy Caucasian males. All subjects received iron supplementation: 100 mg iron *per os* twice daily during the study period. The objectives of this study was the comparison of PK and PD of epoetin from two different formulations (test, reference) at steady state.

After single dose IV administration, the lower limit of the 90% CI of the treatment difference in AUC [76.9, 93.1] fell below the post hoc defined acceptance range of 80-125% although the 90% CIs for Cmax and t1/2 were included. After multiple IV doses (for 4 weeks), however, the 90% CI for both AUC and Cmax fell completely within this acceptance range suggesting similar PK profiles of HX575 and Eprex/Erypo.

Study 2003-07-INJ-4 was a single centre**,** open, randomised, four way, 2x2 sequence, cross over pilot study; single SC dose injection and IV bolus infusion at a dose of 100 IU/kg of HX575 or Eprex/Erypo with a washout-time of at least 14 days between treatments. Duration of treatment: 10 days per study period including blood collection.

In this single-dose pilot **study 2003-07-INJ-4** (N=6), the lower limit of the 90% CI for AUC was below the post hoc defined acceptance range of 80-125% suggesting different bioavailability of HX575 compared to Eprex/Erypo for both IV and SC administration. C_{max} was only comparable after IV administration.

Study 2003-09-–INJ-6, investigating single and multiple doses of SC administered epoetin, did not use Eprex/Erypo as comparator and is therefore not relevant for the demonstration of comparability of HX575 and Eprex/Erypo (data not shown).

Study 2003-12–INJ-7, using multiple dose SC injections, was initially planned as a comparative study with Eprex/Erypo but the comparator was dropped. Therefore, this single-arm study does not contribute to the comparability exercise with the chosen reference product Eprex/Erypo (data not shown).

Study 2006-19-INJ-12 is considered the pivotal PK study for SC use. This was a monocentric, open, randomised, parallel group, repeated dose study. Multiple subcutaneous doses of 100 IU/kg body weight three times a week (t.i.w.) of either Test (HX575) or Reference (Erypo) for a total of 4 weeks were given to 80 healthy Caucasian males.

The primary objective was to assess the biosimilarity of epoetin of HX575 and Eprex at steady state.
Of 80 randomised patients (ITT population), 74 completed the study (PP population). Data taken from this study indicate that the pharmacokinetic parameters of both products were similar. After single and multiple dose SC administration, the 90% CI of the treatment difference in AUC and Cmax fell completely within the acceptance range of 80-125%.

Multiple doses of both medications were overall well tolerated: No relevant differences in incidence or pattern of adverse events were observed and no clinically relevant anti-EPO antibodies were detected in these (immunocompetent) individuals over 4 weeks and IV and SC routes of administration.

Pharmacodynamics

The pharmacodynamics (PD) of erythropoietin is well known and well described in the literature. After IV administration of epoetin, the typical pharmacodynamic profile shows an increase in reticulocytes count within the first 2 weeks followed by an increase in the red blood cell level as manifested by haematocrit or Hb determinations within 2 to 6 weeks. After single SC application an increase in reticulocyte count within 3-4 days with a peak around day 8-11(13) a nd a return to baseline by day 22 has been described (R. Ramakrishan et al. J Clin Pharmacol, 2004; W.K. Cheung et al. Clin Pharmacol Therapeutics, 1998). A linear relationship between reticulocyte AUC and epoetin exposure has been described for single doses up to 1800 IU/kg. (W.K. Cheung et al., Clin Pharmacol Therapeutics, 1998). There is high interindividual variability in the reticulocyte response to epoetin.

The pharmacodynamic effects of HX575 were examined as part of the PK studies as suggested in the *Guidance on similar biological medicinal products containing recombinant erythropoietins*. Reticulocyte count was the main parameter chosen to define the pharmacodynamic response in single dose studies and haemoglobin in multiple dose studies. Comparators were Eprex/Erypo or NeoRecormon (study INJ-6 only). Haematocrit and red blood cell count were also assessed.

In study **2003-08–INJ 5**, blood for determination of Hb, haematocrit (HCT), reticulocyte count and RBC count was drawn at predefined time points up to day 29. Primary confirmatory PD parameter: Absolute haemoglobin response (AUEC= Area under the effective curve) after 28 days of IV treatment with either HX575 or ERYPO. Initially, biosimilarity was assumed if the 90% CI of the AUC ratio was within 80%-125%. The acceptance range was then changed to 97%-103% by protocol amendment based on Hb concentration changes defined as equivalence margins in phase III studies.

After both treatments, the AUEC for Hb was similar for both treatments, as indicated by the narrow 90% CI for the AUEC ratio [98.5%-101.2%] which was enclosed by the a.m. acceptance range. Reticulocyte count, RBC count and HCT were also similar. Overall PD results of the pivotal PK/PD study 2003-08–INJ 5 demonstrated almost superimposable Hb increases after multiple IV administration of 100 IU/kg t.i.w. of HX575 or Eprex/Erypo. The 90% CI for the ratio of the Hb AUEC was in the chosen acceptance range. The 95% CI did not change the conclusion of similar PD profiles.

In the comparative pilot **study 2003-07-INJ-4** blood for determination of reticulocytes, Hb and erythrocytes count was performed pre-dose on day 1 and at 8:00 on days 2 through 10 in each treatment period. Primary PD parameter**:** AUC of reticulocytes. After single dose SC administration, reticulocytes increased similarly with HX575 and Erypo as indicated by the narrow 90% CIs for the treatment difference in $AUC_{0\rightarrow last}$ [87.64 – 103.02] and C_{max} [88.24 – 108.12]. After single dose IV administration, reticulocytes increased similarly with HX575 and Erypo as indicated by the narrow 90% CIs for the treatment differences in $AUC_{0\rightarrow last}$ [92.5 – 112.8] and C_{max} [89.8 – 110.9].

Study INJ-12: Pharmacodynamic effects were assessed in terms of Hb, haematocrit, reticulocyte count and RBC count. Primary confirmatory PD parameter: Absolute haemoglobin response (AUEC= Area under the effective curve) after 28 days of SC treatment with either HX575 or Erypo. Biosimilarity was assumed if the 90% CI of the AUEC ratio was within 97%-103%. Both products revealed a high degree of similarity (Hb, red blood cell count, haematocrit, reticulocytes, transferrin, iron and ferritin). Due to a difference between treatment groups in baseline Hb, the baseline-adjusted confidence interval was used. The ratio and confidence interval amounted to 98.5% [97.7% - 100.2%] and was thus in the pre-defined acceptance range.

Discussion on Clinical Pharmacology

The focus of a "biosimilar" application is the demonstration of comparability between the new product, here HX575, and the reference product, here ERYPO (Janssen Cilag-GmbH, Germany). It is not necessary for a similar biological medicinal product to investigate all aspects of PK that have already been shown for the reference product. Therefore, evaluation of PK aspects like absorption, distribution, metabolism, elimination, interactions and PK in special populations are not required for this application.

The PK data analysis was performed according to the *Note for guidance on the investigation of bioavailability and bioequivalence* (CPMP/EWP/QWP/1401/98) and is acceptable.
The submitted data show similar PK profiles for IV and SC administered HX575 and Eprex/Erypo, under steady state conditions.

Although not required in the *Guidance on similar biological medicinal products containing recombinant erythropoietins* an acceptance range for PD markers was defined by the applicant The preferred PD marker in single dose studies, i.e. reticulocyte count, is not an established surrogate marker for efficacy and multiple dose PD studies are not required because comparative efficacy studies are mandatory. Nevertheless, the PD profiles show that the use of the same IV or SC dose of HX575 and Eprex/Erypo results in similar increases in Hb in healthy volunteers.
The submitted data show similar PD effects for IV and SC administered HX575 and Eprex/Erypo.

Clinical efficacy

The Applicant has provided efficacy and safety results from two double blind, randomised, parallel-group, multicentre phase III studies. **Study INJ-9** was designed to evaluate a 1:1 dose conversion from Eprex/Erypo to HX575 with respect to efficacy based on haemoglobin assessment in CRF patients on haemodialysis. **Study INJ-11** was performed in patients receiving chemotherapy for solid tumours. The primary objective was to assess the efficacy and safety of HX575 in the treatment of chemotherapy-associated anaemia. An Eprex/Erypo-treated group was included as internal control only.

Study number/ Ref.	Test / Reference	N entered/ completed	Primary endpoint
2003-29-INJ-9 pivotal Phase III i.v. study comparative study	HX575 final formulation ERYPO® Janssen Cilag, Germany	HX575: 314 / 261 ERYPO® 164/142	Therapeutic equivalence; mean absolute change in Hb level between the screening/baseline period and the evaluation period in CRF patients on haemodialysis
2003-31-INJ-11 supportive Phase III s.c. study	HX575 final formulation ERYPO® Janssen Cilag, Germany	HX575: 74/60 ERYPO® 40/31	Absolute increase in Hb value of ≥ 2.0 g/dl between the screening/baseline period and the evaluation period in absence of RBC transfusion during the preceding 4 weeks

(i) Study INJ -9: *Epoetin alfa in the treatment of anaemia in patients with chronic renal failure.*

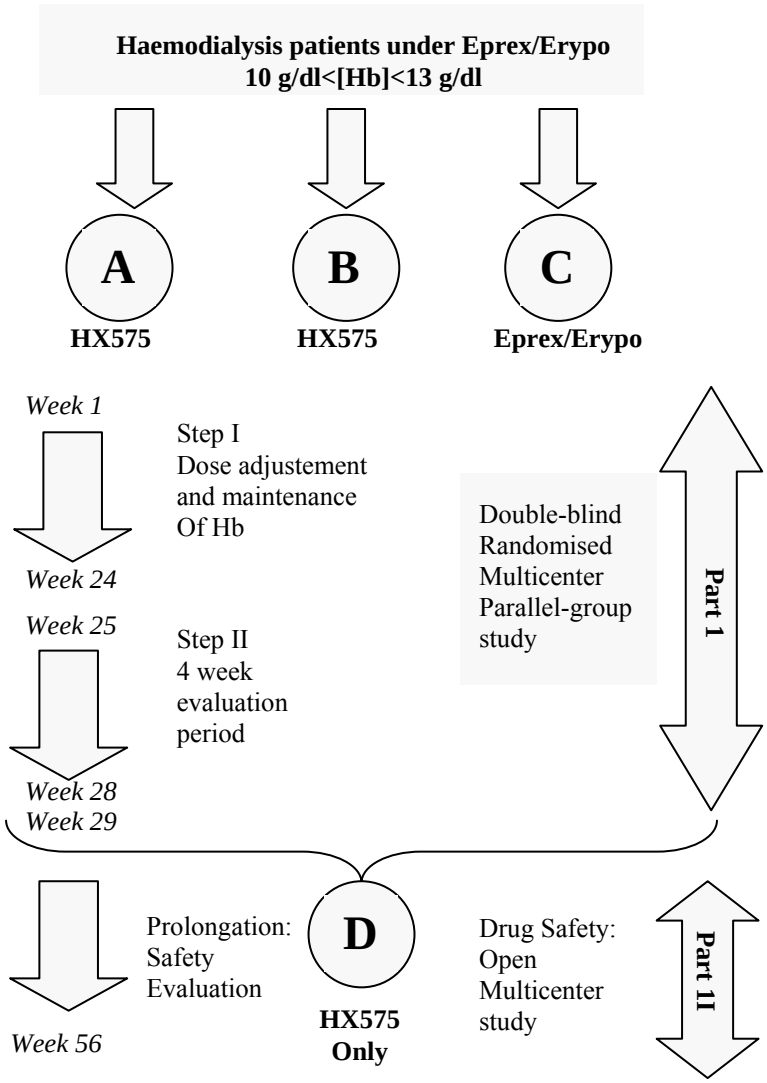
Methods

- **Design**

This was a randomised, double blind (28 weeks), multicentre, parallel-group, study to evaluate the efficacy and safety of HX575 in comparison to ERYPO in patients with renal anaemia on haemodialysis.

The first part of the study was designed as a double-blind, randomized, multicentre, parallel-group equivalence study and consisted of two steps: (i) **Step I** (dose adjustment and maintenance of Hb level until week 24) followed by: **Step II** (evaluation period: four week evaluation period to determine the primary efficacy endpoint; weeks 25 until 28).
The second part was a safety study period (from week 29 to week 56) with all patients switched to open-label HX575.

Figure 1: Study design



- **Study Participants**

Male and female clinically stable haemodialysis patients, i.e. Hb within the target range of 10.0 to 13.0 g/dl for at least 12 weeks before screening and a stable IV dose of Erypo for at least 8 weeks before screening and during screening and a maximal weekly dose of 300 IU/kg body weight. Stable dose was defined as < 25% change up or down in weekly dose and no change in frequency of injections. Patients had to be receiving dialysis for at least 6 months (3 times weekly, t.i.w.) before screening.

- **Treatments**

Eligible patients were randomized 2:1 to receive IV test or reference drug t.i.w., respectively, initially maintaining the dose administered before randomization. Subsequently, dose adjustments were allowed every three weeks according to a pre-specified algorithm.

- **Objectives**

Evaluation of a 1:1conversion from Erypo to HX575 with respect to dosage, efficacy and safety.

- **Outcomes/endpoints**

The **primary endpoint** was the mean absolute change in Hb levels between the screening/baseline period and the evaluation period. Hb level at screening/baseline was defined as the mean of the last two Hb measurements prior to day 1 and the measurement at day 1.

Secondary endpoints:

- Mean absolute change in Hb level for the ITT population.
- Development of weekly Hb values over the course of the study (from day 1 until week 28)
- Percentage of patients with Hb values within the target range during the study.
- Frequency of responders to treatment according to Definition 1 and 2
  Definition 1**:** Mean Hb value during screening /baseline and during evaluation period within target range
  Definition 2: Responder according to definition 1 and change in mean weekly dose ≤ 25%.
- Frequency of patients with Hb values ≥ 10.0 g/dl at each week and continuously for the study (from day 1 until week 28)
- Frequency of patients with changes in the epoetin dosage
- Development of weekly epoetin dosage (in IU and per kg) over the course of the study
- Frequency of patients receiving at least one RBC transfusion
- Numbers of RBC transfusion per patient
- Type of blood for the RBC transfusion
- Overall efficacy as judged by the investigator
- Quality of life assessment

All samples were analysed by a central laboratory.

- **Sample size**

Sample size was calculated to provide 90% power to detect a difference of 0.5 g/dl in Hb between treatment groups, including an assumed drop-out/protocol violation rate of 30%.

- **Blinding (masking)**

At each site, blinded (investigators) and unblinded (study nurses responsible for administration of study medication) study personnel had to be involved in order to preserve blinding of the investigator (different filling quantities in the syringes with the 2.000 IU dose would have allowed identification of type of study medication). The investigator, all other study personnel, and the patients were blind as to which study medication a patient received. The staff of the applicant, the clinical research associates (except the unblinded clinical research associates responsible for drug accountability) as well as data management and biostatistics staff involved in the study also remained blind with respect to the treatment assignments in the main study until all outcome assessments for all patients had been completed and the database had been locked.

- **Statistical methods**

Statistical analysis of primary endpoint

The treatment difference was estimated from an ANCOVA model including factors treatment, centre, mean baseline Hb (< 11.5 and > 11.5 g/dl) as factors and change of the mean weekly dose from screening/baseline to the evaluation period of HX575 or ERYPO from screening/baseline to the evaluation period as a covariate.

An equivalence margin of ± 0.5 g/dl in Hb was chosen for demonstration of comparable efficacy.

The primary efficacy analysis was based on the PP population, which was defined as all patients who completed the main study without any major protocol violations. According to the study protocol, the following criteria applied among others for including patients into this analysis population:

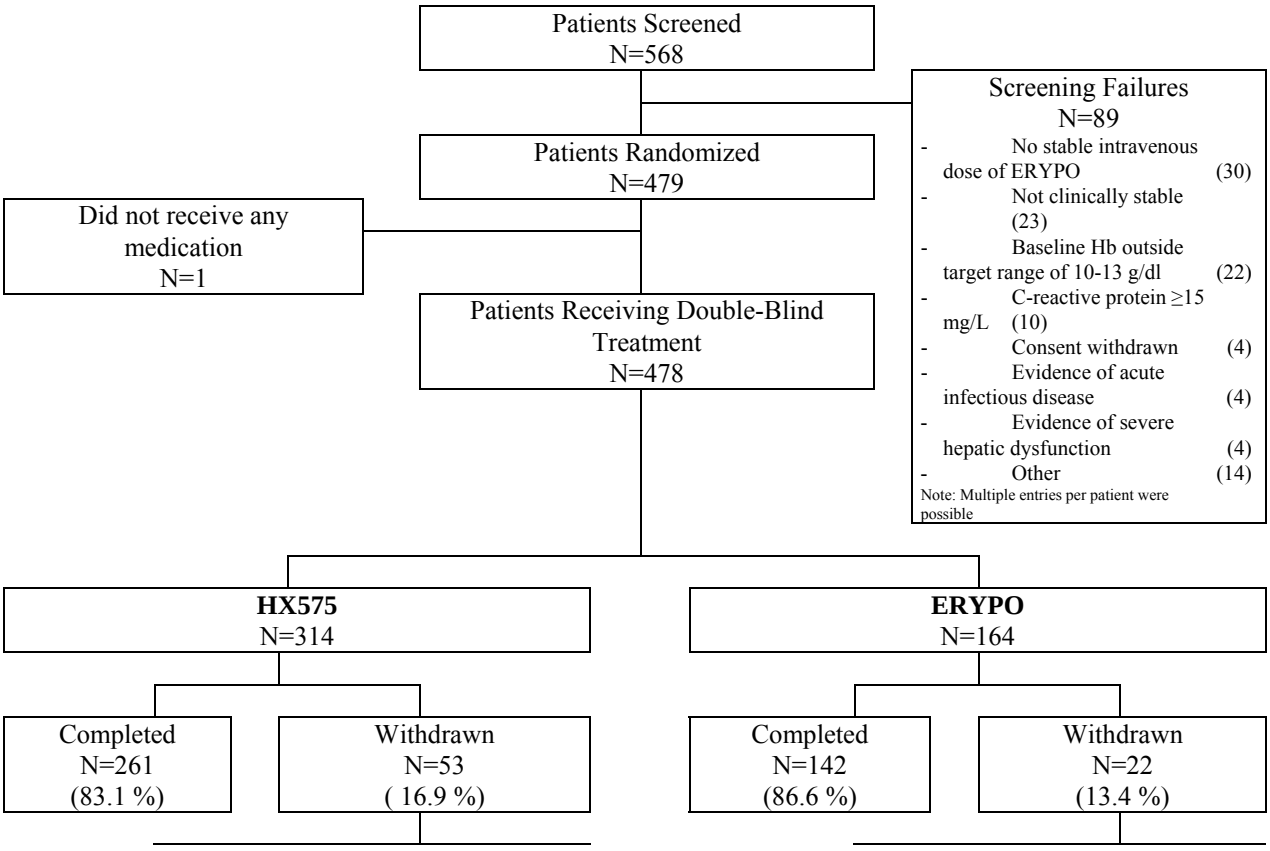
- Receiving only the study treatment to which they were randomised (until week 28)
- Compliant with study drug and dose adjustment algorithm
- Having at least three Hb measurements during the evaluation period (weeks 25 to 28).
- Not receiving any RBC transfusion.
- Adequate iron status

A corresponding analysis for the ITT population, defined as all randomised patients who were treated for at least 4 weeks and had at least one post-baseline value of the primary endpoint Hb, served as a sensitivity analysis.

- **Patient disposition**

Five-hundred and sixty-eight (568) patients were screened, 479 patients (84.3 %) were randomized, 315 (65.8 %) to the HX575 group and 164 (34.2 %) to the Eprex/Erypo group. A total of 261 patients (83.1%) in the HX575 group and 142 patients (86.6%) in the Erypo group, out of those that were randomized and treated, completed the first part of the study.

Participant flow –Data sets analysed



No patient in the HX 575 group and one patient in the Erypo group was withdrawn due to insufficient response.

- **Conduct of the study**

There were no protocol amendments that would affect the study results. No interim analysis was performed.

- **Baseline data**

There were no relevant differences in demographic or anthropometric characteristics between treatment groups (see Tables for PP population below). Similarly, there were no relevant differences in disease specific baseline characteristics (see Tables 3, 4, 5 and 6)

Table 3. Demographic and General Baseline Characteristics - PP Population

		HX575 (N=207)	ERYPO (N=118)
Sex[1]	Male	116 (56.0 %)	72 (61.0 %)
	Female	91 (44.0 %)	46 (39.0 %)
Age[2]	[years]	61.9 ± 14.7 (23-87, 65)	62.1 ± 13.3 (27-82, 63)
Body weight[2]	[kg]	77.8 ± 16.0 (46-138, 76)	75.2 ± 17.8 (38-133, 74)
Ethnic group[1]	Caucasian	206 (99.5 %)	118 (100.0 %)
	All other	1 (0.5 %)	0 (0 %)

[1] Number of patients (%) [2] Mean ± standard deviation (minimum-maximum, median)

Table 4. Disease Specific Baseline Characteristics - PP Population

		HX575 (N=207)	ERYPO (N=118)
Primary cause of anemia or chronic renal failure[1]	Diabetes	42 (20.3 %)	21 (17.8 %)
	Hypertension	26 (12.6 %)	13 (11.0 %)
	Interstitial nephritis	14 (6.8 %)	8 (6.8 %)
	Chronic glomerulonephritis	49 (23.7 %)	35 (29.7 %)
	Polycystic kidney disease	17 (8.2 %)	7 (5.9 %)
	Urologic	9 (4.3 %)	5 (4.2 %)
	Other	31 (15.0 %)	18 (15.3 %)
	Unknown	19 (9.2 %)	11 (9.3 %)
Time since primary diagnosis[2]	**[months]**	98.2 ± 89.1 (7-466, 68)	82.0 ± 71.5 (8-299, 53)
Time since start of dialysis[2]	**[months]**	53.1 ± 56.3 (5-339, 34)	56.0 ± 64.6 (6-295, 34)
Screening/baseline dose of ERYPO[2,3]	**[IU/week]**	7053.9 ± 3666.8 (3000-24000, 6000)	6622.9 ± 3629.2 (3000-20000, 6000)
Screening/baseline Hb level[2,3]	**[g/dl]**	11.7 ± 0.8 (9.9-13.6, 11.7)	11.9 ± 0.7 (10.0-13.3, 11.9)
Serum ferritin[2,4]	**[ng/mL]**	655.1 ± 397.7 (41-1832, 582)	685.5 ± 511.7 (39-3250, 559)
Transferrin saturation[2,4]	**[%]**	24.9 ± 9.2 (9.2-72.8, 23.2)	26.3 ± 10.5 (10.1-85.4, 25.7)

[1] Number of patients (%) [2] Mean ± standard deviation (minimum-maximum, median)
[3] Mean during screening/baseline [4] At visit –1

- **Numbers analysed**

Of the 314 patients treated with HX575, 304 (96.5%) were included in the ITT analysis and 207 (65.9%) in the primary PP analysis. Of the 164 patients treated with ERYPO, 161 (98.2%) were included in the ITT analysis and 118 (72.0%) in the PP analysis.
Most frequent major protocol deviations were 'premature withdrawal' (17.1% and 12.2% in the HX575 and ERYPO group, respectively), 'no stable dose prior to day 1' (8.9% and 6.1%, respectively) and 'no stable dose during treatment period' (8.3% and 5.5%, respectively).

- **Outcomes and estimation**

In the primary **PP population**, mean change in Hb was 0.147 g/dl in the HX575 group and 0.063 g/dl in the ERYPO group (see Table below). The treatment difference was 0.084 g/dl with a 95% CI of [-0.170; 0.338]. Thus, the CI is within the predefined range of ±0.5 g/dl.

In the **ITT population**, mean change in Hb was 0.003 g/dl in the HX575 group and 0.187 g/dl in the ERYPO group (see Table below). The treatment difference was 0.189 g/dl with a 95% CI of [-0.039; 0.418]. As for the primary analysis, the CI is within the predefined range of ±0.5 g/dl.

There was no statistically significant effect of centre (p=0.5800) or change in epoetin dosage (p=0.7517) on the change in Hb. The factor Hb level at baseline (<11.5 and ≥11.5 g/dl) was statistically significant (p < 0.0001).

Table 5: Primary Efficacy results

Primary endpoint	***Mean Absolute Change in Hb Level* (PP population)**	
	HX575 (N=207)	**EPREX/ERYPO(N=118)**
Least square means (g/dl)[1, 2, 3]	0.147 ± 0.092	0.063 ± 0.117
Difference between least square means of HX575 & Eprex/Erypo (change from baseline in HX575 group minus change from baseline in Eprex/Erypo group)[1]	Point estimate of difference [g/dl] 0.084	95% two-sided confidence interval [g/dl] [–0.170; 0.338]

	Analysis of Responder - PP Population			
	HX575 (N=207)		**EPREX/ERYPO(N=118)**	
	n	**%**	**n**	**%**
Responder (definition I)[(i)]	167	80.7 [74.6; 85.8]	96	81.4 [73.1; 87.9]
Responder (definition II)[(ii)]	144	69.6 [62.8; 75.8]	76	64.4 [55.1; 73.0]

[(i)] Patients with mean Hb value during screening/baseline and during evaluation period within target range 10.0-13.0 g/dl.
[(ii)] Responder according to definition (i) and mean weekly dosages between week -3 to -1 and during the evaluation period differ by at most 25%

Table 6: Result of the endpoint "mean relative change in epoetin dose"

	HX575	**EPREX**
	Least square means [%]1, 2, 3	
PP-population	-3.8 ± 1.8 (N = 207)	-7.4 ± 2.1 (N = 118)
Difference between least square means of HX575**& ERYPO (relative change from baseline in** HX575 **group minus relative change from baseline in ERYPO group)1**	Point estimate of difference [%]	95% two-sided confidence interval [%]
PP-population	3.62	[–1.29; 8.54]
ITT-population	6.83	[–2.80; 16.47]
Amended ITT-population	6.79	[–2.61; 16.19]

1 Results from ANCOVA model 2 No missing value replacement 3 Least square means ± standard error of the mean (from ANCOVA model) 4 Amended ITT population as defined for the responses to the d120 LoQ: includes all patients with at least one application of study medication and for whom at least one post-baseline Hb level is available.

Weekly haemoglobin values over the course of the study from day 1 until week 28

Over the whole course of the study, the range of mean Hb values for the **PP population** was 11.6 to 11.9 g/dl for the HX575 group and 11.7 to 12.1 g/dl for the ERYPO group. The mean absolute change in Hb from the screening/baseline period to the evaluation period was 0.0 ± 1.1g/dl in the test group and -0.2 ± 1.1 g/dl in the reference group.
The **ITT analysis** yielded very similar results.

Percentage of patients with Hb values within the target range of 10.0 to 13.0 g/dl during the study

In the **PP population**, 94.2% of the test and 95.8% of the reference group had baseline Hb values within the target range. During the evaluation period, frequencies decreased to 85.5% in the test and 84.7% in the reference group; 29.0 % of the test and 29.7 % of the reference group had Hb values within the target range during the whole treatment period.
The **ITT analysis** showed very similar results.

Frequency of treatment responders

PP population: according to **definition I** (mean Hb within target range during screening/baseline and evaluation period), 80.7% [95% CI: 74.6, 85.8] and 81.4 % [95% CI: 73.1-87.9] of the HX575 and ERYPO group, respectively, were responders. According to **definition II** (change in mean weekly dosage between baseline and evaluation period ≤25%), 69.6% [95% CI: 62.8-75.8] and 64.4% [95% CI: 55.1-73.0] of the HX575 and ERYPO group, respectively, were responders. In the **ITT population**, responder rates were somewhat lower but between treatment differences were consistent.

Frequency of patients with changes in the epoetin dosage

In the **PP population**, at least one dose adaptation of more than 25% during the whole study was made in 16.9% of patients in the HX575 and 19.5% of patients in the ERYPO group.
In the **ITT analysis**, frequencies were 25% and 26.7% respectively.

Development of weekly epoetin dosage (in IU/week) over the course of the study

PP population: From baseline to the evaluation period, the mean weekly epoetin dose decreased in both treatment groups, by 314 IU/week (2.2%) in the HX575 and by 739 IU/week (8.9%) in the ERYPO group (see Table below). When expressed as IU/kg per week, similar results were observed: the mean dosage was slightly higher in the HX575 group than in the ERYPO group (93.7 vs. 92.8 IU/kg per week) during the screening/baseline period and decreased somewhat less to 90.0 IU/kg/week and 82.3 IU/kg/week in the HX575 group and the ERYPO group, respectively, during the evaluation period.

No centre effect was observed.

Table 7. Summary of Weekly Epoetin Dose [IU/Week] - PP Population

	HX575 (N=207)				ERYPO (N=118)			
	n	**Mean**	**SD**	**Median**	**n**	**Mean**	**SD**	**Median**
(Mean of) Screening/baseline period[1]	207	7053.9	3666.8	6000	118	6622.9	3629.2	6000
(Mean of) Evaluation period[2]	207	6740.3	3580.0	6000	118	5883.5	3425.3	5000
Absolute change from screening/baseline period[1] **to evaluation period [IU/week]**	207	–313.6	2061.5	0	118	–739.4	1847.7	0
Relative change from screening/baseline period[1] **to evaluation period [%]**	207	–2.2	25.1	0.0	118	–8.9	21.6	0.0

[1] Mean of screening/baseline period (week –3 to week –1)
[2] Mean of evaluation period (week 25 - 28, or last four weeks in case of early withdrawal)

Frequency of patients receiving at least one RBC/whole blood transfusion

In the **PP population**, two patients of the test group received RBC transfusions during the treatment period vs. no patient in the reference group.
In the **ITT group,** 19 patients (6.3%) of the test group and 5 patients (3.1%) of the reference group received RBC transfusions.

(ii) Study INJ 11: *Treatment of cancer chemotherapy-associated anaemia.*

This was a randomised, multicentre, double blind study to evaluate the efficacy and safety of HX575 in the treatment of chemotherapy associated anaemia in cancer patients. The double-blind treatment period was 12 weeks. The study was not designed as a confirmatory study to demonstrate comparable efficacy and safety between HX575 and the Eprex/Erypo. The Eprex/Erypo group was included as a measure of internal validity only.

Due to the contraindication of Eprex/Erypo for SC use in patients with renal anaemia at the time of clinical development, a comparative SC study as described in the biosimilar guideline could not be performed. Instead, the Applicant has performed a non-comparative controlled study in cancer patients with chemotherapy-associated anaemia in support of the oncology indication applied for. Since the EPO dosages used for cancer patients are usually much higher than those used in CRF patients, such a study was considered as very useful. One hundred and fourteen (114) patients were eligible for inclusion and were randomized and treated with either HX575 or Eprex/Erypo. Seventy-four (74) patients were allocated to treatment with HX575 and 40 patients were allocated to treatment with Eprex/Erypo. The Eprex/Erypo group was included as a measure of internal validity only. The most frequently reported primary sites of malignancy were ovary, lung, and breast.

The primary efficacy endpoint was defined as the proportion of HX 575 treated patients with a Hb response during weeks 5-12 of the study. Hb response was defined as an increase in Hb concentration of ≥ 2.0 g/dl from the mean value from the screening/baseline period in the absence of a red blood cell transfusion during the preceding 4 weeks. The treatment under investigation, HX575, was considered effective if the response rate exceeded the assumed placebo rate (10 %) plus half the difference between active treatment and placebo (20 %), i.e. approx. 30 %. This primary efficacy analysis was based on the ITT population.

Table 8: Hb Response in the HX575 Group - ITT Population

	HX575 (N=60)	
	n	**%**
Non-Responder	23	38.3
Responder	37	61.7
Exact 95 % Confidence Interval for Response Rate	48.2 - 73.9 %	

[1] Hb response is defined as an increase in Hb concentration of >=2.0 g/dl from the mean value from the screening/baseline period at any time point during week 5-12 in the absence of a red blood cell transfusion during the preceding 4 weeks

Altogether 37 of 60 patients (61.7 %) in the HX575 group responded to the treatment according to the above definition. The 95% CI was [48.2%; 73.9%] and therefore above the pre-defined efficacy margin of 30%. In the Eprex/Erypo group, the mean response rate was 44.1% in the ITT group. However, the chosen design and the small sample size make any comparison between HSX575 and Eprex/Erypo difficult.

In conclusion, HX 575 showed the expected effect of an epoetin in cancer patients with chemotherapy-induced anaemia, however, therapeutic equivalence between HX 575 and Erypo for the SC route of administration cannot be concluded from this small exploratory study.

Discussion on Clinical Efficacy

The clinical development programme is in line with the guideline on similar biological medicinal products containing recombinant erythropoietins and previous scientific advice. However, one exception is noted, i.e. the recommendation to provide results from at least two adequately powered, randomised, parallel group clinical trials demonstrating comparable efficacy and safety for both routes of administration in patients with renal anaemia. It is acknowledged that at the time of clinical development Eprex/Erypo could not be used as comparator in SC studies in renal anaemia patients and therefore no second randomised, parallel group clinical trial with the SC route of application could be conducted. Under these circumstances, the deviation from the guideline is considered to be acceptable.

Study INJ-9 was performed in patients with renal anaemia, optimally titrated (prior to randomisation) on the reference product as suggested in the *Guidance on similar biological medicinal products containing recombinant erythropoietins*. The observed difference in Hb change was low between both treatments and within the pre-defined and acceptable equivalence boundaries of ± 0.5 g/dl. All secondary endpoints, most importantly change in epoetin dose, also supported the conclusion of therapeutic equivalence between Eprex/Erypo and HX575.

Comparable efficacy between HX575 and Eprex/Erypo has been established for the IV route of administration. However, study INJ-11 was not designed and too small to establish comparable efficacy for the SC route of administration. Nevertheless, based on the demonstration of equivalent efficacy and steady state pharmacokinetics and pharmacodynamics for IV administered HX575 and Eprex/Erypo, and the finding of similar multiple dose SC pharmacokinetic/pharmacodynamic profiles in healthy volunteers, a difference in efficacy for the SC route of administration appears highly unlikely.

Clinical safety

The clinical safety of HX575 has been assessed in five Phase I studies conducted in healthy volunteers and in two Phase III studies conducted in adult dialysis patients and oncology patients. The total population valid for safety (SAF) consists of 98 healthy volunteers, 478 chronic renal failure patients and 114 cancer patients.

In the submitted studies, the presence of anti-epoetin antibodies was checked at 4-8 week intervals in the renal anaemia population, at 6-week intervals in the oncology population and at 2-week intervals in the multidose PK/PD studies in healthy volunteers.

Adverse events, serious adverse events (SAEs) and deaths

Healthy volunteer studies
In the healthy volunteer population, the SOCs most frequently affected in both treatment groups were gastrointestinal disorders (diarrhoea and nausea), and nervous system disorder (dizziness, paraesthesia). There were no serious, significant or severe adverse events (except one non-related SAE of hearing loss), and all events resolved completely. No anti-epoetin antibody has been identified by ELISA or RIP measurements.

Study INJ-9 (adult dialysis patients)
A total of 314 patients with renal anaemia were exposed to a mean dose of 7,043 IU/week of HX575 administered **IV** for an average of 25.5 weeks. Including the 28-week uncontrolled extension phase, a total of 211 patients were continuously exposed to HX575 for 54 weeks and 117 patients (those that switched from Eprex/Erypo to HX575 at week 28) for 26 weeks.

The majority of patients was older than 65 years of age. The primary cause of anaemia / chronic renal failure, were: chronic glomerulonephritis and diabetes. Other common reasons were hypertension, polycystic kidney disease, interstitial nephritis, and urologic diseases. The mean time since start of dialysis was 56.3 months in the HX575 group, and 54.1 months in patients treated with Eprex/Erypo.

Globally, the adverse event profile was consistent with this advanced dialysis patient population, and comparable between both groups. Vascular disorders were somewhat more frequently reported with

HX575 (32.2% versus 26.8%), mainly vascular hypotensive or hypertensive disorders. Similarly, slightly more cardiac disorders (16.9%), mainly ischemic disorders, were observed with HX575 *versus* Eprex/Erypo (13.4%).

A total of 357 treatment-emergent SAEs were documented in 168 patients of the SAF population: 258 SAEs in 112 patients (35.7%) of the HX575 group, and 99 SAEs in 56 patients (34.1%) of the Eprex/Erypo group.

The death rate was consistent with the severe medical condition of these patients. All deaths but one were assessed as unrelated to the study drug by the investigator, and the coordinating investigator. At baseline, the two populations were comparable with respect to current medical condition, especially regarding cardiovascular condition.

Immunogenicity

Based on the results obtained with the RIP and NAB assays, no increased immunogenicity was found for HX575 vs. Eprex/Erypo. Transient non-neutralising antibodies occurred in HX575 treated and in the Eprex/Erypo treated patients with renal anaemia to a similar extent. Six patients (2 in the HX575 group, 4 in the Eprex/Erypo / HX575 group) had a result above cut-off at visit 28 or visit 42 in the RIP assay. One patient had a first positive RIP result after the switch from Eprex/Erypo to HX575 at the last visit (visit 56) but no follow-up could be provided since this patient had died 3-4 months after study termination due to cardiac insufficiency. Two patients had antibodies from baseline throughout the study, indicating that the previous treatment rather than HX575 may be the culprit. One of the latter patients also had a borderline positive result in the NAB assay indicative for neutralising antibodies. Overall, none of the patients showed any signs of sudden Hb or reticulocyte decrease or any other symptom, which would have been indicative of pure red cell aplasia (PRCA) although the patient with the borderline positive result in the NAB assay required high EPO doses. However, the Applicants could provide evidence with their Day120 Responses that the borderline positive NAB test in this patient occurred on only one occasion and that the patient had no other signs suggestive of PRCA.

The Applicant has also provided results from the **part II of study INJ 9** (weeks 26 to 52). A total of 2662 AEs were reported in 350 patients (90.7%) in the safety period (part II). The number of AEs in part II was 1736 in 223 patients (89.6%) of the HX575 group and 926 in 127 patients (92.7%) of the Eprex/HX575 group. The majority of AEs was of mild or moderate intensity, transient and resolved completely by the end of the study.

Twenty-five AEs in 11 patients (4.4%) in part II in the HX575 group were assessed as being drug-related, whereas one AE in part II in one patient (0.7%) were reported as drug-related in the Eprex/Erypo /HX575 group.

In part II of the study a total of 280 SAEs were documented in 136 patients: 187 SAEs in 87 Patients (34.9%) of the HX575 group, and 93 SAEs in 49 patients (35.8%) of the Eprex/Erypo/HX575 group. All SAEs were assessed as unrelated to study medication. Altogether, 9 patients of the Eprex/Erypo/HX575 group and 5 of the HX575 group (3.6% in each group) died during part II of the study or shortly after end of study. Taken together, the data did not elicit any safety concerns genuine to HX575.

Table 9: Incidence of Treatment-emergent AEs Assessed as Being Causally Related to Study Medication by MedDRA System Organ Class - SAF Population, study INJ-9 (part I)

	HX575 (N=314)	**ERYPO (N=164)**

	Patients with AE		Events	Patients with AE		Events
	N	%		n	%	
TOTAL	21	6.7	41	5	3.0	9
Infections and infestations	6	1.9	8	1	0.6	2
Skin and subcutaneous tissue disorders	5	1.6	5	1	0.6	2
Gastrointestinal disorders	4	1.3	4	1	0.6	2
Injury, poisoning and procedural complications	4	1.3	5	0	0.0	0
Cardiac disorders	3	1.0	3	0	0.0	0
General disorders and administration site conditions	2	0.6	2	1	0.6	1
Musculoskeletal and connective tissue disorders	3	1.0	3	0	0.0	0
Vascular disorders	3	1.0	4	0	0.0	0
Nervous system disorders	2	0.6	2	0	0.0	0
Psychiatric disorders	1	0.3	1	1	0.6	1
Respiratory, thoracic and mediastinal disorders	1	0.3	1	1	0.6	1
Blood and lymphatic system disorders	1	0.3	1	0	0.0	0
Eye disorders	1	0.3	1	0	0.0	0
Investigations	1	0.3	1	0	0.0	0

Source: Table 15.6.1.6.1

Study INJ-11 (cancer patients)
A total of 114 cancer patients with chemotherapy associated anaemia were included in the safety analysis, 74 of whom were exposed to a mean dose of 34,587 IU/week of HX575 administered **SC** for an average of 8.5 weeks (shorter than the planned 12week study duration due to high drop out rate).

The most frequently reported primary sites of malignancy in the SAF population were ovary, lung and breast. No patients with malignant haemopathy were included. Globally, the medical status of these advanced cancer patient population was not significantly different at baseline between both treatment arms. However both arms were not well balanced with regard to the type of cancer, TNM classification and chemotherapy (e.g., Vinca alkaloids and Pyrimidine analogues were more frequently administered to patients in the Eprex/Erypo arm).

Although there was no significant difference between the two groups regarding the tolerability of the treatment, some numerical differences can be outlined:

- nervous system disorders were more frequently reported in HX575 group (20.3% versus 12.5%), as well as neurological signs and symptoms (13.5 % *versus* 2.5%). Of note, nervous system disorders were more frequently reported with Eprex/Erypo in healthy volunteer studies.
- similarly, blood and lymphatic system disorders were reported in 21.6% of patients in HX575 group versus 15% with Eprex/Erypo, as well as neutropenia (6.8% versus 0%).

A total of 106 treatment-emergent SAEs were reported in 52 patients, 66 events in 34 patients (45.9%) of the HX575 group and 40 events in 18 patients (45.0%) of the Erypo group. In general, SAEs concerned problems caused by the underlying disease and chemotherapy. With the exception of one SAE (hypertensive episode) in the HX575 group, all other events were assessed as being unrelated to study drug. No difference between the treatment groups could be seen. However, in contrast with study INJ-9, cardiac disorders SAEs were more frequently reported in Eprex/Erypo group.

A total of 30 patients died during the study or shortly after terminating the study: 18 patients (24.3%) in HX575 group and 12 patients (30.0%) in Eprex/Erypo group. None of these deaths was assessed as drug-related by the investigator. The high incidences of deaths are consistent with the advanced stage of cancer in these patients, and most of them died of progressive disease.

Regarding anti epoetin antibodies, a result above cut-off was detected in one patient in the HX575 group at baseline, before application of the first dose of study medication.

In conclusion no new safety concern has arisen in this clinical trial performed in patients receiving chemotherapy. However, the size of population enrolled is too limited to allow a definitive conclusion.

Overall, the adverse reactions observed in the clinical trials conducted with HX575 are similar to those observed with the reference product Erypro and other epoetins.
Three important risks associated with erythropoietin treatment in general are: 1) occurrence of pure red cell aplasia (PRCA) 2) thrombotic vascular events (TVE) 3) possible tumour growth promoting potential (concern in oncology patients).

Table 10: Incidence of Treatment-emergent AEs Assessed as Being Causally Related to Study Medication by MedDRA System Organ Class - SAF Population, study INJ-11

	HX575 (N=74)			ERYPO (N=40)		
	Patients with AE		Events	Patients with AE		Events
	N	%		n	%	
TOTAL	14	18.9	31	13	32.5	52
Vascular disorders	4	5.4	4	3	7.5	4
Gastrointestinal disorders	1	1.4	2	5	12.5	16
General disorders and administration site conditions	3	4.1	7	3	7.5	4
Nervous system disorders	3	4.1	6	2	5.0	3
Respiratory, thoracic and mediastinal disorders	2	2.7	2	3	7.5	3
Metabolism and nutrition disorders	1	1.4	1	3	7.5	4
Musculoskeletal and connective tissue disorders	2	2.7	2	2	5.0	2
Cardiac disorders	0	0.0	0	3	7.5	4
Eye disorders	1	1.4	1	2	5.0	2
Renal and urinary disorders	0	0.0	0	3	7.5	4
Blood and lymphatic system disorders	1	1.4	1	1	2.5	1
Infections and infestations	0	0.0	0	2	5.0	2
Psychiatric disorders	2	2.7	4	0	0.0	0
Skin and subcutaneous tissue disorders	0	0.0	0	2	5.0	3
Endocrine disorders	1	1.4	1	0	0.0	0

Proposed Studies INJ-13, -14 and -17
The applicant has proposed further studies: 2006-65-INJ-13, 2006-66-INJ-14 and 2007-22-INJ-17 in addition to routine pharmacovigilance activities to further investigate the safety profile of HX 575.

Study 2006-65-INJ-13 is a cohort study which aims to prospectively monitor the incidence of pure red cell aplasia among CKD subjects receiving HX575 S.C. All observed AEs and SAEs will be reported within the scope of the PSURs. The study will commence once the SC use of HX 575 has been approved for the renal anaemia indication.

Study 2006-66-INJ-14 is a cohort study which aims to prospectively monitor the incidence of relevant drug-related adverse events and EPO-related loss of efficacy among chronic renal failure subjects receiving HX575 intravenously. This safety study will provide additional data concerning the risk of thrombotic vascular events (TVE) including serious and life threatening cardiovascular complications. All observed AEs and SAEs will be reported within the scope of the PSURs.

Study 2007-22-INJ-17 is a randomized, controlled, double-blind multicentre safety study to evaluate the safety and immunogenicity of subcutaneous HX575 versus Erypo in the treatment of anaemia associated with chronic renal insufficiency in predialysis patients.

Determination of epoetin antibody levels in the serum will be carried out at a single laboratory using a validated radioimmunoprecipitation assay.

Regarding statistical analysis, as PRCA events may occur (even rarely) in less than one month (minimum = 0.3 month) after initiation of treatment, all PRCA events are considered whatever duration of exposure, as requested by CHMP.

The CHMP was concerned that despite the proposed risk minimisation activities to limit the use in renal failure patients to the IV route, there may still be off-label use in this group of patients. The MAA committed to perform a survey 6 months after HX575 enters the market to establish the actual

use of HX575. This survey will be addressed to nephrologists and dialysis centres and will cover about 85% of the epoetin alfa market.

For each important safety concern, routine minimization measure is proposed. Additional risk minimization activities are considered to be necessary to reduce the potential for off-label sub-cutaneous use.

1.1 Laboratory findings

Study 2003-29-INJ-09 (in patients with renal anaemia)

There were no differences between the treatment groups for the parameters erythrocytes, reticulocytes, haematocrit, leucocytes and platelets. The mean and median values remained stable over time. In general, those patients who had abnormal values at visit –1 also had abnormal values at visits 16 and 28.

Also for clinical chemistry parameters as well as iron, ferritin and transferrin saturation, there were no relevant differences between the treatment groups. Approximately 20 % of patients had clinically relevant abnormal potassium values, and approximately 30 % of patients had clinically relevant abnormal phosphate values in both treatment groups.

Study 2003-31-INJ-11 (in patients with chemotherapy associated anaemia)

There were no treatment differences for the parameters erythrocytes, reticulocytes, haematocrit, leucocytes and platelets. The mean values remained stable over time. In general, those patients that had abnormal values at visit –1 or visit 0 also had abnormal values at visits 6 and 12.

Clinical chemistry parameters, urine analysis, serum iron and ferritin levels and transferrin saturation were not relevantly different between treatment groups. It is known that increased serum ferritin levels occur in patients with malignancies. In both treatment groups, mean serum ferritin levels were elevated.

Discussion on Clinical Safety

Overall, there was no significant difference between the treatment groups for the incidence or type of adverse events. Thus, HX575 revealed an AE profile (including immunogenicity) similar to that of the chosen comparator ERYPO.
Risk of tumour growth potential of erythropoietin stimulating agents in patients with chemotherapy induced anaemia
The risk of tumour growth potential of erythropoietin stimulating agents (class effect) in patients with chemotherapy induced anaemia is currently under discussion in the PhVWP.

Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The MAA submitted a risk management plan, which included a risk minimisation plan

Summary of the risk management plan

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
Pure Red Cell Aplasia (PRCA)	**Routine** • Routine pharmacovigilance **Additional** • Post-authorisation safety study INJ-14 Phase III study INJ-17	**Routine** • Contraindication in section 4.3 of the SPC for use in patients who have previously experience PRCA following treatment with erythropoetins • Warning in section 4.4 of the SPC regarding PRCA • Mention in section 4.8 of the SPC
Potential off-label use regarding s.c. application in renal anaemia patients in respect of missing comparative data on safety and immunogenicity between HX575 and Erypo in these patients .	**Routine** • Routine pharmacovigilance **Additional** • Phase III study INJ-17 • Market survey to monitor potential off-label s.c. use in renal anaemia patients	**Routine** • Advice to use i.v. route in treatment of renal anaemia in Section 4.2 of the SPC. • Warning in section 4,4 of the SPC that iv route only should be used in chronic renal anaemia patients due to lack of immunogenicity data for sc use. **Additional measures to avoid s.c. application in renal anaemia patients** - Educational leaflet Cool boxes with visual label
Thrombotic vascular events (TVE)	**Routine** - Routine pharmacovigilance **Additional** - Post-authorisation safety study INJ-14 Phase 3 study INJ-17	**Routine** - Risk of thrombotic vascular events (TVE) including serious and life threatening cardio-vascular complications including the dose recommendation that the target haemoglobin not exceed 12 g/dl are mentioned in Sections 4.1, 4.2, 4.3, 4.4 and 4.8 of the SPC.
Tumour growth potential	**Routine** - Routine pharmacovigilance **Additional** - Post-authorisation safety study INJ-14 Phase 3 study INJ-17	**Routine** Risk of tumour growth potential are mentioned in Sections 4.4 and 5.1 of the SPC.

The CHMP, having considered the data submitted in the application is of the opinion that the following risk minimisation activities are necessary and sufficient for the safe and effective use of the medicinal product: See as detailed in section 2.3

Overall conclusions, risk/benefit assessment and recommendation

Quality

During the evaluation of HX575 a major objection was initially raised. Satisfactory responses have been provided to resolve this concern.

Other concerns have also been adequately addressed, in particular several commitments made by the applicant and several follow-up measures are defined to provide further information post-approval.

Non-clinical pharmacology and toxicology

Primary pharmacodynamic studies showed similarity between the HX575 and the reference product Eprex/Erypo.

In addition, five non-clinical studies were submitted by the applicant in order to demonstrate the comparability of HX575 to the reference product Eprex/Erypo and to demonstrate the safety and local tolerability of HX575. Pivotal studies were undertaken in dogs and rabbits. The 13-week toxicity study performed in the dog, with intravenously administered 100 or 500 IU/kg HX575 drug product or 500 IU/kg Eprex/Erypo, allowed investigation of potential systemic toxicity of the product. This study revealed no signs of overt toxicity. The lack of investigations following subcutaneous administration was discussed during the procedure. This was considered to be acceptable taking into account that: 1) potential systemic toxicity following subcutaneous administration is covered by the intravenous study, 2) local tolerance has been investigated in the rabbit following subcutaneous administration and 3) animal models are usually not useful to predict immunogenicity in humans.

Local tolerance was tested in two studies in the rabbit following a single intravenous, intramuscular, intra-arterial, intra-venous and subcutaneous injection administration. Results indicated that the epoetin injection solution HX575 had good local tolerability in rabbits via all tested routes of administration for doses up to 10,000 IU/animal. As a result, no local effects are expected following accidental incorrect administration.

Efficacy

The Applicant has provided Pharmacology results from five studies in healthy subjects following single dose and/or repeat dose exposure. Efficacy and safety data were obtained from two double-blind, randomised, multicenter studies investigating efficacy and safety of HX575 for the treatment of anaemia in haemodialysis (INJ-9) or in cancer patients (INJ-11). As notably requested by the CHMP, results from a new pharmacokinetic/pharmacodynamic study (INJ 12) were provided.

Intravenous administration of Epoetin alfa

The submitted PK/PD studies showed comparable pharmacokinetic and pharmacodynamic profiles of HX575 and Eprex/Erypo at steady state in healthy subjects and therefore supports the claimed biosimilarity of both products.

The primary endpoint of study INJ-9 was the mean absolute change in Hb level between the baseline period and the evaluation period. The observed difference in Hb change was low and within the pre-defined and acceptable equivalence boundaries of ± 0.5 g/dl. All secondary endpoints, most importantly change in epoetin dose, also supported the conclusion of therapeutic equivalence between Eprex/Erypo and HX575 after I.V. administration.

Subcutaneous administration of epoetin alfa

(i) Pharmacokinetic/Pharmacodynamic Results

The multiple dose study INJ-12 revealed similar PK and PD profiles of HX 575 and Erypo and therefore supports the claimed biosimilarity of both products.

(ii) Clinical efficacy data

Study INJ-11 was a non-comparative study in cancer patients with chemotherapy-induced anaemia. The primary efficacy endpoint was defined as the Hb response (increase of ≥ 2.0 g/dl from baseline) in the HX575 treatment group during weeks 5-12 of the study in the absence of RBC transfusions. An Eprex/Erypo arm was included for internal validity only.

The study results demonstrate that HX 575 has the expected effects of an epoetin. Due to the desing and the small number of patients, the study does not allow any conclusion on whether this effect is comparable to that of Erypo.

However, the similar pharmacokinetic and pharmacodynamic profiles after multiple dose subcutaneous administration in study INJ-12, together with the equivalent efficacy and pharmacokinetic/pharmacodynamic profiles after multiple IV administration make an efficacy difference for the SC route of administration highly unlikely.

Safety

No new safety concern specific to HX575 has arisen during the clinical trials, and the safety profiles of HX575 and Eprex/Erypo are comparable.

In addition, no increased immunogenicity was found for HX575 compared to Eprex/Erypo and no definite neutralizing antibodies (although one transient borderline result) have been detected. The observational study proposed by the Applicant is considered as sufficient to further investigate the potential immunogenic risk of this biosimilar erythropoietin.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics

Having considered the safety concerns in the risk management plan, the CHMP considered that the proposed activities described in section 3.5 adequately addressed these.

No immunogenicity data for SC use in the population at risk for antibody-induced PRCA, i.e. patients with renal anaemia have been provided by the Applicant because at the time of clinical development Eprex/Erypo could not be used as comparator in SC studies in renal anaemia patients, and therefore no comparative phase 3 study could be conducted. Because of the lack of such data, the SC use is currently not recommended in patients with renal anaemia. The applicant is committed to provide a comparative SC study in accordance with the note for guidance on similar biological medicinal products containing recombinant erythropoietins (EMEA/CHMP/BMWP/94526/2005).

- User consultation

A satisfactory user consultation for readability of the patient leaflet has been undertaken.

Risk-benefit assessment

The submitted data demonstrated similar PK, PD, efficacy and safety of **I.V.** administered HX575 and Eprex/Erypo. Therefore, the CHMP considered the benefit-risk ratio of HX575 positive for the I.V. indications applied for.

In addition, a multiple dose PK/PD study in healthy volunteers, submitted with the D120 response document, demonstrated comparable PK and PD of **S.C.** administered HX575 and Eprex/Erypo. A comparative trial evaluating the S.C. route in CKD patients as suggested in the *Guideline on similar biological medicinal products containing recombinant erythropoietins* has not been performed and this is acceptable because the temporary contraindication of the S.C. route of administration in CKD patients for the reference product precluded the conduct of such a study at the time of clinical development of HX 575. Instead, a non-comparative S.C. trial has been conducted in oncology patients with chemotherapy-induced anaemia, which included an Erypo/Eprex arm as internal control. This study demonstrated efficacy of HX575 according to the pre-defined response criteria.

Despite these short-comings, the benefit-risk ratio is considered positive for S.C. use of HX575 in the oncology indication because 1) the finding of similar PK/PD profiles for the S.C. route of administration together with the similar PK/PD and efficacy for the I.V. route makes a difference in efficacy for the S.C. route of administration highly unlikely, 2) the safety data from the oncology trial did not reveal any safety concerns beyond those known for Eprex/Erypo or other epoetins.

Since the risk of anti-epoetin antibody induced PRCA is highest with S.C. use of epoetin in CKD patients, extrapolation of antibody data from I.V. to S.C. use or from immunocompromised (oncology) to immunocompetent (CKD) patients is not possible. Due to the lack of adequate safety and particularly immunogenicity data in CKD patients (S.C.), the risk-benefit ratio for S.C. use in CKD patients was considered unfavourable. The applicant has planned a comparative efficacy/safety trial be performed according to the *Guideline on similar biological medicinal products containing recombinant erythropoietins*. Use of HX575 should be restricted to I.V. administration in this patient population.

A risk management plan was submitted which adequately addresses all concerns. The CHMP, having considered the data submitted, was of the opinion that pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to further investigate some of the safety concerns and additional risk minimisation activities as detailed in section 2.3 were required.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of HX575 in the treatment of

- anaemia associated with chronic renal failure in paediatric and adult patients on haemodialysis and adult patients on peritoneal dialysis (see Section 4.4).
- severe anaemia of renal origin accompanied by clinical symptoms in adult patients with renal insufficiency not yet undergoing dialysis (see Section 4.4).
- anaemia and reduction of transfusion requirements in adult patients receiving chemotherapy for solid tumours, malignant lymphoma or multiple myeloma, and at risk of transfusion as assessed by the patient's general status (e.g. cardiovascular status, pre-existing anaemia at the start of chemotherapy).
- reduction of exposure to allogenic blood transfusions in adult non-iron deficient patients prior to major elective orthopaedic surgery, having a high perceived risk for transfusion complications. Use should be restricted to patients with moderate anaemia (e.g. Hb 10-13 g/dl) who do not have an autologous predonation programme available and with an expected blood loss of 900 to 1800 ml.

was favourable and therefore recommended the granting of the marketing authorisation.