

## SCIENTIFIC DISCUSSION

**This module reflects the initial scientific discussion and scientific discussion on procedures, which have been finalised before 1 April 2004. For scientific information on procedures after this date please refer to module 8B.**

### 1. Introduction

NeoRecormon is the successor of Recormon, a product already marketed. The active substance is epoetin beta (a recombinant human erythropoietin), a 'Part A' product produced by a genetically modified mammalian cell line (CHO). Recormon is currently marketed under 4 dosage strengths (1,000 IU, 2,000 IU, 5,000 IU and 10,000 IU/vial), each presentation being for single use.

The solvent is provided in two presentations: ampoule or prefilled syringe.

On the occasion of the new application, the company introduced two new dosage strengths of 500 IU and 20,000 IU as well as multidose vials containing 50,000 and 100,000 and new pharmaceutical presentations (two-chamber cartridges to be used with a pen system) for 10,000 and 20,000 IU.

A new pharmaceutical form (solution for injection) in 7 strengths was introduced as an extension of the marketing authorisation. These new presentations provided in pre-filled syringes. Subsequent extension applications added two more strengths of the solution for injection in pre-filled syringe to the marketing authorisation, together with one addition strength of the powder and solvent for solution for injection in cartridge (for use with Reco-pen).

Finally, there are 19 forms and strengths in total, which, in combination with different packaging sizes, result in 39 presentations.

Dosage form and strength	Package size
NeoRecormon 500/1000/2000 IU powder and solvent for solution for injection	1, 5, 10 vials + 1, 5, 10 ampoules of solvent
NeoRecormon 5000/10000 IU powder and solvent for solution for injection	1, 5 vials + 1, 5 ampoules of solvent
NeoRecormon multidose 50000/100000 IU powder and solvent for solution for injection	1 multidose vial + 1 ampoule of solvent
NeoRecormon 10000/20000/60000 IU powder and solvent for solution for injection in cartridge	1 or 3 two-chamber cartridges
NeoRecormon 500/1000/2000/3000/4000/5000/6000/10000/20000 IU solution for injection in pre-filled syringe	1 or 6 pre-filled syringes

Some of the indications which are sought, have been reviewed by the CPMP and have been licensed by member states between 1990 and 1996 (renal anaemia in patients on dialysis, symptomatic renal anaemia on patients not yet undergoing dialysis, increasing the yield of autologous blood, and anaemia of prematurity). The additional indication under review was: prevention and treatment of anaemia in cancer patients.

### 2. Chemical, pharmaceutical and biological aspects

During the assessment of this dossier mainly new pharmaceutical aspects have been reviewed by the rapporteur and co-rapporteur, even though the entire documentation was submitted. Indeed, epoetin beta, as produced by Boehringer Mannheim, is not a new product and, as a consequence, this submission has to be assessed bearing in mind the experience gained on this product, which has been marketed since 1990.

## Composition

For the purpose of this assessment report the pharmaceutical review will focus on:

- the new dosage strength (500 IU/0.5 ml)
- the new formulation for 1000 IU/1 ml and 2000 IU/1 ml dosage strengths
- the new multidose presentations in two chamber cartridge 10000 IU/ 1 ml and 20000 IU/ 1 ml
- new multidose presentations in vial 50,000 IU/10 ml and 100,000 IU/5 ml

The lyophilised finished product represented in the 500, 1000, 2000, 5000 or 10000 IU/vial presentations are composed of the active ingredient and a set of selected excipients. For reconstitution before use, the various lyophilisates are dissolved in water for injection contained in an ampoule (NeoRecormon powder and solvent for solution for injectin) or in a prefilled syringe (NeoRecormon powder and solvent for solution for injection in pre-filled syringe).

The new dosage strength of 500 IU/0.5 ml is a freeze dried product designed to be reconstituted in 0.5 ml solvent. As this is half of the quantity compared to the optimised 1000 IU dosage strength, the composition of the reconstituted solution in terms of excipients is homothetic.

The proposed new “optimised formulation” consists of a revision of the content in some excipients keeping in mind the need to keep as closely as possible to the already approved formulation. Most of the adjustments made in the content of the excipients are self-explanatory (to keep the solution isotonic after reconstitution). Supportive experimental data have been provided for the reduction in CaCl<sub>2</sub> content; all formulations still comply with the requirements of the E.P. This optimised formulation has been already approved as a variation for the 5,000 and 10,000 IU/1 ml presentations of Recormon. Its use is extended also for the 1000 and 2000 IU/vials. This formulation allows the reduction of the volume to be injected into patients and enables more convenient subcutaneous administration.

The rationale for the development of the multi-dose presentations is to avoid any wastage of reconstituted product where the optimised dose cannot be achieved using one of the single-use products. The aim is to provide a preserved solvent compatible with the “optimised formulation” of the lyophilisate. The excipients contained are the same as those for the single use formulations. However, for the three of them (urea, calcium chloride and L-phenylalanine), the quantitative composition was decreased in order to avoid any risk of particle formation during shelf life and after reconstitution.

The 50,000 IU multidose preparation is to be reconstituted in 10 ml preserved solvent before use. The 100,000 IU vial is designated for use where a higher dose in a smaller volume is required, thus the content is reconstituted in a 5 ml solvent.

Both cartridge formulations are reconstituted in 1 ml preserved solvent by placing the cartridge into the Reco-Pen.

The pharmaceutical aspects of pharmaceutical form: the solution for injection in pre-filled syringe was assessed in the light of the first extension application. Further extensions were filled to include additional strengths of the solution for injection in prefilled syringe and the powder and solvent for solution for injection in cartridge.

### Active substance

Epoetin beta's protein sequence, biological activity and immunological reactivity were found to be indistinguishable from erythropoietin isolated from the urine of anaemic patients. Its mechanism of action lies in the stimulation of erythropoiesis.

### Fermentation and production

A well-characterised fermentation strategy is employed, using standard media for the production cell-line CHO-DN2-3 $\alpha$ 3 expressing constitutively the erythropoietin gene. One vial of the WCB is expanded and a batch refeed process is used. A single production run consists of a maximum of 10 harvests per fermentation resulting in a maximum of 10 batches after purification.

### Purification

Each of the 10 harvests is processed separately through four column chromatography purification steps; Blue Sepharose, Hydroxylapatite, RP-HPLC on Vydac-C4 and DEAE Sepharose, resulting in up to 10 batches of purified product. The data presented demonstrate that the purification process is satisfactorily controlled and documented.

The main steps in the characterisation of the active substance employed are: amino acid analysis, carbohydrate analysis, physicochemical and biological characterisation.

Data on the average rhEPO content by harvest, the average rhEPO yield per batch, and on the degree of purity for the rhEPO bulk substances released confirm the consistency of fermentation and purification.

A documentation for the manufacturing and control of the active substances has been provided.

### Specifications and routine tests

The same set of specifications and test procedures have been submitted as already reviewed and approved.

According to the strategy employed by the company, a number of tests are undertaken for each batch, whereas further test parameters referred to as “characterisation assays” are only conducted at the first and last batches of each fermentation run. Up to 10 harvests can be derived from one fermentation run, each of which is processed separately resulting in up to 10 batches.

### Stability of the active substance

Data upon several batches from the BM-Penzberg production meet the specifications for all test parameters and demonstrate stability of rhEPO bulk substance for a storage period of three years. No difference could be observed between storage at -70 °C and -20 °C. These data are reassuring, showing the very good stability of the active ingredient as a bulk solution at -70 °C. It is thus concluded that the Company’s proposal for 5 year shelf-life is considered acceptable.

### **Other ingredients**

All the excipients are contained in the already approved presentations and have been checked. They are acceptable for parenteral administration.

The same colourless type I, 2 ml (10 ml for the multidose) glass vial is used for the NeoRecormon presentations as those for the already authorised forms. A teflonised rubber closure is used.

A special device for repeated withdrawals in the case of the multidose container is provided in order to avoid any trouble with the repeated piercing of the rubber closure.

Pre-filled syringes consisted of glass syringes with a nominal volume of 1 ml. Fluororesin laminated plunger stoppers are used.

### **Product development and finished product**

#### Manufacturing formula

The qualitative and quantitative composition of all single-use and multi-dose preparations is well justified.

#### Manufacturing process

The optimised formulation is now used, allowing the same manufacturing process for the preparation of all single dose presentations. As a result of the development of the new dosage strength, the manufacturing process was reviewed and some process steps reassessed.

The manufacturing process consists of four steps: formulation of the drug product solution, sterile filtration, aseptic filling and freeze-drying (for the powder for solution for injection only). The company has well identified the critical steps (performance of sterile filtration, aseptic conditions during filling, conditions of the freeze-drying process). They have justified the choice of the material and equipment used. The batch sizes have been given and are acceptable.

### Product specifications and tests for release

All the release tests proposed are identical to those already approved for Recormon. The tests and specifications for the solution for injections are identical to those for the powder for solution for injections (except for tests related to the pharmaceutical form).

### Stability tests on the finished medicinal product

For the powder for solution for injection: identical protocols to those used for the already approved formulations have been employed also for the new formulation of 500 IU/0.5 ml and 1000 and 2000 IU/1 ml. The same assessment criteria, tests parameters and storage conditions were applied. All parameters recorded during the stability studies at 5 °C met the specifications for the samples whatever the dosage strength.

In summary, data obtained with the new dosage forms using the optimised formulation are reassuring in terms of stability of the finished product. Thus, the 2 years shelf life at 2-8 °C seems acceptable.

A specific study for the investigation of the influence of interruptions in the cooling chain was provided for the multidose vials as well as the cartridges.

Regarding the stability of the multidose presentations after reconstitution, it can be concluded from the studies performed that the reconstituted solution can be used for up to one calendar month when stored at 2-8 °C.

The shelf life for NeoRecormon (powder and solvent for solution for injection) for the following strengths: 500 IU, 1000 IU, 2000 IU, 5000 IU and 10000 IU single dose and 50000 IU and 10000 IU multidose was extended to 3 years at 2 – 8 °C.

For the solution for injection in pre-filled syringes: when stored at 2 – 8 °C, a shelf life of 24 months is justified.

### Stability of the solvent

The two presentations used for the solvent (one-point-cut glass ampoule and pre-filled syringe) have already been approved for Recormon. The solvent is the same (water for injection). No modification has been made to the already approved presentations. Taking into account the experience of the company in the manufacturing process, it is concluded that the proposed shelf-life of 3 years for the one-point-cut glass ampoule and 2 years for the pre-filled syringe are well justified.

Stability testing has been also performed on the preserved solvent for the multidose presentations, in ampoules stored at 5 °C, 25 °C, 30 °C during 24 months, at 40 °C during 12 months and at 50 °C during 3 months. All the results obtained are in compliance with the specifications and confirm that the solvent can be stored at room temperature for 24 months, which is fully compatible with the proposed storage time for the lyophilisate.

## **3. Toxicopharmacological aspects**

### **Pharmacodynamics**

#### **Pharmacodynamic effects relating to the proposed indications**

The pharmacodynamics of epoetin beta in healthy animals have been demonstrated in numerous preclinical studies of various animal studies and different ages. A marked stimulation of erythropoiesis which was clearly dependent on dose and duration of administration was elicited. The PCV rose rapidly to levels considerably above normal. Thus, animals treated with high dose levels of epoetin beta (rats up to 10,000 U/kg/day), developed a PCV of >80 Vol% over the first three weeks.

#### **General pharmacodynamics**

Epoetin beta did not have any effect on the peripheral leukocyte or platelet counts. No increases in the concentrations of urea and creatinine were seen. It does not have any notable effect on locomotor activity in mice after administration of 30 and 100 U/kg intraperitoneally (ip). Stimulation of locomotor activity was seen after 300 and 1000 U/kg ip. There were no striking changes (except for a slight increase in arterial blood pressure) in hemodynamics or blood chemistry in conscious dogs after

a single administration of 1000 U/kg epoetin beta iv. After 3 administrations of the same dose within 5 days, dogs displayed a clear rise in platelet count.

### **Pharmacokinetics**

Serum levels of epoetin beta after i.v. and s.c. injection into dogs and rats were compared with those in humans. Total body clearance increased in the order man<dog<rat. Terminal half life after s.c. injection was clearly longer than that after i.v. injection both in patients and in dogs. A striking difference between animals and patients was the higher bioavailability from the subcutaneous depot in dogs and rats.

### **Toxicology**

#### **Single dose toxicity studies**

In acute toxicity study performed in mice and single dose intravenous pilot study in beagle dogs no effect was observed with 6000 IU/kg bw. In acute toxicity study performed in rats (intravenous administration) accelerated erythropoiesis was seen from 3,000 IU/kg bw. The acute lethal dose in mice was found over 45,000 IU/kg and in guinea pigs over 14,000 IU/kg.

#### **Repeated dose toxicity studies**

Four week study in rats (subcutaneous administration) in order to investigate myelofibrosis in early stage and its relation with increase PCV showed an increase in hematopoiesis and hyperaemia of bone marrow.

In 3 month s.c. test in dogs and in rats, deaths were occurred in the middle and high dose groups attributed to renal and myocardial thrombosis. Drug-induced polycythemia was developed from the first week due to the high doses administrated. Antibodies were developed in some animals from each dose level. Severe but reversible myelofibrosis occurred. Bone marrow was the target in chronic toxicity studies both after i.v. and s.c. administration. In the 3-month i.v. study in dogs myelofibrosis was the only adverse effect in 7/10 animals after 3,000 IU/kg which often aggravated by osteosclerosis but did not influence the clinical or haematological parameters. It was concluded that development of myelofibrosis is dependent on the level of the PCV.

#### **Reproductive function, embryo-foetal and perinatal toxicity**

No reproductive risks were revealed in i.v. and s.c. reproductive toxicology studies in animals. The only finding observed was kinked tails. Polysorbate 20, an ingredient in the formulation of epoetin beta did not elicit any adverse effects in pregnant rats and is not responsible for the kinked tail malformation observed. Treatment of female rats with epoetin beta caused adverse effects in both the maternal and F1 generation.

#### **Mutagenic potential**

Epoetin beta did not exhibit any genotoxic potential in the Ames test and a micronucleus test. Neither gene mutations were triggered nor chromosome breakage recorded.

In an in vitro mammalian test conducted to amplify and complete the test battery, no evidence of mutagenic activity was shown either in the presence or the absence of metabolic activation. In an in vitro metaphase analysis in human lymphocytes, there was no indication in chromosomal damage either in the presence or the absence of metabolic activation.

It can be concluded that there is no evidence of either mutagenic or clastogenic activity.

#### **Carcinogenic potential**

The following studies were performed: Investigation of the carcinogenic potential of murine epoetin during long term administration in mice, effect of epoetin beta on proliferation and colony formation of human tumour cell lines in vitro and in vivo, as well as proliferation of human myeloma cells and a rat study in which implanted tumours were treated with cyclophosphamide and epoetin beta. These studies have demonstrated that epoetin beta has no tumourigenic potential, especially there was no influence on tumour progression.

#### **Local tolerance**

Reports on local intravenous or subcutaneous tolerance revealed no problems with intravenous or subcutaneous administration of epoetin beta in the applied formulations.

#### **4. Clinical aspects**

##### **Introduction**

In the application for NeoRecormon the following indications are reviewed:

- treatment of anaemia associated with chronic renal failure (renal anaemia) in patients on dialysis and of symptomatic renal anaemia in patients not yet undergoing dialysis
- increase the yield of autologous blood from patients in a pre-donation programme with moderate anaemia (Hb 10 - 13 g/dl [6.21 - 8.07 mmol/l], no iron deficiency) if blood conserving procedures are not available or insufficient
- prevention of anaemia of prematurity in infants with a birth weight of 750 to 1500 g and a gestational age of less than 34 weeks.
- prevention and treatment of anaemia in patients with solid tumours treated with platinum-based chemotherapy.

New studies were submitted for the multidose preparations which contain additional preservatives.

##### **Pharmacodynamics**

Biological effects of epoetin beta were investigated in vitro (bone marrow cultures from volunteers) in view of demonstrating its effect on the various haemopoietic precursor cells and to determine whether epoetin beta has a cytotoxic effect on human bone marrow cells.

Epoetin beta stimulates human erythroid bone marrow precursor cells and produces a dose-related stimulation of the growth of human bone marrow cells towards erythropoiesis.

No stimulation of megacaryotic differentiation, but an inhibition of the formation of granulocytic macrocytic colonies in high concentration occurred. No indication exists of a cytotoxic effect of epoetin on human bone marrow cells. An allergenic potential test study in healthy volunteers was negative.

In comparison studies on the pharmacological effects of i.v. vs. s.c. administration it was shown that 300 IU/kg s.c. is equivalent to 400 IU/kg i.v. in terms of red cell volume available for autologous blood donation.

In conclusion epoetin beta increases peripheral hematopoietic progenitor cells and may affect erythroid and myeloid cell lineages. Iron deficiency, underlying infections, malignant processes, myelodysplastic disorders, folic acid, B12 deficiencies diminish the response to epoetin beta and supplementation has to be made consequently during the course of epoetin beta treatment.

##### **Pharmacokinetics**

It was found that the elimination kinetics of epoetin beta is independent of the dose given.

The increase in epoetin beta plasma concentration after s.c. administration is more moderate than after i.v. injection.

The terminal half-life is between 4 and 12 h after i.v. dosing and 8-22 h after s.c. administration.

The relative bioavailability after s.c. administration is 23-52% lower than after i.v., independently of the dose given.

Pharmacodynamic and pharmacokinetic investigations were not performed with the multidose forms, since the formulation has not changed and the small amount of preservative is not expected to make any difference in pharmacokinetics. On the other hand, safety and tolerability of the solvent of multidose form after s.c. Administration was assessed in volunteers. No effect on haematological variables was found.

## Clinical studies

### 1. Treatment of anaemia of chronic renal failure

#### Efficacy

MF n°	Patient with	No. evaluable for efficacy (epoetin beta)	Design	Epoetin beta dose	Duration of treatment
3787	haemodialysis	90 (90)	ROD	40, 80 or 120 IU/kg 3x/ week i.v.	Up to 18 months
3787	haemodialysis	84 (84)	ROD	Maintenance, adjusted to haematocrit, i.v.	Up to 36 months
3787	haemodialysis	53 (53)	ROD	Maintenance, adjusted to haematocrit, s.c., i.v.	s.c.: up to 18 months
3981	haemodialysis	99 (53)	RBP	80 IU 3x/week for correction, 40 IU for maintenance, i.v.	Corr. 1 month Maint.: up to 6 months
3826	haemodialysis	14 (14)	OS	100 IU/kg 3x/week, i.v.	15 months
3911	Transfusion or ferritin > 700 ng/ml, haemodialysis	304 (304)	OS	80 or 120 IU/kg 3x/week, i.v.	Up to 10 months
3911	See above	48 (48)	OS	See above	Up to 14 months
4174	Haematocrit ≤ 28%, haemodialysis	41 (41)	OS	20 IU/kg 3x/week, dose titr. i.v.	12 months
4173	Haematocrit ≤ 28%, haemodialysis	90	RBA	40 IU/kg 3x/week, titr. steps of 20 IU/kg, s.c., i.v.	13 months
4135	Haematocrit ≤ 28% or blood transfusion, haemodialysis	338 (170)	ROU	20 IU/kg 3x/week, titr. steps of 20 IU/kg s.c.	12 months
4129	Haematocrit ≤ 28%, haemodialysis	66 (66)	OS	20 IU/kg 3x/week, titr. steps of 20 IU/kg s.c.	12 months
4083	haemodialysis	12 (12)	OS	s.c. : change from daily adm.to 3x/week, weekly dose unchanged, s.c.	At least 4 months
4100	Peritoneal dialysis	98 (98)	ROD	5, 10 or 20 IU/kg daily, s.c.	16 months
4169	Dialysis treated with Cambridge EPO s.c. or i.v. for at least 6 months	286 (Penzberg 143, Cambridge 143)	RBA	Penzberg or Cambridge EPO, maintenance dose adjusted to haematocrit, 3x/week s.c. i.v.	12 months

4200/4201	Predialysis Haematocrit $\leq$ 30%	225 (225)	OS	500 IU daily or 100 IU 3x/week if BW $\leq$ 75 kg ; double dose if BW > 75 kg s.c.	Up to 11 months
3904	Children, haematocrit $\leq$ 28%, $\leq$ 3 transfusions last 6 months or ferritin $\geq$ 700 ng/ml, dialysis	126 (126)	OS	40, 80 or 100 IU/kg 3x/week or 300 IU/kg 1w/week i.v.	26 months
4323	Children, end-stage renal failure	41 (41)	OS	Maintenance, s.c., dose adjusted for haematocrit	12 weeks

R = randomised, O = open label, B = double blind, S = single group, A = active control group, P = placebo control group, U = untreated control group, D = dose response group(s)

A total of 1663 patients were included in studies designed to correct renal anaemia in dialysis and pre dialysis patients. The main results were:

- Dose-dependent increases in the reticulocyte count and in hematocrit were observed from the first and second week.
- An increase in hematocrit of about 0.5-1% is expected with the recommended dose regimens.

The target hematocrit was reached by most patients after 12 weeks. The need for regular transfusions was abolished earlier (usually at 4 weeks). The recommendations for the starting doses were the same for the children as in adults, but the effects of the epoetin beta were age-dependent. No impact on growth retardation was found.

#### Safety

Most common treatment related adverse effects are: increase in blood pressure or aggravation of existing hypertension, especially in the case of rapid PCV increase. Thromboembolic adverse effects were classified as serious in 9.9% of patients studied. A moderate dose-dependent rise in platelet count was observed especially after i.v. administration. A fall in serum ferritin values simultaneously with rise of haematocrit was observed leading to iron substitution. Rarely, transient increases in serum potassium and phosphatases have been observed.

The most frequently reported causes of death were adverse effects related to cardiovascular system, followed in frequency by infections.

#### Conclusion

On the above mentioned grounds the CPMP confirmed a favourable risk/benefit assessment.

In October 2002, Roche Registration Ltd. submitted a type II variation application for a new frequency of subcutaneous administration in the maintenance phase of the treatment of anaemia associated with chronic renal failure, namely a "once every two weeks" administration. This application was supported by a clinical pharmacology study (BP15984) and a clinical therapeutic trial (BA16108).

#### Study BP15984

This study was a parallel group, randomised, double blind, placebo-controlled single centre exploratory trial in healthy volunteers (n = 54). The goal was to determine epoetin beta concentrations over various dosing intervals. Three dosing schedules were followed: 50 IU/kg 3 times per week, 150 IU/kg once weekly and 300 IU/kg once every 2 weeks. The same cumulative dose of 600 IU/kg of epoetin beta was administered in each treatment group over a 4-week period followed by a 3-week follow-up period. The three active treatment groups and the corresponding placebo groups were comparable with respect to demographic data (gender, age, weight, height and race).

The results showed that both the once weekly and thrice weekly dosing interval led to epoetin beta concentrations above baseline for the entire week.

### Study BA16108

This was an open-label, non-randomised, two cohort trial to compare the efficacy of maintenance therapy with subcutaneous epoetin beta in clinically stable adult patients with chronic renal anaemia on peritoneal dialysis who switched from previously twice or thrice weekly to “once weekly”, or from previously “once weekly” to once every two weeks administration. The study consisted of a 4-week run-in phase and a subsequent 25-week treatment phase.

The results showed that Mean Hb levels decreased in both groups, the decrease being more pronounced in the “once every two weeks” group, but the lower limits of the 95% confidence intervals for the mean changes in Hb from baseline to weeks 13-25 did not exceed the pre-defined limit of – 0.75 g/dL. Hb levels can be maintained when switching patients from “once weekly” to “once every two weeks” dosing regimen, but increases in epoetin beta dose are expected in a substantial number of patients.

There was no excess incidence rate of AE or SAE in the once every two weeks administration compared to the once or thrice weekly dosing regimen.

## **2. Autologous blood donation from patients scheduled for elective surgery**

### Efficacy

MF n <sup>o</sup>	Patient with	No. evaluable for efficacy (epoetin beta)	Design	Epoetin beta dose	Duration of treatment
4185	Elective orthopaedic surgery	127 (99)	RBP	100, 200, 400, 800 IU/kg x 2 /week, i.v.	4 weeks
4228	Elective cardiac surgery	197 (159)	RBP	100, 200, 400, 800 IU/kg x 2 /week, i.v.	4 weeks
4312	Total hip surgery	95 (50)	ROU	500 IU/ kg x 2 /week, s.c.	3 weeks

R = randomised, O = open label, B = double blind, P = placebo control group, U = untreated control group

In study 4185 and 4228, the primary endpoint was the gain in Red Cell Volume. Furthermore, in study 4312, the primary endpoint was the proportion of patients with peri-operative blood transfusion. Treatment with epoetin beta increases the amount of autologous blood available at the time of the elective surgery. In study 4228, 71 % of patients of the 800 IU group were able to donate 6 times or more, versus only 32 % of the placebo patients. Similar results were found in study 4185. The period of anaemia after blood donation is shortened. The dosages are higher than in renal anaemia 200 to 800 IU/kg bw i.v. or 150 to 600 IU/kg bw s.c. twice a week over 4 weeks prior to surgery. The oral substitution of iron is essential. The decision on the use prior to elective surgery requires consideration of:

- no iron deficiency
- hematocrit of > 34%
- expected need for transfusion

Apart from two orthopaedic patients, all other patients in studies 4185 and 4228 needed blood transfusion. A pronounced drop in hematocrit was noted during the first two weeks.

In study 4312, the proportion of patient with transfusions and the number of units transfused were statistically significantly reduced with epoetin beta vs. control. Moreover the need for homologous transfusions was reduced by two thirds after treatment with epoetin beta.

Despite oral substitution of iron, a functional iron deficiency occurred in many patients, particularly in those receiving epoetin beta.

## Safety

A total of 475 patients were analysed in the indication autologous blood donation. Adverse events were reported in above half of the epoetin patients compared with 35 % in controls. Most common adverse events were coronary heart disease (9.7 % vs. 5.1 %) and upper respiratory tract infections (5.0 % vs. 1.7 %) as well as typical complaints of blood donation. Myocardial infarctions, which were observed only in epoetin treated patients, occurred in the cardiosurgical population, and were mostly directly related to cardiosurgical problems.

The decision on the use on the ABD requires considerations of the patient blood volume, baseline PCV and expected need for transfusions. Nomograms presented in the SPC are useful in determining the effective dose. The occurrence of thromboembolic events in the treated population was discussed in detail and statement was introduced in the SPC to make the physician aware of the need to balance the expected efficacy with the increased risk of occurrence of thromboembolic events.

## Conclusion

The CPMP considered that this indication can be approved of a favourable risk/benefit balance in a very specific patients population described in the SPC as follows:

“NeoRecormon is indicated for increasing the yield of autologous blood from patients in a pre-donation programme. Its use in this indication must be balanced against the reported increased risk of thromboembolic events. Treatment should only be given to patients with moderate anaemia (Hb 10 - 13 g/dl [6.21 - 8.07 mmol/l], no iron deficiency) if blood conserving procedures are not available or insufficient when the scheduled major elective surgery requires a large volume of blood (4 or more units of blood for females or 5 or more units for males).”

### **3. Prevention of anaemia of prematurity**

MF n°	Infants with	No. evaluable for efficacy (epoetin beta)	Design	Epoetin beta dose	Duration of treatment
4105	Gestational age 28 – 32 weeks	93 (43)	ROU	30 IU/kg every third day	3 weeks
4216	Gestational age 28 – 33 weeks	18 (18)	OD	100, 200 or 400 IU/kg every other day	1.5 weeks
4268	Birth weight 750 – 1499 g	177 (85)	RBU	250 IU/kg 3x/week	6 weeks

R = randomised, O = open label, B = double blind, U = untreated control group, D = dose response group(s)

The first two studies were pilot studies, carried out to select a dose. Study 4268 was the pivotal study.

Epoetin beta therapy started on day 3 of life. Infants with prolonged ventilation or haemolysis were excluded. The dosage was 750 IU/kg bw and week, 17 injections within 39 days. The relation between effect and birth weight was analysed as besides the body weight, additional factors influence the anaemia.

## Efficacy

Although a slight rise in reticulocytes count was noted, there was no relevant reduction in the need for transfusions in the first 14 days of treatment. It means that epoetin beta has no acute effect as blood transfusions have. Success rates however, proved to be dependent on baseline birth weight and haematocrit. Results supported efficacy of epoetin beta for the prevention of anaemia of prematurity in infants with a birth weight of 750 to 1500 g and a gestational age of less than 34 weeks. Epoetin beta was likely to benefit more untransfused infants, than infants who have already been transfused. Despite iron substitution the percentage of infants with low iron stores rose from 11% to 59% in the epoetin group and from 11% to 19% in the control group, therefore oral iron treatment should begin as early as possible. The reconstituted solution should be administered subcutaneously at doses of 3x250 IU/kg body weight and by week in the first six weeks of life, preferably starting by day 3 of life. The treatment should not exceed 6 weeks.

## Safety

In total 406 premature infants (213 treated with epoetin beta) were analysed. The most frequently reported adverse events were sepsis/meningitis/arthritis (incidence not relevantly different in epoetin beta group versus the control group). Serious adverse events occurred in 8.5 % of the epoetin beta patients and 11.0 % of controls.

Multidose forms are contra indicated for use in new born infants since serious adverse effects related to intravenous administration of benzyl alcohol (solvent) are expected, especially in premature infants where the metabolic pathway of benzyl alcohol may not be functional.

## Conclusion

Taking into consideration the expected benefit for the premature babies, and the fact that the medicinal product will be used in this indication in specialised units, the CPMP concluded that this indication can be approved. Additional comparative clinical data would be useful to confirm the safety profile in this particular patient population.

### **4. Prevention and treatment of anaemia in patients with solid tumours treated with platinum-based chemotherapy**

MF n <sup>o</sup>	Patient with	No. evaluable for efficacy (epoetin beta)	Design	Epoetin beta dose	Duration of treatment
4249	Ovarian cancer, platinum based chemotherapy	120 (85)	ROU	150 or 350 IU/kg 3x/week s.c.	24 weeks
4321	Various solid cancers, platinum based chemotherapy	108 (57)	ROU	5000 IU daily	3 months

R = randomised, O = open label, U = untreated control group

On the basis of the clinical results provided, showing evidence of clinical benefit in terms of reduction of blood transfusions, with an acceptable safety profile, the CPMP considered that a licence should be granted for the treatment of anaemia in adults of more than 18 years of age with solid tumours receiving a platinum based regimen. The starting dose should be 150 IU/kg 3 times a week. If Hb falls by more than 1 g/dL after the first cycle of chemotherapy, this treatment may fail.

### **5. Treatment of anaemia in patients with lymphoid malignancies**

In June 2000, Roche Registration Ltd. submitted a type II variation application to extend the indication of NeoRecormon for the treatment of anaemia in adult patients with multiple myeloma (MM), low grade non-Hodgskin's lymphoma (NHL) or chronic lymphocytic leukaemia (CLL), who have a relative erythropoietin deficiency and are receiving anti-tumor therapy.

The MAH submitted 5 clinical studies (a total of 976 cancer patients, 817 of these with a hematological malignancy) in support of the extension of indication. The main clinical development program comprised three randomised-controlled studies (MF4467, MF4313 and MF4250).

Study	Patient with	No. evaluable for efficacy (epoetin beta)	Design	Epoetin beta dose	Duration of treatment
MF4467	MM, NHL, CLL	343	R PC DB PG	150 IU/kg 3x/week	16 weeks
MF4313	MM, NHL, CLL	146	R O PG	1000, 2000, 5000 or 10000 U daily	8 weeks
MF4250	MM, NHL (incl. CLL)	144	R O PG	2000 to 10000U daily	24 weeks

MF4421	Malignant disease	262 (138 with MM, NHL, CLL)	R O PG	150 IU/kg 3x/week	12 weeks
MF4403	Malignant disease	104 (58 with MM, NHL, CLL)	NC	150 IU/kg 3x/week	18 or 24 weeks

R = randomised, PC = Placebo Controlled, DB = Double blind, PG = parallel group, O = open label, NC = noncomparative.

Study MF4313 was a dose finding study in transfusion-independent patients that also demonstrated the effectiveness of epoetin beta in this population and MF4250 was a therapeutic study that was planned to provide confirmatory evidence of efficacy. Study MF4467 is a randomised phase III pivotal study in patients with MM, NH or CLL who have a relative erythropoietin deficiency. This study is placebo controlled and stratified on the type of tumours. The primary endpoint was the proportion of transfusion-free patients between week 5 and week 16 after start of study treatment. The proportion of patients who required transfusion or died during study week 5-16 was 33.3 % in the epoetin beta group, compared with 52.4 % in the placebo group ( $p < 0.0012$ ), giving a relative risk reduction of 43 %. The beneficial effect of epoetin beta was also demonstrated in the subgroup analysis of MM patients. In the NHL and CLL subpopulation, the primary efficacy endpoint reached statistical significance only in the prespecified alternative analysis (endpoint: transfusion-and severe anaemia-free survival), which included patients with severe anaemia as treatment failures. The data demonstrated that epoetin beta has also a significant impact on quality of life in the subgroups of patients with NHL and CLL. Epoetin beta treatment was associated with improvement in other secondary efficacy parameters (haemoglobin level) in all three malignancy types.

In June 2002, Roche Registration Ltd. submitted a type II variation application for a new frequency of subcutaneous administration in the maintenance phase of the treatment of anaemia associated in adult patients with lymphoid malignancies; a “once weekly” administration in addition to the already approved 3 times and 7 times per week.

The application was supported by one clinical pharmacology study (BP15984 [7200]), this study has been already once submitted for the earlier renal anaemia variation procedure and one clinical therapeutic trial (BO16196B [8039]). In addition, the pivotal study of once weekly administration in renal anaemia (BA15959 [8034]) was submitted as supportive data.

#### Clinical aspects

##### Study BP15984

The results showed that both the once weekly and thrice weekly dosing interval led to epoetin beta concentrations above baseline for the entire week. The dose-normalised AUC was higher in the once weekly and once every 2 weeks as compared to the thrice-weekly dosing interval. In study BP 15984, AEs were similar in all treatment groups and between placebo and treatments.

##### Study BO16196B- Study in Lymphoid Malignancies

This study was an open label, randomised, controlled multicentre study of two parallel groups in patients with lymphoid malignancies (multiple myeloma, NHL and CLL), transfusion independent anaemia (haemoglobin [Hb] 9-11 g/dL, no transfusion in the 2 months prior to planned start of study treatment) and serum erythropoietin less than 100 mU/mL. This was the pivotal study in patients with lymphoid malignancies. The primary objective of the study was to demonstrate that once weekly epoetin beta therapy was at least as effective as thrice weekly administration of epoetin beta to anaemic patients with lymphoid tumours. A total of 241 patients were randomly allocated to once weekly treatment (n=119) or thrice weekly treatment (n=122). No clinical relevant differences in laboratory values or vital signs between the two groups.

Analyses on the primary endpoint provided consistent evidence that differences between the groups did not exceed 0.6g/dL. In addition, all secondary variables supported comparable efficacy of the two

regimens. Increases from baseline in haematocrit (Hct) were comparable in both groups, with a mean increase from baseline in Hct of 6.7 vol% in the once weekly group and 6.8 vol% in the thrice weekly group.

#### Study BA15959- Study in Renal Anaemia

This study had already been submitted to provide support for once weekly vs. thrice weekly administration in patients suffering from renal anaemia. One hundred seventy three haemodialysis patients with chronic renal failure were randomly allocated to receive their previous weekly epoetin beta dose as a once weekly s.c. injection (n=84) or in divided doses thrice weekly (n=89).

The two treatment regimens were shown to be therapeutically similar in maintaining adequate and stable hematocrit.

#### Efficacy

There was no clinically relevant difference with regard to erythropoiesis and pharmacokinetic parameters between thrice weekly and once weekly s.c. injection of NeoRecormon in patients suffering from anaemia due to lymphoid malignancies. Since the dose is ultimately individually titrated in every patient, the small differences observed in the studies BP15984 and BO16196B with regard to efficacy are of no concern. The most apparent potential benefits of a once weekly s.c. administration are a reduction in the number of injections and an increased compliance of patients, given that NeoRecormon is for self-administration.

#### Safety

The comparative review of the different treatment groups does not raise any concerns of an increased risk in the once weekly group in either of the 3 clinical studies submitted for evaluation

#### **Overall safety analysis**

The overall safety analysis of the use of epoetin beta in the indications: renal anaemia, autologous blood donation, anaemia of prematurity and anaemia of solid tumours are already mentioned.

Most common adverse events were: cardiovascular events (mainly hypertension), upper and lower respiratory tract infections, changes in laboratory parameters such as: hyperkalemia and increase of liver enzymes, injection site reactions. The most frequently reported adverse effects at withdrawal in the case of patients with renal failure were hypertension and shunt thrombosis.

Due to the very nature of the study population most of the deaths reported were from progression of their underlying diseases.

Adverse events of special interest were thromboembolic, hypertensive, allergic events and neoplasms.

In anaemia of prematurity 4 thromboembolic events were reported as being serious none of which was assessed as being possibly related to epoetin beta therapy.

In oncologic indications there was one serious thromboembolic event assessed as being possibly related to epoetin beta therapy.

In renal anaemia one case of angio-oedema and in oncologic indications one case of urticaria were reported as being serious and assessed as possibly related to epoetin beta therapy.

There were no reports of newly developed neoplasms assessed as being possibly related to epoetin beta therapy.

The safety profile of studies in patients with MM, NHL or CLL is reassuring and does not indicate any new major concern when compared to the previously approved indications for NeoRecormon. The company will monitor closely hypertension, headache, hypercalcaemia, bone pain and gastrointestinal adverse events.

#### **Post marketing experience**

Six Periodic safety update reports (PSUR) have been submitted by the company and have been assessed by the rapporteur.

The outcome of the PSURs did not change the benefit/risk ratio of epoetin beta. As a result of the first PSUR (covering the period 1.9.94-15.1.98), changes have been implemented in the SPC to cover observed adverse reactions (hypersensitivity reactions, rash and urticaria). After the second PSUR (covering the period 16.1.98-15.7.98), the SPC has been amended to include the occurrence of thromboembolic events (in the indication Anaemia in oncology) and flu-like symptoms. No changes of the SPC were necessary after assessment of the third and fourth PSUR. Following the assessment of the fifth PSUR (covering period 1.7.99-15.1.00), a statement was included in sections 4.8 and 5.1 indicating that in very rare case, neutralising anti-erythropoietin antibodies with or without pure red cell aplasia occurred during rHuEPO therapy.

## **5. Overall conclusions and benefit/risk assessment**

On the basis of the assessment of the dossier as described in this assessment report, taking into consideration the oral explanations provided by the company during the hearing held on 15 October 1996, the CPMP after considerable discussions and in depth evaluation of the risk/benefit balance in each proposed indication, amended in detail the proposed Summary of Product Characteristics, in order to ensure that all the consideration were properly reflected.

On 16 November 2000, the CPMP considered that NeoRecormon showed adequate evidence of efficacy for extension of the indication to the treatment of anaemia in adult patients with multiple myeloma, low grade non-Hodgkin's lymphoma or chronic lymphocytic leukaemia, who have a relative erythropoietin deficiency and are receiving anti-tumor therapy, as well as a satisfactory risk/benefit profile and therefore recommended that the Marketing Authorisation should be extended for this indication.

To date the chemical, pharmaceutical and biological part of the dossier concerning Neorecormon remains carefully documented and overall is satisfactory. The final data on quality, safety and efficacy which were provided after the CPMP opinion was granted did not affect the benefit/risk ratio of Neorecormon but led to adequate changes to the product information.