

23 June 2011

EMA/812237/2011

Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Retacrit

epoetin zeta

Procedure No.: EMEA/H/C/000872/II/0036

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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CHMP variation assessment report

Type II variation EMEA/H/C/000872/II/0036

Invented name/name:	Retacrit
International non-proprietary name/common	epoetin zeta
name:	
Indication summary (as last approved):	treatment of anaemia
Marketing authorisation holder:	Hospira UK Ltd.

1. Scope of the variation and changes to the dossier

Scope of the variation:	Addition of the indication " Retacrit can be used to reduce exposure to allogeneic 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 expected moderate blood loss (900 to 1800 ml)" in section 4.1 of the Summary of Product Characteristics (SmpC). Sections 4.2, 4.3, 4.4 and 4.8 of the SmPC and sections 1, 2 and 3 of the Package Leaflet, outlining the mode of administration, contraindications, undesirable effects, special warnings and precautions for use, have been updated as a consequence. Furthermore, Annex II has been updated in order to include the new version number of the Risk Management Plan (version 8.0) and has been aligned in accordance with the latest QRD template (version 7.3.1, March 2010). Minor editorial changes have also been implemented.
Rapporteur:	Martina Weise
Co-Rapporteur:	Ian Hudson
Product presentations affected:	See Annex A to the Opinion

Dossier modules/sections affected:	1, 2 and 5
Product Information affected:	Summary of Product Characteristics, Annex II and Package Leaflet (Attachment 1 - changes highlighted)

2. Steps taken for the assessment

Step	Step date
Submission date:	26 February 2011
Start of procedure:	27 March 2011
Rapporteur's assessment report circulated on:	20 May 2011
Co-Rapporteur's assessment report circulated on:	16 May 2011
Rapporteur's updated assessment report circulated on:	15 June 2011
CHMP opinion:	23 June 2011

3. Scientific discussion

3.1. Introduction

Erythropoietin, a glycosylated protein of 165 amino acids with a molecular weight of approximately 34,000 daltons, is an essential growth factor required for production of red blood cells. The stimulus for erythropoietin production is believed to be the oxygen content of blood delivered to the renal interstitial cells. When the peritubular renal cells are functioning correctly, individuals with low haemoglobin concentrations will produce increased quantities of erythropoietin, resulting in increased red blood cell production.

Over the past fifteen years it has been shown in several trials that genetically engineered erythropoietin (epoetin) administered to anaemic chronic renal failure patients resulted in clinically significant increases in haemoglobin. Epoetin alfa, the first available recombinant human erythropoietin, has been given to treat anaemia due to chronic renal failure in patients on dialysis as well as in those not yet receiving dialysis.

Epoetin zeta (Retacrit) contains a recombinant human erythropoietin (rhu-EPO, ATC code BO3XA01), as active ingredient. Biosimilarity has been claimed to Epoetin alfa (Erypo) as the reference product.

The currently approved indications of Retacrit in the European Union are:

- Treatment of symptomatic anaemia associated with chronic renal failure (CRF) in adult and paediatric patients:
 - Treatment of anaemia associated with chronic renal failure in adult and paediatric
 - patients on haemodialysis and adult patients on peritoneal dialysis (See section 4.4).
 Treatment of severe anaemia of renal origin accompanied by clinical symptoms in adult
 - patients with renal insufficiency not yet undergoing dialysis (See section 4.4).
- Treatment of 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).
- Retacrit can be used to increase the yield of autologous blood from patients in a predonation programme. Its use in this indication must be balanced against the reported risk of thromboembolic events. Treatment should only be given to patients with moderate anaemia (no iron deficiency), if blood saving 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).

In September 2009, the MAH submitted an interim report for a comparative clinical trial in the maintenance treatment of patients with renal anaemia using the subcutaneous (SC) route of administration (Study 411-54-07-08-0000). Based on these results, the addition of the SC route was approved for the indications of renal anaemia on 06 April 2010 (variation II-20).

In the present type II variation, the MAH has submitted data from Study 411-54-07-08-0000 to support an extension of the current indication to include "Retacrit can be used to reduce exposure to allogeneic 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 expected moderate blood loss (900 to 1800 ml)."

Sections 4.1, 4.2, 4.3, 4.4, and 4.8 of the SmPC and sections 1, 2 and 3 of the Package Leaflet have been updated as a consequence. Annex II has been updated with the new version number of the Risk Management Plan (RMP) and aligned in accordance with the latest version of the QRD template. Minor editorial changes have also been included.

3.2 Clinical pharmacology

For the purpose of this variation, no new pharmacokinetic (PK) or pharmacodynamic studies have been submitted.

Pharmacokinetics

No new pharmacokinetic studies have been submitted.

Pharmacodynamics

No new pharmacodynamic studies have been submitted.

Discussion on clinical pharmacology

Based on previously submitted pharmacokinetic studies (411-54-05-05-0000, 411-54-03-09-0001) which were evaluated at the time of the initial marketing authorisation application, it was concluded that the pharmacokinetic profiles after a single intra-venous (IV) bolus injection of 10,000 IU of Epoetin zeta and Epoetin alfa (Erypo) and after a single SC injection of 10,000 IU of Epoetin zeta and Epoetin alfa were practically identical. Bioequivalence was demonstrated for Epoetin zeta within the narrow confidence intervals of 80-125%. The demonstration of bioequivalence between the two SC administered formulations is of major importance since this finding supports the SC administration of Epoetin zeta in indications that are approved for SC use.

3.3 Clinical efficacy

Data were submitted from Study 411-54-07-08-0000, in which the efficacy of Epoetin zeta administered SC for maintenance treatment of renal anaemia was compared to Epoetin alfa (Erypo). The results have been previously assessed as part of variation II-20.

Main studies

Study 411-54-07-08-0000

Evaluation of the Therapeutic Equivalence of Two Different Formulations containing Epoetin (Epoetin STADA vs. Erypo) Administered Subcutaneously for the Maintenance Treatment of Renal Anaemia.

<u>METHODS</u>

Study Participants

According to the final version of the study protocol, 400 patients who fulfilled the inclusion criteria and did not present any of the exclusion criteria were needed to complete the present trial. After receiving a written patient information / informed consent form and after all questions were explained, the patients were asked for signing the informed consent and were thereafter screened with respect to inclusion and exclusion criteria.

The inclusion criteria were as follows:

- male or female patients, aged 18-75 years
- haemodialysis patients with end-stage renal failure and renal anaemia currently on epoetin treatment for at least 3 months
- patients on stable, adequate dialysis for at least three months (defined as no clinically relevant changes of dialysis regimen and/or dialyser)
- informed consent given in a written form after being provided with detailed information about the nature, risks, and scope of the clinical trial as well as the expected desirable and adverse effects of the drug.

The exclusion criteria were as follows:

- contraindication for the test drug
- relative or absolute iron deficiency at the end of run-in period
- myelodysplastic syndrome
- documented bleeding disorders
- platelet count below 100x109/l
- known, clinically manifested deficiency of folic acid and/or vitamin B12 (irrespective whether currently treated or not)
- known bone marrow fibrosis (osteitis fibrosa cystica)
- clinically relevant changes of dialysis regimen and/or dialyser during the trial
- clinically relevant increase of CRP (higher than 10 mg/dl) for at least 2 weeks
- any blood transfusion within the last 3 months prior main study phase
- acute bleeding and/or recently documented haemorrhage
- hypersensitivity to epoetin
- epoetin dosage > 3x200 IU/kg/week
- detectable anti-epoetin antibodies
- uncontrolled hypertension
 - any of the following within the 6 months prior main study phase:
- myocardial infarction,
 - stroke / cerebrovascular insult (minor stroke) or TIA (transient ischemic attack) / intracerebral bleeding / cerebral infarction,
 - severe/unstable angina,
 - coronary/peripheral artery bypass graft,
 - decompensated congestive heart failure (NYHA class III IV),
 - cerebrovascular incident or transient ischemic attack,
 - pulmonary embolism,
 - deep vein thrombosis, or other thromboembolic event.
- known epilepsy
- liver cirrhosis with clinical evidence of complications (portal hypertension, splenomegaly, ascites)
- patients with confirmed aluminium intoxication
- confirmed, clinically relevant haemolysis and/or occult blood loss
- presence of malignant tumours
- clinically relevant malnutrition
- pregnancy or lactation period in female patients
- severe physical or mental concomitant diseases that might hamper the realisation of the trial according to protocol or the evaluation of efficacy or safety
- anamnestic or current alcohol abuse i.e. consumption of more than 10 units of alcohol per week or a history of alcoholism or drug/chemical abuse (one unit of alcohol equals 250 ml of beer, 125 ml wine or 25 ml of spirits)
- participation in another clinical trial with a different test drug than the one tested in the present trial within the last 12 weeks
- legal incapacity and/or other circumstances rendering the patient unable to understand
- the nature, scope and possible consequences of the study

- unreliability or lack of cooperation
- lack of a possibility to attend the visits required by protocol.

Treatments

Patients were randomized to receive either Test product (Epoetin zeta, pre-filled syringes, STADA Arzneimittel, AG, Germany) or Reference product (Erypo, epoetin alfa pre-filled syringes, JANSSEN-CILAG GmbH, Germany). For each phase of the study, epoetin was administered at the unit dose of 1000, 2000, 3000, 4000 or 5000 IU, 1-3 times weekly, sub-cutaneously, at the end of dialysis.

Open Run-in Phase:

The trial began with an open run-in period of 12-16 week duration. All patients received a subcutaneous administration of Epoetin zeta.

Main study phase:

Treatment for 28 weeks with either the Test product or the Reference product.

Follow-up extension phase:

After the end of the main study phase, all patients could continue treatment for further 54 weeks with Epoetin zeta.

Objectives

The primary objective of the trial was to prove the therapeutic equivalence of Epoetin zeta to a reference product Epoetin alfa administered subcutaneously for maintaining the haemoglobin concentration in anaemic patients with end-stage renal failure on chronic haemodialysis.

The secondary objective of the present trial was to gather data regarding the safety and tolerability of Epoetin zeta (with particular focus on the formation of anti-epoetin antibodies) when administered subcutaneously.

The aim of the open follow-up extension period was to gather data regarding the long-term safety, tolerability, and efficacy of Epoetin zeta under open, non-controlled conditions.

Outcomes/endpoints

Primary endpoints:

- mean haemoglobin level during the last 4 weeks of treatment,
- mean weekly epoetin dosage per kg body weight during the last 4 weeks of treatment.

Secondary endpoints:

- mean haematocrit levels during main study phase,
- proportion of patients with any permanent changes of haemoglobin levels of more than 1 g/dl during main study phase,
- proportion of patients with any transient changes of haemoglobin levels of more than 1 g/dl during main study phase,
- proportion of patients with any permanent dose change during main study phase,
- proportion of patients with any transient dose change during main study phase,
- proportion of patients with any haemoglobin measurement outside the target
- range during main study phase,
- incidence of blood transfusions.

Safety endpoints:

- incidence of haemoglobin levels above 13 g/dl,
- occurrence of anti-epoetin antibodies,

- ratings of tolerability,
- evaluation of adverse events.

Sample Size

The planned sample size was 400 patients (200 per group), which was expected to give a >80% power for the two-sided proof of equivalence. A total number of 707 male and female patients with end-stage renal failure on chronic haemodialysis were screened after giving their consent in written form. After careful consideration of all inclusion and exclusion criteria, 28 patients were not eligible for the trial. Therefore, only 679 patients entered the open run-in treatment period with the test product (Epoetin zeta).

Randomisation

Patients who fulfilled the criterion for randomisation (target haemoglobin within the range between 10.5-11.5 g/dl with constant s.c. Epoetin zeta dosage and without an intra-individual change in haemoglobin of more than 0.5 g/dl over 4 weeks) could be randomised to start the main study phase. Randomisation was performed in blocks; the block size was 6.

After 12 to 18 weeks treatment (open run-in period), 462 patients were eligible to start observer-blind treatment (main study phase) and were randomised to one of both study drugs (Epoetin zeta or Epoetin alfa) (safety population) at an unchanged dose as reached in the last 4 weeks of the run-in period.

Two hundred and thirty-two patients were allocated to the test medication and 230 patients to the reference drug. Twelve patients (4 treated with test drug and 8 treated with the reference preparation) were excluded from the full analysis set (n=450). Further 131 patients were excluded from the per protocol set due to major protocol deviations. Therefore, the per protocol set consists of 319 patients.

Blinding

After the end of the open run-in period, each patient was randomly assigned to one of two study drugs, either to the test product (Epoetin zeta) or to the reference product (Epoetin alfa). For the presentations 1000 IU, 2000 IU, and 3000 IU per syringe the volume of the solution is different between test and reference product. In this case only the double-dummy technique could ensure double-blind conditions.

Due to the fact that it is not ethical to administer to all patients a double number of injections, no blinding was used in the present trial. Only the person(s) involved in decision-making, e.g. dose adjustment, was masked to treatment allocation. This/these person(s) had no access to the study medication. They were also not allowed to administer the study medication.

Whilst, the main phase of the study was observer blind, the follow-up extension phase was not controlled. A total number of 346 male and female patients who had completed the blinded treatment period of the trial (main study) started treatment with the test product Epoetin zeta in the open follow-up extension period.

Statistical Hypothesis and Planned Sample Size

Main study phase

From the statistical point of view, the question of therapeutic equivalence was approached by calculating the 95% confidence interval of the difference between both treatment groups of the primary endpoints:

- mean haemoglobin level during the last 4 weeks of treatment,
- mean weekly epoetin dosage per kg body weight during the last 4 weeks of treatment.

These confidence intervals were compared with the pre-defined clinical acceptance ranges for the corresponding parameters (\pm 0.5 g/dl for haemoglobin and \pm 45 IU/kg/week for epoetin dosage, based on the respective reference means). The intervals were calculated by means of ANOVA.

The statistical evaluation of the primary endpoint "mean weekly epoetin dosage per kg body weight during the last 4 weeks of treatment" was performed based on the nominal dosage declared on the labels of the pre-filled syringes.

As the dosage of epoetin and the corresponding level of haemoglobin are closely interrelated, a hierarchic test strategy was used in the present trial. The test on a higher level of hierarchy can only be performed, should the target of the previous level be fulfilled. The overall equivalence statement is consistent with a positive outcome on both levels of hierarchy. Due to this reason, no adjustment of alpha values was required on the separate levels. The levels of hierarchy were defined as follows:

Level 1: Calculation of the 95% confidence interval of the difference (test - reference) of the mean haemoglobin level during the last 4 weeks of treatment and comparison with the pre-defined acceptance range.

Level 2: Calculation of the 95% confidence interval of the difference (test - reference) of the mean weekly epoetin dosage per kg body weight during the last 4 weeks of treatment and comparison with the pre-defined acceptance range.

The statistical analysis was performed on three different patient populations:

- Safety population (all patients who started therapy with randomised study medication).
- Full analysis set (all patients who were treated more than 4 weeks with randomised study medication).
- Per protocol population (excluding cases of major protocol violation and drop-outs).

Open Follow-up Extension Phase

The statistical analysis of the results of the open follow-up extension period were only descriptive. Depending on their distribution the target parameters were presented with their means, SD, SEM, median and quartiles or with their incidences.

RESULTS



Recruitment

The study period was from 06 February 2008 until 19 April 2010. A total of 679 patients were recruited in 42 centres across five countries. For the main study phase, recruitment took place in 14 centres in Bulgaria, 1 centre in Germany, 18 centres in Poland, 5 centres in Romania, 4 centres in Serbia. The open follow-up extension phase involved 35 centres, including 14 centres in Bulgaria, 15 centres in Poland, 3 centres in Romania, 3 centres in Serbia.

Conduct of the study

The following changes in the conduct of the study were made:

- Amendment 01 (dated 17-Jun-2008) to officially introduce the follow-up period after the end of the blinded treatment.

No further changes in the conduct of the study or planned analysis were done. None had a major impact on the conduct of the study.

Baseline data

The majority of patients enrolled in the trial belonged to the age group of 12 to 65 years (=360), 102 patients were older than 65 years. In total, 272 patients were male and 190 were female. All patients enrolled were Caucasians.

The mean age of the patients was 55.6 ± 12.47 years (Epoetin zeta) and 55.2 ± 12.58 years (Epoetin alfa). The mean height was 167.9 ± 8.77 cm (Epoetin zeta) and 167.0 ± 9.50 cm (Epoetin alfa). The mean weight of patients treated with Epoetin zeta group was 70.5 ± 15.11 kg and 70.8 ± 15.83 kg for patients treated with Epoetin alfa. The mean values for the body mass index (BMI) were 24.9 ± 4.46 kg/m2 for Epoetin zeta and 25.3 ± 4.89 kg/m2 for Epoetin alfa. Both treatment groups are comparable regarding their demographic data.

Important baseline characteristics concern the history and information about renal failure and haemodialysis. The maximal time since the patients suffered from end-stage renal failure was 254 months in patients treated with Epoetin zeta, with a median of 37.0 months, and 310 months in patients treated with Epoetin alfa, with a median of 36.5 months (tables 43 and 44, chapter 14.1.4.1). The diagnosis leading to renal failure was primarily glomerulonephritis (31.5% in the Epoetin zeta group and 30.0% in the Epoetin alfa group), followed by hypertensive nephropathy (15.5%, Epoetin zeta and 14.8%, Epoetin alfa). Other diagnoses were given for 39.7% of patients treated with Epoetin zeta and for 44.3% of patients treated with Epoetin alfa.

Information on haemodialysis such as frequency, average duration, KT/V index, and urea reduction ratio (URR) was recorded. Although URR was not a part of the requested measurements it was included into the evaluation since it was used instead of KT/V index by some of the study centres in Bulgaria. URR is used besides KT/V, to measure how effectively a dialysis treatment removed waste products from the body. The mean frequency of haemodialysis was 3 times per week in patients of both treatment groups. The average duration was 4.1 hours and the average KT/V index was 1.3 in both treatment groups. The results of URR show mean values of $64.9 \pm 10.99\%$ for the Epoetin zeta group and $64.6 \pm 10.36\%$ for patients treated with Epoetin alfa.

Information regarding life style and habits were recorded for the amount of consumption of alcohol and nicotine as well as for the intake of any special diet. Most of the patients were non-smokers and consumed no alcohol (each 92.7% in the test group and 91.3% in the reference group). A special diet was registered in 29.3% of the patients in the test group and 27.0% of the patients in the reference group.

Previous diseases, surgeries and injuries (medical history) which ended prior to study start were also recorded. In total 342 findings were registered in 122 patients of the test group and 318 findings were recorded in 115 patients treated with reference. The majority of patients suffered from conditions belonging to the SOC surgical and medical procedures with 160 findings in 84 patients of the test group and 152 findings in 84 patients of the reference group. The most common condition within this SOC were arteriovenous fistula operations (128 cases in 104 patients altogether in both treatment groups). The next common SOC was infections and infestations, with 34 findings in 19 patients of the test group and 28 findings in 24 patients of the reference group; mainly pneumonia and bronchitis were registered within this SOC. Gastrointestinal disorders were recorded for 41 patients with 49 findings (Epoetin zeta group: 20 cases in 18 patients; Epoetin alfa group: 29 cases in 23 patients), whereas the most frequent diagnosis within this group was duodenal ulcer in each 4 patients in both treatment groups.

Numbers analysed

The principal reasons for premature study discontinuation were:

- any adverse event after which a continuation of treatment would constitute an unacceptably high risk for the patient,
- any new or intercurrent disease likely to interfere with the conduct of the study,
- patient is unwilling to adhere to the study requirement, e.g. non-compliance or
- no cooperation,
- occurrence of an exclusion criterion.

Whenever a patient withdrew or discontinued the study, the circumstances of the withdrawal or discontinuation had to be recorded in detail in the CRF and a complete final examination as scheduled for final visit should be conducted as far as possible.

	Total	Epoetin zeta	Epoetin alfa
No of patients Planned for completion	400		
No patients Screened	707		
No patients Enrolled	679		
No Patients Randomized	462	232	230
No included in Safety population	462	232	230
No included in Full Analysis Set	450	228	222
No included in Per protocol Set	319	154	165

Table 1: Summary of Analysis Population

Outcomes and estimation

Primary endpoints

The mean haemoglobin level during the last 4 weeks was 10.94 ± 0.84 g/dl for patients treated with Epoetin zeta and 11.02 ± 0.94 g/dl for patients treated with Epoetin alfa. The 95% confidence interval of the difference (test - reference) of the mean haemoglobin level during the last 4 weeks of treatment (level 1 of the hierarchic test strategy) was between -0.28 g/dl and 0.12 g/dl and thus entirely within the pre-defined equivalence range (± 0.5 g/dl).

The mean weekly epoetin dosage per kg body weight during the last 4 weeks of treatment was 97.0 \pm 94.3 IU/kg/week (Epoetin zeta) and 86.0 \pm 78.0 IU/kg/week (Epoetin alfa). The 95% confidence interval of the difference (test - reference) of the mean weekly epoetin dosage per kg body weight during the last 4 weeks of treatment (level 2 of the hierarchic test strategy) was between -8.03 IU/kg/week and 30.00 IU/kg/week and thus also within the pre-defined equivalence range of \pm 45 IU/kg/week.

The 95% confidence intervals were within the pre-defined acceptance ranges for both primary endpoints. According to the criteria set in the study protocol it could be concluded that the test product Epoetin zeta is equivalent with the reference product Epoetin alfa in respect of its clinical efficacy.

The results obtained for the full analysis set of patients were practically identical with those observed in the per protocol population. The results of both primary endpoints (haemoglobin and dosage) are presented in tables 2 and 3 as well as in figures 1 and 2.

The graphical presentation demonstrated that both products, Epoetin zeta and Epoetin alfa, were effective regarding their ability to maintain haemoglobin levels within the target range of 10.0-12.0 g/dl (10.5-11.5 \pm 0.5 g/dl).

Table 2. Mean haemoglobin value [g/dl] over last 4 weeks - Descriptive statistics by treatment group, per protocol population

Treatment	Haemoglobin [g/dl]								
	ND	N	Mean	SD	Min	Q25	Median	Q75	Max
Test	0	154	10.94	0.84	8.45	10.45	10.98	11.45	13.10
Reference	0	165	11.02	0.94	7.68	10.68	11.18	11.55	13.28

Table 3. Mean epoetin dose [IU/week/kg BW] over last 4 weeks - Descriptive statistics by treatment group, per protocol population

Treatment	Epoetin dose [IU/kg/week]								
	ND	N	Mean	SD	Min	Q25	Median	Q75	Max
Test	0	154	97.0	94.3	12.4	39.6	65.4	107.2	555.6
Reference	0	165	86.0	78.0	8.5	36.0	62.5	115.4	482.5





Figure 2. Mean weekly epoetin dosage per kg body weight during the last 4 weeks of treatment



Secondary endpoints

Mean haematocrit levels during main study phase:

The difference between the mean haematocrit levels during the main study phase for patients treated with Epoetin zeta and patients treated with Epoetin alfa is minor and not statistically significant: 33.7 \pm 2.0% (test) and 34.0 \pm 1.9% (reference).

Table 4: Mean haematocrit levels [%] over main study phase - Descriptive statistics,per protocol population

Treatment	Haematocrit [%]								
	ND N Mean SD Min Q25 Median Q75 Max								
Test	0	154	33.7	2.0	28.5	32.5	33.6	35.0	39.7
Reference	0	165	34.0	1.9	27.1	33.1	34.0	35.0	39.7

<u>Proportion of patients with any permanent or transient changes of haemoglobin levels of more than 1</u> g/dl during main study phase:

In the group of patients treated with the test product 66 patients (42.9%) had a permanent and 131 patients (85.1%) had a transient change of haemoglobin of more than 1 g/dl. In the reference product group 59 patients (35.8%) had a permanent haemoglobin change, whilst 148 patients (89.7%) had a transient change.

Proportion of patients with any permanent or transient dose change during main study phase: One hundred thirty-five patients (87.7%) treated with Epoetin zeta had a permanent and 139 patients (90.3%) had a transient dose change. A permanent dosage change in patients treated with Epoetin alfa was necessary in 136 patients (82.4%), whilst transient dosage changes occurred in 141 patients (85.5%).

<u>Proportion of patients with any haemoglobin measurement outside the target range during main study phase:</u>

In the course of the treatment haemoglobin values outside the target range (10.0-12.0 g/dl) were observed in 134 patients (87.0%) of the Epoetin zeta group and in 143 patients (86.7%) of the Epoetin alfa group.

Incidence of blood transfusions:

During the open run-in phase with the test product no blood transfusions were registered. In the course of the main study phase 2 single blood transfusions were performed in the test group (Epoetin zeta).

Evaluation of efficacy parameters for the open follow-up extension period:

The mean nominal weekly epoetin dosage in the course of the open follow-up extension period was between 90.7 \pm 84.5 IU/kg/week and 109.1 \pm 98.2 IU/kg/week. The mean haemoglobin values, measured in monthly intervals, varied between 10.7 and 11.2 g/dl, and confirmed the observation of the main study that Epoetin zeta is effective to maintain haemoglobin levels between the target range of 10.0-12.0 g/dl (10.5-11.5 \pm 0.5 g/dl). The mean haematocrit levels were between 32.6 and 34.4%. The incidences of transient/permanent Hb and dosage changes as well as the proportion of patients with any Hb value outside target range are similar to those observed in the main study. In the course of the follow-up period 16 patients received one blood transfusion; five patients needed 2 transfusions, and in one case 3 blood transfusions were necessary.

Supportive studies

No new supportive studies have been submitted together with this variation.

Discussion on clinical efficacy

According to the EMA guidance on similar medicinal products containing recombinant erythropoietins (EMEA/CHMP/BMWP/94526/2005 Corr., 2006) comparable clinical efficacy between the similar and the reference product should be demonstrated in at least two adequately powered, randomised, parallel-group clinical trials. The clinical trials should include a 'correction phase' study during anaemia correction and a 'maintenance phase' study in patients on epoetin maintenance therapy. Clinical comparability should be demonstrated for both routes of administration, IV and SC administration. According to the EMA guidance on non-clinical and clinical development of similar biological medicinal products containing recombinant erythropoietins, (EMEA/CHMP/BMWP/301636/2008 Corr.*), extrapolation to other indications of the reference medicinal product can be claimed.

In the case of Epoetin zeta, a correction phase and a maintenance phase study were already performed (Studies 411-54-04-05-0000 and 411-54- 04-04-0000) for the IV route of administration. These studies proved that the test product is able to achieve (correction phase study) and to maintain (maintenance phase study) target haemoglobin (Hb) concentrations in anaemic patients with end-stage renal failure.

Following the granting of the Marketing Authorisation in the European Union for the IV route of administration in renal anaemia, only one further trial was necessary to prove the efficacy and safety of Epoetin zeta for the SC route of administration in patients with renal anaemia. Both a correction phase and a maintenance phase trial were considered suitable to provide the above-mentioned evidence. The MAH therefore performed a maintenance phase trial.

The primary objective of the maintenance study (411-54-07-08-000) was to prove the therapeutic equivalence of Epoetin zeta to the reference product Epoetin alfa administered SC for maintaining the Hb concentration in anaemic patients with end-stage renal failure on chronic haemodialysis between 10.0 and 12.0 g/dl.

The results of the main phase of the maintenance study showed comparable efficacy and safety (see below, Discussion on Clinical Safety) for the SC use of Epoetin zeta and Epoetin alfa. For the primary endpoints haemoglobin and epoetin dosage, the study showed that the 95% confidence intervals for the differences between Epoetin zeta and Epoetin alfa were within the predefined acceptance ranges. The results for the secondary endpoints support equivalent efficacy of test and reference.

As the therapeutic equivalence of Epoetin zeta to the reference product Epoetin alfa administered SC was demonstrated with Study 411-54-07-08-000 in anaemic patients with end-stage renal failure, it

can be concluded that SC administration of Epoetin zeta can be used in patients prior to major elective orthopaedic surgery in order to avoid exposure to allogeneic blood transfusions.

Therefore the CHMP was of the opinion that section 4.1 of the SmPC should be amended to include the following indication; "*Retacrit can be used to reduce exposure to allogeneic 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 expected moderate blood loss (900 to 1800 ml)."*

Section 1 "What Retacrit is and what it is used for" of the Package Leaflet should also be aligned to state: "*Retacrit is used - in moderately anaemic adult patients about to undergo major orthopaedic (bone) surgery (for example hip or knee replacement therapy) to reduce the need for blood transfusions.*"

In line with the inclusion of this new indication, section 4.2 "Posology" of the SmPC should be updated to include the following recommendation: "Treatment of adult patients scheduled for major elective orthopaedic surgery. *Retacrit should be administered subcutaneously. A dose of 600 IU/kg body weight should be administered, once weekly for three weeks (on day 21, 14 and 7) prior to surgery and on the day of surgery (day 0). If the lead time before surgery needs to be shortened to less than three weeks, a dose of 300 IU/kg body weight should be given daily for 10 consecutive days prior to surgery, on the day of surgery and for four days immediately thereafter. When performing haematologic assessments during the preoperative period, if the haemoglobin level reaches 15 g/dl, or higher, administration of Retacrit should be stopped and further doses should not be given. Iron deficiencies should be treated prior to starting treatment with Retacrit. In addition, all patients should receive adequate iron supplementation (e.g. 200 mg oral elemental iron daily) throughout the course of Retacrit treatment. If possible, iron supplementation should be started prior to treatment with Retacrit, to achieve adequate iron stores."*

In line with the SmPC amendment, Section 3 "How to use Retacrit" of the Package Leaflet should also be updated to state: "Use in adult patients scheduled for major orthopaedic (bone) surgery. A dose of 600 IU/kg is given by injection under the skin once weekly for 3 weeks before surgery and on the day of surgery. In cases where there is a need to shorten the period before the operation is carried out, a dose of 300 IU/kg is given on each of the 10 days before surgery, on the day of surgery and for 4 days immediately afterwards. If blood tests in the period before the operation show your haemoglobin level to be too high, the treatment will be stopped. It is also important that levels of iron in your blood are normal throughout Retacrit treatment. Where appropriate you will receive oral doses of iron each day, ideally starting before Retacrit treatment.

3.4 Clinical safety

Data were submitted from Study 411-54-07-08-0000, in which the safety of Epoetin zeta administered SC for maintenance treatment of renal anaemia was compared to Epoetin alfa, with particular focus on the formation of anti-epoetin antibodies.

Extent of Exposure

The safety population of the main study phase consisted of 462 patients, whereas the full analysis set, in which all patients who were treated for more than 4 weeks with randomised study medication, consisted of 450 patients (Epoetin zeta: 228 patients; Epoetin alfa: 222 patients). Of the patients who were treated in the main study phase with Epoetin zeta or Epoetin alfa a total number of 346 patients entered the open follow-up extension period of treatment with Epoetin zeta for up to 54 weeks and were evaluated in the final report on drug safety dated 13 August 2010.

Number of	Test (N=232)	Reference (N=230)	total
AEs reported	357	292	649
Patients with AEs	91	92	183
- female	37	42	79
- male	54	50	104
Serious AEs	91	51	142
Patients with SAEs	38	30	68
Deaths	16	7	23
Patients withdrawn due to AE	21	10	31

Table 5. Summary of adverse events, main study phase, safety population

Common Adverse Events

During the blind treatment period, 649 adverse events (test: 357 AEs in 91 patients; reference: 292 AEs in 92 patients occurred. The adverse events belonged mainly to SOCs of infections and infestations (n=64, test group; n=47, reference group), injury, poisoning and procedural complications (n=42, test group; n=32, reference group), and gastrointestinal disorders (n=37, test group; n=26, reference group). A summary of AEs by body systems and events occurring in \geq 1% of patients in either treatment group and preferred term is presented in the table below.

Table 6: Summary of adverse events by body system and preferred term, mainstudy phase

Body system / preferred term ¹	Epoetin zeta (n = 232) n (%)	Epoetin alfa (n = 230) n (%)
Patients with at least one AE	91 (39.2)	92 (40.0)
Infections and infestations	35 (15.1)	34 (14.8)
Bronchitis	8 (3.4)	5 (2.2)
Nasopharyngitis	5 (2.2)	9 (3.9)
Urinary tract infection	6 (2.6)	1 (0.4)
Endocrine disorders	3 (1.3)	0
Metabolism and nutrition disorders	14 (6.0)	13 (5.7)
Hypoglycaemia	4 (1.7)	1 (0.4)
Psychiatric disorders	4 (1.7)	0
Insomnia	3 (1.3)	0
Nervous system disorders	19 (8.2)	11 (4.8)
Headache	11 (4.7)	4 (1.7)
Eye disorders	3 (1.3)	1 (0.4)
Conjunctivitis	3 (1.3)	0
Cardiac disorders	17 (7.3)	14 (6.1)
Atrial fibrillation	5 (2.2)	2 (0.9)
Tachycardia	3 (1.3)	4 (1.7)
Vascular disorders	17 (7.3)	17 (7.4)
Hypertension	9 (3.9)	11 (4.8)

Body system / preferred term ¹	Epoetin zeta (n = 232) n (%)	Epoetin alfa (n = 230) n (%)
Hypotension	3 (1.3)	2 (0.9)
Respiratory, thoracic and mediastinal disorders	6 (2.6)	8 (3.5)
Gastrointestinal disorders	27 (11.6)	18 (7.8)
Diarrhoea	12 (5.2)	5 (2.2)
Nausea	3 (1.3)	2 (0.9)
Gastritis	1 (0.4)	5 (2.2)
Skin and subcutaneous tissue disorders	6 (2.6)	5 (2.2)
Musculoskeletal and connective tissue disorders	16 (6.9)	17 (7.4)
Arthralgia	4 (1.7)	3 (1.3)
Back pain	4 (1.7)	3 (1.3)
Pain in extremity	3 (1.3)	9 (3.9)
Renal and urinary disorders	6 (2.6)	2 (0.9)
Haematuria	5 (2.2)	0
General and administration site conditions	9 (3.9)	12 (5.2)
Investigations	5 (2.2)	2 (0.9)
Injury, poisoning and procedural complications	23 (9.9)	26 (11.3)
Arteriovenous fistula site complication	4 (1.7)	1 (0.4)
Arteriovenous fistula thrombosis	4 (1.7)	3 (1.3)
Haemodialysis induced symptom	6 (2.6)	8 (3.5)
Procedural hypotension	3 (1.3)	4 (1.7)
Surgical and medical procedures	15 (6.5)	15 (6.5)
Arteriovenous fistula operation	4 (1.7)	3 (1.3)
Renal transplant	4 (1.7)	2 (0.9)

The most frequently reported AEs occurring in at least 5 patients (> 2%) in either treatment group were: diarrhoea (12 patients in Epoetin zeta group and 5 patients in Epoetin alfa group), headache (11 patients in Epoetin zeta group and 4 patients in Epoetin alfa group), hypertension (9 patients in Epoetin zeta group and 11 patients in Epoetin alfa group), pain in extremity (3 patients in Epoetin zeta group and 9 patients in Epoetin alfa group), nasopharyngitis (5 patients in Epoetin zeta group and 9 patients in Epoetin alfa group), nasopharyngitis (5 patients in Epoetin zeta group and 9 patients in Epoetin alfa group), bronchitis (8 patients in Epoetin zeta group and 5 patients in Epoetin alfa group), urinary tract infection (6 patients in Epoetin zeta group and 1 patient in Epoetin alfa group), haemodialysis induced symptom (6 patients in Epoetin zeta group and 8 patients in Epoetin alfa group), atrial fibrillation (5 patients in Epoetin zeta group and 2 patients in Epoetin alfa group), haematuria (5 patients in Epoetin zeta group and none in the Epoetin alfa group), and gastritis (1 patient in Epoetin zeta group and 5 patients in Epoetin zeta group).

Deaths

A total number of 11 patients died in the course of the open run-in phase with the test product (Epoetin zeta) before being randomised. The relationship between study medication and the serious adverse events, which led to the deaths, were assessed as not related in all cases.

During the observer-blind main study phase a total number of 23 patients died, 16 patients under treatment with the test drug and 7 patients under treatment with the reference product. These patients experienced 45 serious adverse events, which belonged mainly to the group of nervous system disorders, followed by cardiac disorders and general disorders and administration site

conditions. Only in 1 case, a patient who was treated with reference product, the relationship between study medication and the serious adverse events which led to death was assessed as possible. Additional to that, in one patient treated with the test product, the relationship between study medication and the serious adverse events which led to death was assessed as possible related by the sponsor, whilst investigator assessment was unlikely.

Additional analyses of deaths were performed in order to find out if there are any reasons for the imbalance in the number of deaths between test and reference group. The following parameters were evaluated: reasons for renal failure, previous diseases / medications, concomitant diseases / medications, haemoglobin levels, epoetin dose, blood pressure, withdrawals of study medication due to AE or SAE, deaths per centre and country, as well as the effect of additional risk factors by means of a logistic regression. It was observed that patients who died during treatment with the test preparation:

• were more severely ill as compared to the remaining patients in this group as they had a significantly higher incidence of myocardial ischaemia, diabetic neuropathy, chronic obstructive pulmonary disease, and aortic aneurysm;

- had lower haemoglobin levels as the remaining patients in this group;
- had significant higher epoetin doses as the remaining patients in this group.

A higher proportion of patients was observed for centers in Bulgaria, which was associated with significantly worse KT/V index as compared to all other countries. Further risk factors had no relevant effect on the incidence of cases of death.

A total number of 35 patients died in the course of the open follow-up extension period up to 54 weeks. The largest number of deaths is attributed or associated with cardiac disorders, infections and infestations, and nervous system disorders. In two cases (Cardiopulmonary failure, General disorders) the relationship between study medication and the serious adverse events which led to death were assessed as not assessable and in one case (Cerebrovascular accident) as possibly related. In all other cases no causal relationship between the intake of study drug and the serious adverse events which led to death were assessed and the serious adverse events which led to death were assessed and the serious adverse events which led to death was reported.

Adverse events and serious adverse events

The majority of serious adverse events (n=146) in the blind treatment period belonged to the SOC group of surgical and medical procedures (14.9% and 21.2% of all SAEs under test and reference treatment, respectively; mainly renal transplantation), cardiac disorders (13.8% and 17.3% of all SAEs under test and reference treatment, respectively; mainly arterial fibrillation), and nervous system disorders (14.9% and 13.5% of all SAEs under test and reference treatment, respectively; mainly haemorrhagic stroke). Differences in frequency of adverse events in general and according to MedDRA SOCs between both treatment groups could not be observed.

The analysis of adverse events and serious adverse events, which included severity, outcome, relationship to study medication as well as the action taken with study medication revealed no differences between treatments.

Category	Number (%) of patients experiencing events			
	Epoetin zeta (n = 232)	Epoetin alfa (n = 230)		
At least one SAE	38 (16.4)	30 (13.0)		
Severity of AE				
- mild	6 (2.6)	11 (4.8)		
- moderate	18 (7.9)	12 (5.2)		
- severe	24 (10.3)	12 (5.2)		
Relationship of AE to study medication				
- possible	1 (0.4)	1 (0.4)		
- probable	1 (0.4)	0		
Outcome				
- recovered with sequelae	3 (1.3)	5 (2.2)		
- not recovered (excluding fatal cases)	2 (0.9)	0		

Table 7: Overview of serious adverse events, main treatment phase

The majority of serious adverse events (n=204) during the open follow-up extension period belonged to the group of gastrointestinal disorders (33 SAEs in 13 patients), followed by the groups of infections and infestations (31 SAEs in 24 patients), cardiac disorders (28 SAEs in 21 patients), and surgical and medical procedures (21 SAEs in 16 patients).

Incidence of haemoglobin levels above 13 g/dl

The incidence of haemoglobin levels above 13 g/dl was one of the safety endpoints in the present trial, because high haemoglobin values are associated with an increased risk of serious cardiovascular complications in patients with chronic renal failure. In more than 90% of patients no Hb values above 13 g/dl were registered in open run-in treatment period with the test product. In the main study phase the proportion of patients with no Hb values above 13 g/dl decreased (76.7% for the Epoetin zeta treatment group and 76.2% for the Epoetin alfa treatment group) with no significant differences between both treatment groups.

In the course of the open follow-up extension period 83.2% of all patients had no Hb values above 13 g/dl.

Anti-epoetin antibodies

All patients were tested for the presence of anti-epoetin antibodies (last available blood sample). No case of anti-epoetin antibodies was noted in the very sensitive screening assay. Furthermore, no clinical signs for pure red cell aplasia were observed in any patient in the course of the whole trial (main study and open follow-up extension period).

Discussion on clinical safety

The safety profile of recombinant human erythropoietin is well established. Special aspects of the safety profile that are reflected in the precautions and warnings section of the reference Epoetin alfa SmPC (Erypo) are the potential for hypertension and the necessity of closely monitoring the blood pressure, the risk of thrombotic events, particularly in cancer patients and patients scheduled for major elective orthopaedic surgery, monitoring of Hb levels, the use with caution in the presence of epilepsy and chronic liver failure, and the recommendation for iron supplementation. The frequency and type of AEs reported for patients treated with SC administration of Epoetin zeta were shown to be very similar to the frequency and type of AEs reported for patients treated with SC administration of Epoetin alfa.

Therefore, the CHMP was of the opinion that section 4.3 "Contraindications" of the SmPC should be aligned with that of the reference product to state the following: "*In the indication of major elective orthopaedic surgery: severe coronary, peripheral arterial, carotid or cerebral vascular disease, including patients with recent myocardial infarction or cerebral vascular accident.*

Section 2. "Before you use Retacrit" of the Package Leaflet should also be aligned to state: "Do not use Retacrit. – if you are due to have major orthopaedic surgery, such as hip or knee replacement, and: you have severe heart disease or severe vascular disorder of the veins or arteries; you had a heart attach or stroke recently."

Similarly, section 4.4 "Special warnings and precautions for use" of the SmPC should be aligned to state the following: "Patients scheduled for major elective orthopaedic surgery. In patients scheduled for major elective orthopaedic surgery the cause of anaemia should be established and treated, if possible, before the start of Retacrit treatment. Thrombotic events can be a risk in this population and this possibility should be carefully weighed against the benefit to be derived from the treatment.

Patients should receive adequate antithrombotic prophylaxis, as thrombotic and vascular events may occur in surgical patients, especially in those with underlying cardiovascular disease. In addition, special precaution should be taken in patients with predisposition for development of DVTs. Moreover, in patients with a baseline haemoglobin of > 13 g/dl, the possibility that Retacrit treatment may be associated with an increased risk of postoperative thrombotic/vascular events cannot be excluded. Therefore, it should not be used in patients with baseline haemoglobin > 13 g/dl."

In addition, Section 4.8 "Undesirable effects" should be amended with the following wording: "Surgery Patients. In patients with a baseline haemoglobin of > 13 g/dl, the possibility that Retacrit treatment may be associated with an increased risk of postoperative thrombotic/vascular events cannot be excluded."

The evaluation of long-term safety data up to 1 year of Epoetin zeta administered subcutaneously to at least 200 patients with renal anaemia was part of a comprehensive Risk Management Plan. The results of the follow-up extension period of study 411-54-07-08-000 showed that the Hb levels were maintained within the predefined target range. Results for epoetin doses and further results for the secondary endpoints did not show meaningful differences compared to the results of the main study phase. The final results did not reveal any new safety concern. No anti-epoetin antibodies have been detected by the MAH and no neutralizing antibodies have been reported.

Further safety data will be obtained of ongoing safety studies. The MAH is conducting a Post-Authorisation Safety Cohort Observation Study (PASCO II, PMS-830-09-0082) (see EU-RMP, Table 8) which aims to recruit a number of 6700 patients with an observation period of 3 years per patient (to ensure a cumulative follow-up of 20.000 patient years). The primary aim of the study is to estimate the incidence of pure red cell aplasia in patients with renal anaemia treated with epoetin zeta.

Risk Management Plan

The MAA submitted an updated risk management plan, version 8.0. The EU-RMP is summarized in the table below, and does not include any news safety issues that differ from its previous version:

Table 8. Summary	/ of the	EU Risk	Management Plan
			_

Safety issue	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Pure Red Cell Aplasia (PRCA)	 Ongoing Routine pharmacovigilance including targeted questionnaires 	 Contraindication in section 4.3 of the SPC for use in patients who have previously experienced PRCA following treatment with erythropoetins
	 Post-authorisation safety cohort observation of Retacrit (epoetin zeta) for the treatment of renal anaemia (PMS-830-07-0043) 	 Warning in section 4.4 of the SPC regarding PRCA Mention in section 4.8 of the SPC
	 Post-authorisation safety cohort observation of Retacrit (epoetin zeta) subcutaneously for the treatment of renal anaemia (PMS-830-09-0082) 	
	treatment of renal anaemia (PMS-830-09-0082) Completed	

Safety issue	Proposed pharmacovigilance activities	Proposed risk minimisation activities
	 Study to evaluate safety and tolerability of epoetin zeta administered IV for the maintenance treatment of renal anaemia (CT-830-04-0004) Prospective open non- controlled multi-centre study to evaluate safety and tolerability of epoetin zeta administered SC for the treatment of anaemia in cancer patients (CT-830-05- 0009) 	
	• Clinical study investigating the therapeutic equivalence of two different formulations containing epoetin (Epoetin zeta vs. Erypo) administered subcutaneously for the maintenance treatment of renal anaemia (CT-830-07-0047)	
Increased risk of	Ongoing	Completed activities:
PRCA with subcutaneous administration in renal failure patients	 Routine pharmacovigilance including targeted questionnaires 	Educational leaflet
	 Post-authorisation safety cohort observation of Retacrit (epoetin zeta) for the treatment of renal anaemia (PMS-830-07-0043) 	
	 Post-authorisation safety cohort observation of Retacrit (epoetin zeta) subcutaneously for the treatment of renal anaemia (PMS-830-09-0082) 	
	Completed	
	 Clinical study investigating the therapeutic equivalence of two different formulations containing epoetin (Epoetin zeta vs. Erypo) administered subcutaneously for the maintenance treatment of renal anaemia (CT-830-07-0047) 	
	Drug utilisation audit	
	 Study to evaluate safety and tolerability of epoetin zeta administered IV for the maintenance treatment of renal anaemia (CT-830-04-0004) 	
	 Prospective open non- controlled multi-centre study to evaluate safety and tolerability of epoetin zeta administered SC for the treatment of anaemia in cancer patients (CT-830-05- 0009) 	

Safety issue	Proposed pharmacovigilance activities	Proposed risk minimisation activities
	Obsolete • Drug utilisation study on use of epoetin zeta	
Thrombotic vascular events (TVE) including cerebrovascular events	 Ongoing Routine pharmacovigilance including targeted questionnaires Post-authorisation safety cohort observation of Retacrit (epoetin zeta) for the treatment of renal anaemia (PMS-830-07-0043) + registry study and literature study Post-authorisation safety cohort observation of Retacrit (epoetin zeta) subcutaneously for the treatment of renal anaemia (PMS-830-09-0082) 	 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.
	 Completed Study to evaluate safety and tolerability of epoetin zeta administered IV for the maintenance treatment of renal anaemia (CT-830-04-0004) Prospective open non-controlled multi-centre study to evaluate safety and tolerability of epoetin zeta administered SC for the treatment of anaemia in cancer patients (CT-830-05-0009) 	

Tumour Growth Potentially increased Mortality in Renal Anaemia Patients	 Ongoing Routine pharmacovigilance Post-authorisation safety cohort observation of Retacrit (epoetin zeta) for the treatment of renal anaemia (PMS-830-07-0043) Completed Study to evaluate safety and tolerability of epoetin zeta administered IV for the maintenance treatment of renal anaemia (CT-830-04-0004) 	 Section 4.4 of the SPC provides a respective warning that an increased risk of death and serious cardiovascular events was observed when erythropoiesis stimulating agents (ESAs) were administered to target a haemoglobin of greater than 12 g/dl (7.5 mmol/l). A Dear Health Care professional Communication had been sent by health authorities.
Tumour Growth Potential/ Excess Mortality in Cancer Patients	 Ongoing Routine pharmacovigilance Epidemiological study based on health care insurance data to further investigate the differences in mortality between patients treated with ESAs or treated with transfusions alone for chemotherapy-induced anemia Completed Prospective open non- controlled multi-centre study to evaluate safety and tolerability of epoetin zeta administered SC for the treatment of anaemia in cancer patients (CT-830-05- 0009) 	 Risk of tumour growth potential is mentioned in Sections 4.4 and 5.1 of the SPC. Risk of excess mortality has been addressed by 3 type II variations implementing changes t o the SPC after the initial marketing authorisation. The indication for epoetin in chemotherapy associated anaemia had been restricted and ESA are not longer recommended for patients with a reasonably long life expectancy A Dear Health Care professional Communication had been sent by health authorities.

General safety and	Ongoing	
long term use	Routine pharmacovigilance	
	 Post-authorisation safety cohort observation of Retacrit (epoetin zeta) for the treatment of renal anaemia (PMS-830-07-0043) 	
	 Post-authorisation safety cohort observation of Retacrit (epoetin zeta) subcutaneously for the treatment of renal anaemia (PMS-830-09-0082) 	
	Completed	
	 Clinical study investigating the therapeutic equivalence of two different formulations containing epoetin (Epoetin zeta vs. Erypo) administered subcutaneously for the maintenance treatment of renal anaemia (CT-830-07-0047) - open follow-up extension period 	
	• Study to evaluate safety and tolerability of epoetin zeta administered IV for the maintenance treatment of renal anaemia (CT-830-04-0004)	

The Risk Management Plan has been adequately updated in order to reflect the new indication.

In addition, the CHMP considered that the MAH should take the following minor points into consideration when an update of the Risk management Plan is submitted:

The EU-RMP should be aligned with the EU-RMP template (Doc.Ref. EMEA/192632/2006). This update should include aligning sections 1.10 and 5 and completing section 2.4 with all additional pharmacovigilance measures with defined dates for the submission of final data.

No further measures are currently to be taken concerning the Pharmacovigilance Plan.

Annex II.B has been updated in accordance with the latest QRD template (version 7.3.1, March 2010), and to include the new RMP version number as follows: "*Risk Management Plan. The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version <u>8.0</u> of the Risk Management Plan (RMP) presented in Module 1.8.2. of the Marketing Authorisation Application and any subsequent updates of the RMP agreed by the CHMP."*

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

4. Benefit-Risk Balance

Benefits

Beneficial effects

As mentioned in the revised CHMP guidance on non-clinical and clinical development of similar biological medicinal products containing recombinant erythropoietins, (EMEA/CHMP/BMWP/301636/ 2008 Corr.*), the mechanism of action of epoetin is the same in all its current indications, and therefore, the efficacy of subcutaneous Epoetin zeta (Retacrit) in orthopaedic surgery is expected to be

comparable to that of Epoetin alfa (Erypo) given that comparable efficacy has been demonstrated in the sensitive model of renal anaemia in study 411-54-07-08-0000.

<u>Risks</u>

Unfavourable effects

In the above mentioned study, the safety profile of subcutaneous Epoetin zeta (Retacrit) has been shown to be broadly comparable to that of Epoetin alfa (Erypo) in patients with renal anaemia. No additional safety issues are expected in orthopaedic patients.

Balance

Importance of favourable and unfavourable effects

The benefit-risk balance of Epoetin zeta (Retacrit) in moderately anaemic adult patients scheduled for major orthopaedic surgery is expected to be comparable to the benefit-risk balance of the reference product Epoetin alfa (Erypo); it is therefore considered positive within the same restricted conditions of use.

Benefit-risk balance

Discussion on the benefit-risk assessment

The application has demonstrated comparable efficacy and safety for Epoetin zeta (Retacrit) and Epoetin alfa (Erypo) in separate clinical studies for both routes of administration (SC and IV). Extrapolation of efficacy and safety data to the new indication has been performed based on demonstrated similarity in physicochemical characteristics, efficacy and safety between test and reference products, same mechanism of action/same receptor involved, and absence of additional/unique safety concerns in the new indication.

The Risk Management Plan has been updated in order to reflect the new indication. No further measures are currently to be taken concerning the Pharmacovigilance Plan.

Therefore, the CHMP considered that the Benefit-Risk ratio of Epoetin zeta (Retacrit) to reduce exposure to allogeneic blood transfusions in adult non-iron deficient patients prior to major elective orthopaedic surgery, having a high perceived risk for transfusion complications, is positive.

Consequential changes to sections 4.1, 4.2, 4.3, 4.4 and 4.8 of the SmPC and to the Package Leaflet were introduced.

Further, the MAH has updated Annex II.B, in accordance with the QRD template v.7.3.1, and to reflect the latest version of the Risk Management Plan (version 8.0) agreed with the CHMP, which is acceptable. Minor editorial changes have also been implemented.

5. Conclusion

On 23 June 2011 the CHMP considered this Type II variation to be acceptable. Amendments were introduced in the Summary of Product Characteristics, Annex II and Package Leaflet