PRODUCT INFORMATION
NOVICRIT® Solution for Injection

Use in Cancer
In some studies, use of Erythropoiesis Stimulating Agents (ESAs) to treat anaemia in patients with cancer has been associated with increased mortality. ESAs should only be used to treat anaemia that has developed as a result of concomitantly administered chemotherapy, and only when blood transfusion is not considered appropriate. Haemoglobin levels should not exceed 120g/L (see PRECAUTIONS).

NAME OF THE MEDICINE

Chemical name: Epoetin lambda *(rch)*
Chemical structure:

Empirical formula: $C_{809}H_{1299}N_{229}O_{239}S_5$

Molecular weight: About 28,000 Daltons. The protein moiety, a single chain polypeptide of 165 amino acids, has a molecular weight of 18,243 Daltons. The carbohydrate moiety with three N-linked and one O-linked carbohydrate groups corresponds to a weight fraction of approximately 40%.

DESCRIPTION

Active ingredient: Epoetin lambda *(rch)*.

Excipients: Dibasic dihydrate sodium phosphate, monobasic dihydrate sodium phosphate, sodium chloride, glycine, polysorbate 80, hydrochloric acid, sodium hydroxide and water for injections.

Novicrit is supplied in a pre-filled syringe as a clear, colourless solution for injection.

Erythropoietin is an endogenous glycoprotein that stimulates red blood cell production. It is normally produced by the kidney and regulated by the level of tissue oxygenation. Epoetin lambda (rch) (CHO) is purified from a Chinese hamster ovary (CHO) cell line into which the gene coding for human erythropoietin has been inserted. Epoetin lambda (rch) is

indistinguishable from human erythropoietin in biological activity and immunological reactivity.

Epoetin lambda (rch) has been developed as a similar biological medicinal product to epoetin alfa.

PHARMACOLOGY

Erythropoietin stimulates erythropoiesis in anaemic patients with chronic renal failure in whom the endogenous production of erythropoietin is impaired. Because of the length of time required for erythropoiesis (several days for erythroid progenitors to mature and be released into the circulation), a clinically significant increase in haemoglobin is usually not observed in less than two weeks and may require up to ten weeks in some patients.

The primary pharmacodynamics of epoetin lambda (rch) were assessed *in vitro* using an ELISA, by surface plasmon resonance spectroscopy and by use of a cell-based assay assessing the response to an erythropoietic stimulus. Comparable responses of epoetin lambda (rch) and the reference product epoetin alfa (rch) were obtained.

The biological efficacy of epoetin lambda (rch) has been demonstrated *in vivo* using a normocythaemic mouse assay. After administration of epoetin lambda (rch), the reticulocyte counts increased similar to the reference product epoetin alfa.

A 5-day *in vivo* pharmacodynamic-pharmacokinetic study in Beagle dogs was performed which used reticulocyte pharmacodynamics as biomarker. After three to four days of epoetin lambda (rch) injection a clear rise in reticulocytes was observed, which was reversible upon cessation of treatment. There was no remarkable difference between epoetin lambda (rch) and the reference product epoetin alfa (rch).

Phase I studies investigating haematological pharmacodynamic parameters following intravenous and subcutaneous single and repeated dosing have demonstrated comparable pharmacodynamics of epoetin lambda (rch) to a reference epoetin alfa (rch) preparation.

Table 1: Study results from an open, randomized, pivotal IV Phase I study

AUEC	Epoetin lambda (N=37)	Epoetin alfa (N=39)	Ratio [%] and 90% CI*
Haemoglobin [g*h/dL]	10056 ± 354	10071 ± 365	99.9 [98.5 – 101.2]
Red blood cells [h/pL]	3322 ± 181	3303 ± 175	100.6 [98.5 – 102.7]
Haematocrit [h]	288 ± 12	289 ± 10	99.6 [98.2 – 101.0]
Reticulocytes [%*h]	1740 ± 186	1788 ± 253	96.8 [92.4 – 101.9]

* based on a parametric approach (ANOVA) for all parameters except for reticulocytes

Table 2: Study results from an open, randomized, pivotal SC Phase I study

AUEC	Epoetin lambda (N=37)	Epoetin alfa (N=37)	Ratio [%] and 90% CI*
Haemoglobin [g*h/dL]	10248 ± 494	10469 ± 495	98.9 [97.7 – 100.2]
Red blood cells [h/pL]	3378 ± 184	3511 ± 207	98.7 [97.5 – 99.8]
Haematocrit [h]	300 ± 14	308 ± 13	98.7 [97.3 – 100.0]
Reticulocytes [%*h]	1525 ± 267	1660 ± 274	93.4 [88.3 – 98.8]

* based on a parametric approach (baseline-adjusted ANCOVA)

Pharmacokinetics

Absorption
Following subcutaneous injection, serum levels are much lower than the levels achieved following intravenous injection; the levels increase slowly and reach a peak between 6 and 24 hours post-dose. The peak is always well below the peak achieved using the intravenous route (approximately 1/20 of the value). Following subcutaneous injection, erythropoietin serum levels remain elevated above baseline for about 72 hours. There is no accumulation when three times weekly dosing is used; the levels remain the same, whether they are determined 24 hours after the first injection or 24 hours after the last injection.

Metabolism
Metabolism data was not studied for epoetin lambda.

Elimination
After intravenous administration, the mean half-lives in normal volunteers ranged from 2.5 to 6.7 hours. The half-life is difficult to evaluate for the subcutaneous route and is estimated to be about 24 hours.

Bioavailability
The bioavailability of subcutaneous injectable erythropoietin is much lower than that of the intravenous medicine (approximately 20 to 30%).

PK in special populations
No information is available in young or elderly patients. Due to decreased metabolism, patients with hepatic dysfunction may have increased erythropoiesis with epoetin lambda (rch).

Bioequivalence
Phase I studies investigating pharmacokinetic parameters following intravenous and subcutaneous repeated dosing have demonstrated the bioequivalence of Novicrit to a reference epoetin alfa (rch) preparation.

Bioequivalence after multiple intravenous administration was demonstrated in an open, randomised, parallel study in 80 healthy volunteers receiving 100IU/kg body weight 3 times per week for 4 weeks. The pharmacokinetic parameters are summarised below.

	Ratio	90% Confidence interval	Mean ± SD [Epoetin lambda (rch)]	Mean ± SD [Epoetin alfa (rch)]
C_{max}	97.5%	91.1 – 104.5	2189mIU/mL ± 393.7	2262mIU/mL ± 422.0
AUC	89.2%	82.5 – 96.2	8422mIU/mL•h ± 2419	9224mIU/mL•h ± 1850
$t_{1/2}$	87.8%	75.3 – 100.0	4.14h ± 1.71	4.74h ± 2.00

Bioequivalence after multiple subcutaneous administration was demonstrated in an open, randomised, parallel study in 80 healthy volunteers receiving 100IU/kg body weight 3 times per week for 4 weeks. The pharmacokinetic parameters are summarised below.

	Ratio	90% Confidence interval	Mean ± SD [Epoetin lambda (rch)]	Mean ± SD [Epoetin alfa (rch)]
C_{max}	97.6%	84.2 – 113.1	82.410mIU/mL ± 48.69	82.817mIU/mL ± 34.06
AUC	96.9%	88.2 – 106.5	2044.9mIU/mL•h ± 587.9	2095.0mIU/mL•h ± 486.4
$t_{1/2}$	97.9%	81.0 – 118.2	18.28h ± 8.50	18.16h ± 7.52

These results demonstrate that Novicrit is bioequivalent to a reference epoetin alfa (rch) preparation with respect to the pharmacokinetic parameters AUC and C_{max} after multiple intravenous and multiple subcutaneous application.

CLINICAL TRIALS

Comparable safety and efficacy of epoetin lambda (rch) to epoetin alfa (rch) has been demonstrated in anaemia of chronic renal failure (IV administration) and chemotherapy-induced anaemia.

Epoetin alfa (rch) has been studied in a series of placebo controlled, double blind trials in a total of 131 anaemic cancer patients. Within this group, 72 patients were treated with concomitant noncisplatin containing chemotherapy regimens and 59 patients were treated with concomitant cisplatin containing chemotherapy regimens. Patients were randomised to epoetin alfa (rch) 150IU/kg or placebo subcutaneously three times a week for 12 weeks.

Epoetin alfa (rch) therapy was associated with a significantly ($p < 0.008$) greater haematocrit response than in the corresponding placebo treated patients (see Table 3).

Table 3: Epoetin alfa (rch) – Haematocrit [%]: mean change from baseline to final value*

Study	Epoetin alfa (rch)	Placebo
Chemotherapy	7.6	1.3
Cisplatin	6.9	0.6

* Significant higher in epoetin alfa (rch) patients than in placebo patients ($p < 0.008$)

In the two types of chemotherapy studies (utilising an epoetin alfa (rch) dose of 150IU/kg three times weekly) the mean number of units of blood transfused per patient after the first month of therapy was significantly ($p < 0.02$) lower in patients treated with epoetin alfa (rch) (0.71 units in months 2, 3) than in corresponding placebo treated patients (1.84 units in months 2, 3). Moreover, the proportion of patients transfused during months 2 and 3 of therapy combined was significantly ($p < 0.03$) lower in the patients treated with epoetin alfa (rch) than in the corresponding placebo treated patients (22 versus 43%).

Comparable intensity of chemotherapy in the epoetin alfa (rch) and placebo groups in the chemotherapy trials was suggested by a similar area under the neutrophil time curve in patients treated with epoetin alfa (rch) and placebo treated patients as well as by a similar proportion of patients in groups treated with epoetin alfa (rch) and placebo treated groups whose absolute neutrophil counts fell below 1,000 cells/microliter. Available evidence suggests that patients with lymphoid and solid cancers respond equivalently to epoetin alfa (rch) therapy and that patients with or without tumour infiltration of the bone marrow respond equivalently to epoetin alfa (rch) therapy.

Efficacy and safety of epoetin alfa (rch) in the prevention and treatment of anaemia of cancer have not been demonstrated in children.

Epoetin alfa (rch) has been studied in a placebo controlled, double blind trial enrolling 316 patients scheduled for major, elective orthopaedic hip or knee surgery who were expected to require $\geq$ 2 units of blood. Patients were randomly assigned to receive epoetin alfa (rch) 300IU/kg, epoetin alfa (rch) 100IU/kg or placebo by subcutaneous injection for ten days before surgery, on the day of surgery and for four days after surgery. All patients received oral iron and a low dose postoperative warfarin regimen.

Treatment with epoetin alfa (rch) 300 IU/kg significantly ($p=0.024$) reduced the risk of allogeneic transfusion in patients with a pretreatment haemoglobin of > 100 to $\leq$ 130g/L; 5/31 (16%) of epoetin alfa (rch) 300 IU/kg, 6/26 (23%) of epoetin alfa (rch) 100IU/kg and 13/29 (45%) of placebo treated patients were transfused.

In the > 100 to $\leq$ 130g/L pretreatment stratum, the mean number of units transfused per epoetin alfa (rch) treated patient (0.45 units blood for 300 IU/kg, 0.42 units blood for 100 IU/kg) was less than the mean transfused per placebo treated patient (1.14 units) (overall $p=0.028$). In addition, mean haemoglobin, haematocrit and reticulocyte counts increased significantly during the presurgery period in epoetin alfa (rch) treated patients.

Epoetin alfa (rch) was also studied in an open label, parallel group trial enrolling 145 subjects with a pretreatment haemoglobin level of $\geq$ 100 to $\leq$ 130 g/L who were scheduled for major orthopaedic hip or knee surgery and who were not participating in an autologous program.

Subjects were randomly assigned to receive one of two subcutaneous dosing regimens of epoetin alfa (rch) (600 IU/kg once weekly for three weeks prior to surgery and on the day of surgery or 300 IU/kg once daily for ten days prior to surgery, on the day of surgery and for four days after surgery). All subjects received oral iron and appropriate pharmacological anticoagulation therapy.

From pretreatment to presurgery, the mean increase in haemoglobin in the 600 IU/kg weekly group (14.4g/L) was greater than observed in the 300 IU/kg daily group.

The erythropoietic response observed in both treatment groups resulted in similar transfusion rates (11/169 (16%) in the 600 IU/kg weekly group and 14/71 (20%) in the 300 IU/kg daily group). The mean number of units transfused per subject was approximately 0.3 units in both treatment groups.

Using linear logistic models it can be calculated that for a patient with an entry haemoglobin level of 100g/L, use of 300 IU/kg daily or 600 IU/kg weekly would reduce the probability of transfusion to about 38%, compared to 58% in the same patient receiving a 100 IU/kg daily regimen, or 81% in a patient given no epoetin alfa (rch) therapy.

Similarly, at a higher entry haemoglobin of 120g/L, the 300 IU/kg daily or 600 IU/kg weekly regimens would reduce the probability of transfusion to about 18%, compared to 35% in the same patient receiving 100 IU/kg daily, or 61% in a patient receiving no epoetin alfa (rch).

In autologous blood donation, a double blind study was conducted in 204 patients scheduled to undergo elective orthopaedic surgery with haematocrits $\leq$ 39% and no underlying anaemia due to iron deficiency. On average, patients treated with epoetin alfa (rch) 600 IU/kg twice weekly for three weeks were able to predeposit significantly more units of blood (4.5 units) than placebo treated patients (3.0 units) ($p < 0.001$). Also, significantly more patients treated with epoetin alfa (rch) ($p < 0.05$) were able to predeposit between three and six units, inclusively, of autologous blood than the corresponding placebo treated patients. Virtually all (98%) of epoetin alfa (rch) treated patients predeposited three or more units, compared with 69% of placebo treated patients. While 37% of placebo patients were able to predeposit four or five units, 81% of epoetin alfa (rch) patients predeposited four or more units. Among the evaluable patients, fewer patients who received epoetin alfa (rch) required allogeneic transfusions (19.8%) than placebo patients (31%).

In a second placebo controlled study, 55 patients with low haematocrits were enrolled 2:2:1 to receive epoetin alfa (rch) 600 IU/kg, epoetin alfa (rch) 300 IU/kg or placebo twice weekly for three weeks. A significantly greater amount of autologous blood ($p < 0.005$) was donated by the epoetin alfa (rch) treated patients (4.68 vs. 4.42 vs. 2.89 units). Likewise 84, 79 and 11% of patients were able to donate four or more units over the three week study.

A randomised, double-blind, multi-centre phase III study (study number 2003-29-INJ-9) was conducted to evaluate therapeutic equivalence in terms of haemoglobin response of epoetin lambda (rch) versus the reference product epoetin alfa (rch) in the long-term intravenous treatment of anaemia in haemodialysis patients after a 1:1 dose conversion from epoetin alfa (rch) to epoetin lambda (rch). The study included 478 haemodialysis patients with CRF that were treated with the reference product at time of inclusion to the study.

In the first part (double-blind) of the study patients were randomly assigned to continue treatment with their original therapy (N=164) or to switch to epoetin lambda (rch) (N=314).

In the evaluation phase (weeks 25-28) patients treated with epoetin lambda (rch) showed a comparable Hb-level after treatment with epoetin lambda (rch) to their Hb-level at start of the treatment. No relevant differences regarding dosing could be observed. Epoetin lambda

(rch) has shown to be therapeutically equivalent to epoetin alfa (rch) with respect to Hb response in haemodialysis patients after a 1:1 switch.

In the second (open) part of the study patients of the reference group were changed to epoetin lambda and treated for another 28 weeks. The switch to epoetin lambda did not demonstrate any safety relevant changes.

The long-term safety profiles of epoetin lambda (rch) and epoetin alfa (rch) were comparable. No formation of anti-epoetin antibodies was detected. The safety and efficacy of subcutaneous administration of epoetin lambda (rch) in patients with chronic renal failure has not been studied.

A randomised, double-blind, multi-centre phase III study (study number 2003-31-INJ-11) was conducted to assess the efficacy and safety of epoetin lambda (rch) in the treatment of chemotherapy-induced, symptomatic anaemia in patients with solid tumours.

114 patients were treated with epoetin lambda (rch) or epoetin alfa (rch) three times a week subcutaneously for 12 weeks. Doses were raised in case of insufficient increase of Hb respectively reticulocytes after 4 or 8 weeks.

In 62% of patients under epoetin lambda (rch) treatment the Hb level increased by $\geq$ 20g/L with the confidence interval being entirely above the predefined threshold of 30%. In the epoetin lambda (rch) group, 32% of patients required transfusions versus 38% in the epoetin alfa (rch) group. None of the secondary efficacy endpoints showed relevant differences between the treatment groups and also the safety profiles were similar.

An open label, single arm, multicentre phase III study (study number HX575-308) was conducted to evaluate the safety and immunogenicity of HX575 epoetin lambda administered subcutaneously in the treatment of anaemia associated with chronic kidney disease in pre-dialysis and dialysis patients.

Patient eligibility was assessed during a 4-weel screening period, after which patients entered a 52 week treatment period. A 6-month safety follow-up was conducted for patients with binding, non-neutralising anti-erythropoietin antibodies. Doses were individually titrated to maintain haemoglobin concentrations in the range between 10 and 12g/dL, amd the dosing frequency was adjusted as required. A total of 416 patients were included in the safety population and 303 in the per protocol population.

For ESA naïve patients the starting dose for correcting anaemia was 25 IU/kg of body weight 3 times per week or 75 IU/kg of body weight once per week from analysis week 1 to week 5. After analysis week 5 dose adjustments were possible.F

Binding anti-epoetin antibodies were detected via radioimmunoprecipitation (RIP) assay in seven (1.7%, incidence rate of 0.019) of patients in the safety population at some time during the study. No patient developed neutralising antibodies as tested in a cell-based neutralising anti-erythropoietin antibody assay. The ‘detected by RIP assay binding antibodies’ had no clinical impact on the treatment efficacy. There were no clinical signs of immunogenicity or hypersensitivity.

Prior to study treatment, binding anti-epoetin antibodies were detected in thirteen (eight ESA naïve and 5 ESA pre-treated) of 993 patients (1.3%) via RIP assay during screening. Therfore, given the high sensitivity of the RIP assay, with a potential 1% false-positive rate, the low antibody titres of most positive samples and the fact there was no increase in titer over consecutive visits with continued HX575 treatment, a persistent anti-drug antibody response can be excluded.

Epoetin lambda (rch) was shown to be efficacious in the treatment of chemotherapy-associated anaemia in solid tumour patients with a safety profile not differing from what is expected in this therapeutic area.

Epoetin lambda (rch) has not been studied in patients scheduled for elective surgery, either to treat moderate anaemia or to augment autologous blood collection (see INDICATIONS). However, comparable efficacy and safety can be expected in these patients since comparable efficacy and safety to epoetin alfa (rch) has been demonstrated in the anaemia of chronic renal failure (IV administration) and chemotherapy-induced anaemia settings.

INDICATIONS

Treatment of patients with symptomatic or transfusion requiring anaemia associated with chronic renal failure to improve their quality of life by improving energy levels, exercise performance, fatigue and sleep patterns and by reducing the need for blood transfusions.

Treatment of anaemia in patients with nonmyeloid malignancies where anaemia develops as a result of concomitantly administered chemotherapy, and where blood transfusion is not considered appropriate.

Adult patients with mild to moderate anaemia (haemoglobin > 100 to ≤ 130 g/L) scheduled for elective surgery with an expected moderate blood loss (two to four units or 900 to 1,800 mL) to reduce exposure to allogeneic blood transfusion and to facilitate erythropoietic recovery.

Augment autologous blood collection and to limit the decline in haemoglobin in anaemic adult patients who are scheduled for major elective surgery and who are not expected to predeposit their complete perioperative blood needs.

CONTRAINDICATIONS

- Uncontrolled hypertension.
- Known sensitivity to mammalian cell derived products.
- Hypersensitivity to the active substance or to any of the excipients.
- Patients scheduled for elective surgery, who are not participating in an autologous blood predeposit program and who have severe coronary, peripheral arterial, carotid or cerebral

vascular disease, including patients with recent myocardial infarction or cerebral vascular accident.
- Surgery patients who for any reason cannot receive adequate antithrombotic prophylaxis or treatment.
- Patients who develop pure red cell aplasia (PRCA) following treatment with any erythropoietin should not receive epoetin lambda (rch) or any other erythropoietin (see PRECAUTIONS).

All contraindications associated with autologous blood predonation programmes should be respected in patients being supplemented with epoetin lambda (rch).

PRECAUTIONS

Cardiovascular and thrombotic events / Increased mortality

An increased incidence of thrombotic vascular events (TVEs) has been observed in patients receiving Erythropoiesis-stimulating agents ESAs such as epoetin lambda (rch)(see ADVERSE EFFECTS). Cardiovascular and thrombotic vascular events such as myocardial ischaemia, myocardial infarction, cerebrovascular accidents (cerebral haemorrhage and cerebral infarction), transient ischaemic attacks, deep venous thrombosis, arterial thrombosis, pulmonary emboli, retinal thrombosis and haemodialysis graft occlusion have been reported in patients receiving erythropoietic agents such as epoetin lambda (rch) (see also PRECAUTIONS – Use in Chronic Renal Failure Patients).

The reported risk of TVEs should be carefully weighed against the benefits to be derived from treatment with epoetin lambda (rch) particularly in patients with pre-existing risk factors. Epoetin lambda (rch) and other erythropoiesis-stimulating agents increased the risk for death and for serious cardiovascular events in controlled trials when administered to target a haemoglobin of greater than120 g/L. There was an increased risk of serious arterial and venous thromboembolic events, including myocardial infarction, stroke, congestive heart failure and haemodialysis graft occlusion. A rate of haemoglobin rise of greater than 10g/L over 2 weeks may also contribute to these risks.

In all patients, haemoglobin levels should be closely monitored due to potential increased risk of thromboembolic events and fatal outcomes when patients are treated at haemoglobin levels above the target range for the indication for use.

Use in cancer patients

Epoetin lambda (rch) is a growth factor that primarily stimulates red cell production. Like all growth factors there is a theoretical concern that epoetin lambda (rch) could act as a growth factor for any tumour type, particularly myeloid malignancies.

Cancer patients on NOVICRIT should have haemoglobin levels measured on a regular basis until a stable level is achieved and periodically thereafter.

As with all growth factors, there is a concern that ESAs could stimulate the growth of tumours. In controlled clinical studies, use of epoetin alfa (rch) and other ESAs have shown:

- *decreased locoregional control in patients with advanced head and neck cancer receiving radiation therapy when administered to a haemoglobin target of greater than 140 g/L,*
- *shortened overall survival and increased deaths attributed to disease progression at 4 months in patients with metastatic breast cancer receiving chemotherapy when administered to a haemoglobin target of 120-140 g/L,*
- *Another ESA (darbepoetin alfa) increased risk of death when administered to target a haemoglobin of 120 g/L in patients with active malignant disease receiving neither chemotherapy nor radiation therapy. ESAs are not indicated for use in this patient population.*

In view of the above, the decision to administer recombinant erythropoietin treatment should be based on a benefit-risk assessment with the participation of the individual patient, which should take into account the specific clinical context. Factors to consider in this assessment include: the type of tumour and its stage; the degree of anaemia; life-expectancy; the environment in which the patient is being treated; and patient preference.

A study comparing another erythropoiesis-stimulating agent with placebo in patients with anaemia of cancer who were not being treated with chemotherapy demonstrated no benefit in terms of reduced transfusion requirements. In addition, there were an increased number of deaths in the active group (26% vs. 20%). Epoetin lambda (rch) should only be used to treat cancer patients with anaemia where the anaemia has arisen as a result of concomitantly administered chemotherapy. The target haemoglobin should be up to 120g/L in men and women and it should not be exceeded.

Hypertension

Patients with uncontrolled hypertension should not be treated with epoetin lambda (rch); blood pressure should be controlled adequately before initiation of therapy. Blood pressure may rise during treatment of anaemia with epoetin lambda (rch). Hypertensive encephalopathy and seizures have been observed.

Special care should be taken to closely monitor and control blood pressure in patients treated with epoetin lambda (rch). During epoetin lambda (rch) therapy, patients should be advised of the importance of compliance with antihypertensive therapy and dietary restrictions. If blood pressure is difficult to control after initiation of appropriate measures, the dose of epoetin lambda (rch) should be reduced or temporarily withheld until haemoglobin begins to decrease (see DOSAGE AND ADMINISTRATION).

Pure red cell aplasia

In chronic renal failure patients, antibody mediated pure red cell aplasia (PRCA) (erythroblastopenia) has been rarely reported after months to years of treatment with erythropoietins. Cases also have been rarely reported in patients with hepatitis C treated with interferon and ribavirin, when ESAs are used concomitantly. ESAs are not approved in the management of anaemia associated with hepatitis C.

In most of these PRCA patients antibodies to erythropoietins have been reported. In patients developing sudden lack of efficacy typical causes of nonresponse should be investigated. If no cause is identified, a bone marrow examination should be considered.

If PRCA is diagnosed, epoetin lambda (rch) must be immediately discontinued and testing for erythropoietin antibodies should be considered. If antibodies to erythropoietin are detected, patients should not be switched to another ESA product as anti-erythropoietin antibodies cross-react with other erythropoietins. Other causes of pure red cell aplasia should be excluded, and appropriate therapy instituted.

PRCA most commonly occurs in patients with chronic renal failure who have received erythropoietins via the subcutaneous route. The subcutaneous route should only be used when intravenous access is not readily available. No other ESA therapy should be commenced because of the risk of cross-reaction.

Seizures

Seizures have occurred in patients with CRF receiving epoetin lambda (rch) with a frequency of 3 to 7%, usually during the first 90 days of treatment. Therefore, NOVICRIT should be used with caution in patients with epilepsy, history of seizures, or medical conditions associated with a predisposition to seizure activity such as CNS infections and brain metastases. Blood pressure and premonitory neurological symptoms should be closely monitored. Patients should be cautioned to avoid potentially hazardous activities such as driving or operating heavy machinery during this period.

Iron Supplementation

Iron status should be assessed in all patients prior to therapy. Further monitoring of serum iron, ferritin and total iron binding capacity is indicated monthly for the first three months of therapy and three monthly thereafter. Virtually all patients will eventually need supplemental iron therapy.

Other causes of anaemia (iron, folate or Vitamin B12 deficiency, aluminium intoxication, infection or inflammation, blood loss, haemolysis and bone marrow fibrosis of any origin) should be evaluated and treated prior to initiating therapy with NOVICRIT, and when deciding to increase the dose. In most cases, the ferritin values in the serum fall simultaneously with the rise in packed cell volume. In order to ensure optimum response to NOVICRIT, adequate iron stores should be assured and iron supplementation should be administered if necessary:

- For chronic renal failure patients, iron supplementation (elemental iron 200-300 mg/day orally for adults and 100-200 mg/day orally for paediatrics) is recommended if serum ferritin levels are below 100 ng/mL.
- For cancer patients, iron supplementation (elemental iron 200-300 mg/day orally) is recommended if transferring saturation is below 20%.
- For patients in an autologous predonation programme, iron supplementation (elemental iron 200 mg/day orally) should be administered several weeks prior to initiating the autologous predeposit in order to achieve high iron stores prior to starting NOVICRIT therapy, and throughout the course of NOVICRIT therapy.
- For patients scheduled for major elective orthopaedic surgery, iron supplementation (elemental iron 200 mg/day orally) should be administered throughout the course of NOVICRIT therapy. If possible, iron supplementation should be intiated prior to starting NOVICRIT therapy to achieve adequate iron stores.

General

Epoetin lambda (rch) should be used with caution in those patients with pre-existing hypertension, ischaemic vascular disease, or suspected allergy to any components of the product, porphyria or gout.

The safety and efficacy of epoetin lambda (rch) therapy have not been established in patients with underlying haematological diseases (e.g. haemolytic anaemia, sickle cell anaemia, thalassemia, porphyria).

Erythropoiesis-stimulating agents (ESAs) are not necessarily equivalent. Therefore, it should be emphasised that patients should only be switched from one ESA (such as epoetin lambda) to another ESA with the authorisation of the treating physician. In order to improve the traceability of ESAs, the trade name of the administered ESA should be clearly recorded (or stated) in the patient file.

There may be a moderate dose-dependent rise in the platelet count within the normal range during treatment with epoetin lambda (rch). This regresses during the course of continued therapy.Development of thrombocytosis is very rare. It is recommended that the platelet count is regularly monitored during the first eight weeks of therapy.

Rarely, development of or exacerbation of porphyria has been observed in epoetin alfa-treated patients with chronic renal failure. Epoetin alfa has not caused increased urinary excretion of porphyrin metabolites in normal volunteers, even in the presence of a rapid erythropoietic response. Nevertheless, epoetin lambda (rch) should be used with caution in patients with known porphyria.

Increased serum uric acid may occur in patients whose haemoglobin is rising more than approximately 20g/L per month. Consequently, epoetin lambda (rch) should be used with caution in patients with a history of gout.

NOVICRIT should also be used with caution in patients with chronic liver failure. The safety and dosage regime of epoetin lambda (rch) has not been established in the presence of hepatic dysfunction. Due to decreased metabolism, patients with hepatic dysfunction may have increased erythropoiesis with epoetin lambda (rch).

Use in Chronic Renal Failure Patients

Chronic renal failure patients being treated with epoetin lambda should have haemoglobin levels measured on a regular basis until a stable level is achieved, and periodically thereafter.

In chronic renal failure patients the rate of increase in haemoglobin should be approximately 10 g/L per month and should not exceed 20 g/L per month to minimise risks of an increase in hypertension. Dose should be reduced when haemoglobin approaches 120 g/L.

In patients with chronic renal failure, maintenance haemoglobin concentration should not exceed the upper limit of the target haemoglobin concentration range as recommended under Dosage and Administration. In controlled trials, haemoglobin levels targeted to 130 g/L were

associated with a higher risk of cardiovascular or cerebrovascular events, including stroke and death.

Patients with chronic renal failure and insufficient haemogloblin response to ESA therapy may be at even greater risk for cardiovascular or cerebrovascular events and mortality than other patients.

Shunt thromboses have occurred in haemodialysis patients, especially in those who have a tendency to hypotension or whose arteriovenous fistulae exhibit complications (e.g., stenoses, aneurysms, etc.) Early shunt revision and thrombosis prophylaxis by administration of acetylsalicylic acid, for example, is recommended in these patients.

Renal dialysis

Correction of anaemia with epoetin lambda (rch) does not appear to affect dialysis efficiency.

Hyperkalaemia has been observed in isolated cases. However, an increase in appetite could lead to increased potassium intake and hyperkalaemia in both dialysis and predialysis patients. This and other alterations in serum chemistry should be managed by dietary alterations and modifications of the dialysis prescription if appropriate. Serum electrolytes should be monitored in chronic renal failure patients. If an elevated (or rising) serum potassium level is detected then, in addition to appropriate treatment of the hyperkalaemia, consideration should be given to ceasing epoetin lambda (rch) administration until hyperkalaemia has been corrected.

As a result of an increase in packed cell volume, haemodialysis patients receiving NOVICRIT frequently require an increase in heparin dose during dialysis. If heparinisation is not optimal, occlusion of the dialysis system is possible.

In some female chronic renal failure patients, menses have resumed following epoetin alfa (rch) therapy; the possibility of potential pregnancy should be discussed and the need for contraception evaluated.

In some preclinical toxicological studies in dogs and rats, but not in monkeys, epoetin alfa (rch) therapy was associated with subclinical bone marrow fibrosis. Bone marrow fibrosis is a known complication of chronic renal failure in humans and may be related to secondary hyperparathyroidism or unknown factors. The incidence of bone marrow fibrosis was not increased in a study of dialysis patients who were treated with epoetin alfa (rch) for 12 to 19 months compared to the incidence of bone marrow fibrosis in a matched control group of dialysis patients who had not been treated with epoetin alfa (rch). In a 13 week study, dogs were treated subcutaneously or intravenously with 80, 240 or 520IU/kg/day. The majority of dogs treated subcutaneously and 50% of dogs treated intravenously developed anaemia with or without bone marrow hypoplasia. The cause of these observations is unknown, however, no cases of paradoxical anaemia have been reported in haematologically normal humans treated with epoetin alfa (rch), making the significance of the findings in dogs unclear.

Use in Patients Scheduled for Elective Surgery

Potentially correctable anaemia should be investigated and appropriately treated before considering therapy with epoetin lambda (rch) prior to elective surgery. In patients with a baseline haemoglobin of > 130g/L (8.1mmol/L), the possibility that epoetin lambda (rch) 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 a baseline haemoglobin > 130g/L (8.1mmol/L).

Good blood management practices should always be used in the perisurgical setting.

Use in Surgery Patients in an Autologous Pre-Donation Programme (ABD)

All special precautions associated with autologous predonation programs, especially routine volume replacement, should be respected.

Effects on fertility

Intravenous administration of epoetin alfa (rch) at dose levels of 20 to 500IU/kg/day in rats caused decreased fertility.

Use in pregnancy [Category B3]

Epoetin lambda (rch) should be administered during pregnancy only if clearly needed. It is not known whether epoetin lambda (rch) crosses the placenta or whether it can cause foetal harm when administered to a pregnant woman. Animal studies have shown no evidence of teratogenic activity in rats or rabbits at epoetin alfa (rch) dosages up to 500IU/kg/day administered intravenously. However, intravenous administration of epoetin alfa (rch) at dose levels of 20 to 500IU/kg/day in rats caused increased preimplantation and postimplantation loss, decreased foetal weight and retardation of ossification.

In pregnant surgical patients participating in an autologous blood predonation program, the use of epoetin lambda (rch) is not recommended.

Use in lactation

Epoetin lambda (rch) should be administered during lactation only if clearly needed. It is not known whether epoetin lambda (rch) is excreted in breast milk or whether it can cause harm to the infant when administered to a lactating woman. Intravenous administration of epoetin alfa (rch) to lactating rats at 500IU/kg/day causes retardation of growth and development of the offspring.

In lactating surgical patients participating in an autologous blood predonation programme, the use of epoetin lambda (rch) is not recommended.

Paediatric Use

Efficacy. Clinical trials of epoetin alfa (rch) in children supported the following effects: correction of anaemia; reduction or elimination of transfusion requirements; improvement of the bleeding tendency in uraemia; increased weight and appetite; and the reduction of cytotoxic antibodies. Possible but not conclusive effects were an improvement in exercise capacity and short-term cardiovascular effects. Long-term cardiovascular effects, effects on

growth rate, improved prospects for renal transplantation and improved quality of life were unproved.

Safety. Incomplete information is available, particularly on the rate of change of haemoglobin and blood pressure.
Dose. Available data support a dose of 25IU/kg three times a week rather than 50IU/kg three times a week.

Carcinogenicity

Long-term carcinogenicity studies have not been carried out. There are conflicting reports in the literature regarding whether erythropoietins may play a role as tumour proliferators. These reports, based on *in vitro* findings from human tumour samples, are of uncertain significance in the clinical situation.

Genotoxicity

In a standard series of assays for genotoxic potential, epoetin alfa (rch) did not induce gene mutations or cause chromosomal damage.

Effect on ability to drive or operate machinery

Due to the increased risk of hypertension during the initial phase of epoetin lambda (rch) treatment, patients with chronic renal failure should use caution when performing potentially hazardous activities, such as driving or operating machinery, until the optimal maintenance dose of epoetin lambda (rch) has been established.

INTERACTIONS WITH OTHER MEDICINES

There are no known clinically significant interactions with other medicines but the effect of epoetin lambda (rch) may be potentiated by the simultaneous therapeutic administration of a haematinic agent such as ferrous sulfate when a deficiency state exists.

Drugs that decrease erythropoiesis may decrease the response to NOVICRIT.

Since cyclosporin is bound by red blood cells, there is potential for a medicine interaction. If epoetin lambda (rch) is given concomitantly with cyclosporin, blood levels of cyclosporin should be monitored and the dose of cyclosporin adjusted as the haematocrit rises.

In patients with metastatic breast cancer, subcutaneous co-administration of 40,000IU/mL epoetin alfa with trastuzumab (6mg/kg) had no effect on the pharmacokinetics of trastuzumab.

ADVERSE EFFECTS

Epoetin lambda has been demonstrated to have equivalent pharmacokinetics and pharmacodynamics to epoetin alfa. The adverse effects observed with epoetin alfa would therefore be expected to occur with epoetin lambda.

Adverse effects observed with epoetin alfa

The most frequent adverse drug reaction during treatment with epoetin alfa is a dose-dependent increase in blood pressure or aggravation of existing hypertension. Monitoring of the blood pressure should be performed, particularly at the start of therapy. Other common adverse drug reactions observed in clinical trials of epoetin alfa are diarrhoea, nausea, headache, influenza-like illness, pyrexia, rash, and vomiting. Influenza-like illness including headaches, joint pains, myalgia, and pyrexia may occur especially at the start of treatment.

Serious adverse drug reactions include venous and arterial thromboses and embolism (including some with fatal outcomes), such as deep venous thrombosis, pulmonary emboli, arterial thrombosis, retinal thrombosis, and shunt thrombosis (including dialysis equipment). In a cumulative analysis of 10 double-blind, randomised, placebo-controlled trials in subjects with cancer receiving chemotherapy, deep venous thrombosis was reported in 2.1% and pulmonary embolism in 1.2% of the 1564 subjects exposed to epoetin alfa, compared to 1.2% and 1.2%, respectively, of the 1207 subjects exposed to placebo. Additionally, cerebrovascular accidents (including cerebral infarction and cerebral haemorrhage) and transient ischaemic attacks have been reported in clinical trials of epoetin alfa.

Hypersensitivity reactions, including cases of rash, urticaria, anaphylactic reaction, and angioneurotic oedema have been reported.

Hypertensive crises with encephalopathy and seizures, requiring the immediate attention of a physician and intensive medical care, have also occurred during epoetin alfa treatment in patients with previously normal or low blood pressure. Particular attention should be paid to sudden stabbing migraine-like headaches as a possible warning signal.

Hyperkalaemia, cough, respiratory congestion, bone pain, porphyria, bone pain in extremity, have also been reported.

The overall safety profile of epoetin alfa was evaluated in 142 subjects with chronic renal failure (CRF) and in 765 subjects with cancer who participated in placebo-controlled, double-blind clinical registration trials. Adverse drug reactions reported by ≥ 0.2% of epoetin alfa-treated subjects in these trials are shown in Table 4.

Table 4: Adverse Drug Reactions Reported by ≥ 0.2% of Subjects in Clinical Registration Trials with epoetin alfa.

System/Organ Class Adverse Drug Reaction	Epoetin alfa Clinical Trial Data			
	CRF		Cancer	
	Epoetin alfa N=96 (%)	Placebo N=46 (%)	Epoetin alfa N=488 (%)	Placebo N=277 (%)
Blood & Lymphatic System Disorders				
Thrombocythaemia	NR	NR	0.2	NR
Nervous System Disorders				
Cerebral Haemorrhage*	NR	NR	0.41	NR
Seizures	2.1	2.2	0.2	NR
Headache	33	46	3.7	3.6

System/Organ Class Adverse Drug Reaction	Epoetin alfa Clinical Trial Data CRF		Cancer	
	Epoetin alfa N=96 (%)	Placebo N=46 (%)	Epoetin alfa N=488 (%)	Placebo N=277 (%)
Vascular Disorders				
Deep Vein Thrombosis*	NR	NR	1.6	0.36
Hypertension	4.1	NR	2.5	1.1
Gastrointestinal Disorders				
Nausea	10.7	7.6	17	32
Diarrhoea	1	NR	5.7	4.4
Vomiting	2.1	NR	4.9	5.4
Skin and Subcutaneous Tissue Disorders				
Rash	1	NR	1.2	1.1
Musculoskeletal, Connective Tissue, and Bone Disorders				
Arthralgia	23	20	1.4	1.8
Myalgia	NR	NR	1	1.4
General Disorders and Administration Site Conditions				
Influenza-Like Illness	19	26	4.9	3.3
Pyrexia	NR	NR	12	11
Injury, Poisoning, and Procedural Complications				
Shunt Thromboses (including dialysis equipment)	1.1	2.2	NA	NA

KEY: NR=not reported; NA=not applicable.
*Including cases with a fatal outcome.

Additional adverse drug reactions with unknown incidence rates identified through other controlled and non-controlled clinical trials with epoetin alfa are shown in Table 5.

Table 5: Additional Adverse Drug Reactions With Unknown Incidence Rate Identified in Other Clinical Trials of Epoetin alfa

System/Organ Class Adverse Drug Reaction[b]
Immune System Disorders
Anaphylactic Reaction
Hypersensitivity
Nervous System Disorders
Cerebrovascular Accident[a]
Hypertensive Encephalopathy
Transient Ischaemic Attacks
Eye Disorders
Retinal Thrombosis
Vascular Disorders
Hypertensive Crisis
Arterial Thrombosis
Respiratory, Thoracic, and Mediastinal Disorders
Pulmonary embolism[a]

Skin and Subcutaneous Tissue Disorders
Urticaria
Angioneurotic Oedema
Congenital and Familial/Genetic Disorders
Porphyria
General Disorders and Administration Site Conditions
Drug Ineffective
Peripheral Oedema
Injection Site Reaction

[a] Including cases with fatal outcomes.
[b] Venous and arterial thromboembolic events have been reported in patients receiving epoetin alfa (see PRECAUTIONS).

Renal Failure Patients
In chronic renal failure patients, haemoglobin levels greater than 120g/L may be associated with a higher risk of cardiovascular events, including death (see PRECAUTIONS).

Shunt thromboses have occurred in haemodialysis patients, especially in those who have a tendency to hypotension or whose arteriovenous fistulae exhibit complications.

Cancer Patients
Thromboembolic events (see PRECAUTIONS) have been reported in cancer patients receiving erythropoietic agents, including epoetin alfa. An investigational study in women with metastatic breast cancer intended to determine whether erythropoietin treatment that extended beyond the correction of anaemia could improve treatment outcomes. However, in that study overall mortality, mortality attributed to disease progression, and incidence of fatal thromboembolic events were all higher in patients receiving epoetin alfa than in those receiving placebo.

Post-marketing data:

Adverse drug reactions identified during post-marketing experience with epoetin alfa are included in Table 4. In the table, the frequencies are provided according to the following convention:

Very common	≥ 1/10
Common	≥ 1/100 and < 1/10
Uncommon	≥ 1/1,000 and <1/100
Rare	≥ 1/10,000, <1/1,000
Very rare	< 1/10,000, including isolated reports

Antibody-mediated pure red cell aplasia has been very rarely reported (<1/10,000 cases per patient-year) after months to years of treatment with epoetin alfa.

Table 6: Adverse Drug Reactions Identified During Post-marketing Experience with epoetin lambda by Frequency Category Estimated from Spontaneous Reporting Rates

System/Organ Class	
Frequency	Adverse Drug Reaction
Nervous system disorders	
Common	Stroke
Cardiac disorders	
Frequency not known	Myocardial infarction
Blood & Lymphatic System Disorders	
Very rare	Erythropoietin Antibody-Mediated Pure Red Cell Aplasia, Thrombocythaemia
Investigations	
Very rare	Anti-erythropoietin Antibody Positive

Adverse effects observed in clinical trials with epoetin lambda

Adverse effects identified during clinical trials with epoetin lambda are shown in Table 7.

Table 7: Adverse Drug Reactions Reported by > 2.5% of Subjects During Clinical Registration Trials with Epoetin lambda

System/Organ Class	Epoetin lambda Clinical Trial Data			
Adverse Drug Reaction	CRF (IV)		Cancer (SC)	
	Epoetin lambda N=314 (%)	Epoetin alfa N=164 (%)	Epoetin lambda N=74 (%)	Epoetin alfa N=40 (%)
Metabolism and nutrition disorders				
Anorexia	NR	NR	NR	7.5
Nervous system disorders				
Dizziness	NR	NR	4.1	NR
Vascular disorders				
Hypertension	NR	NR	4.1	2.5
Gastrointestinal disorders				
Nausea	0.3	NR	NR	7.5
Vomiting	NR	0.6	NR	7.5
Abdominal pain	0.3	NR	NR	5.0
Abdominal pain upper	NR	NR	NR	5.0

KEY: NR=not reported.

Cases of pure red cell aplasia / anti-erythropoietin neutralising antibody development have been reported following subcutaneous administration of epoetin lambda to patients with chronic renal failure.

DOSAGE AND ADMINISTRATION

During therapy, haematological parameters should be monitored regularly. Doses must be individualised to ensure that haemoglobin is maintained at an appropriate level for each patient.

As a single anaphylactic reaction was observed in one patient during the course of clinical testing, it is recommended that the first dose be administered under medical supervision.

Adult patients scheduled for elective surgery

Before considering therapy with Novicrit prior to elective surgery, it is important to investigate and provide appropriate treatment for potentially correctable anaemia.

In patients scheduled for elective surgery adequate antithrombotic prophylaxis is strongly recommended.

The subcutaneous route of administration should be used.

The recommended dose regimen is 600 IU/kg Novicrit given weekly for three weeks (days -21, -14, and -7) prior to surgery and on the day of surgery. In cases where there is a medical need to shorten the lead time before surgery to less than three weeks, 300 IU/kg Novicrit should be given daily for ten consecutive days prior to surgery, on the day of surgery and for four days immediately thereafter. The administration of Novicrit should be stopped as soon as the haemoglobin level reaches 150g/L in the preoperative period, even if not all the planned Novicrit doses have been given.

All patients being treated with Novicrit should receive adequate iron supplementation (e.g. oral elemental iron 200 mg daily) throughout the course of Novicrit treatment. If possible, iron supplementation should be started prior to Novicrit therapy, to achieve adequate iron stores.

Anaemic adult surgery patients in an autologous predonation program

The intravenous route should be used. The recommended dose is 300 to 600 IU/kg twice weekly for three weeks, together with at least 200 mg oral elemental iron daily.

Chronic renal failure patients

In patients with chronic renal failure, where intravenous access is routinely available (haemodyalisis patients) administration by the intravenous route is preferable. Where intravenous access is not readily available (patient not yet on dialysis and peritoneal dialysis patients) Novicrit may be administered subcutaneously (see PRECAUTIONS, Pure Red Cell Aplasia).

In patients maintained on haemodialysis, Novicrit should always be administered after completion of dialysis.

Treatment with Novicrit is divided into the following two stages:

Correction phase:

The initial dose of Novicrit is 50IU/kg bodyweight three times a week, by intravenous or subcutaneous injection. If the haemoglobin does not increase by 10g/L after one month of treatment, the dosage may be raised to 75IU/kg three times/week. If further increments are needed, they should be at 25IU/kg, three times/week, at monthly intervals, to achieve a haemoglobin not to exceed 120g/L. This level should not be exceeded in patients with chronic renal failure. Maximum dose should not exceed 3 x 200IU/kg per week.

Maintenance phase:

The intravenous or subcutaneous dose has to be adjusted individually to maintain a haemoglobin not to exceed 120g/L.

The maintenance dose should be individualised for each chronic renal failure patient. The recommended total weekly dose is between 75 and 300IU/kg.

For patients who are converted from the subcutaneous route to intravenous route, the same dose should be used, and the haemoglobin should be followed carefully (e.g. weekly) so that appropriate changes in Novicrit dose can be made to keep the haemoglobin within the target range.

Dose adjustment:

If the haemoglobin is increasing and approaching 120g/L, the dose should be reduced by approximately 25%. If the haemoglobin continues to increase, the dose should be temporarily withheld until the haemoglobin begins to decrease, at which point therapy should be reinitiated at a dose approximately 25% below the previous dose. If the haemoglobin increases by more than 10g/L in any 2-week period, the dose should be decreased by approximately 25%. If dose reduction is needed the amount given per dose should be reduced or the number of weekly injections reduced or both.

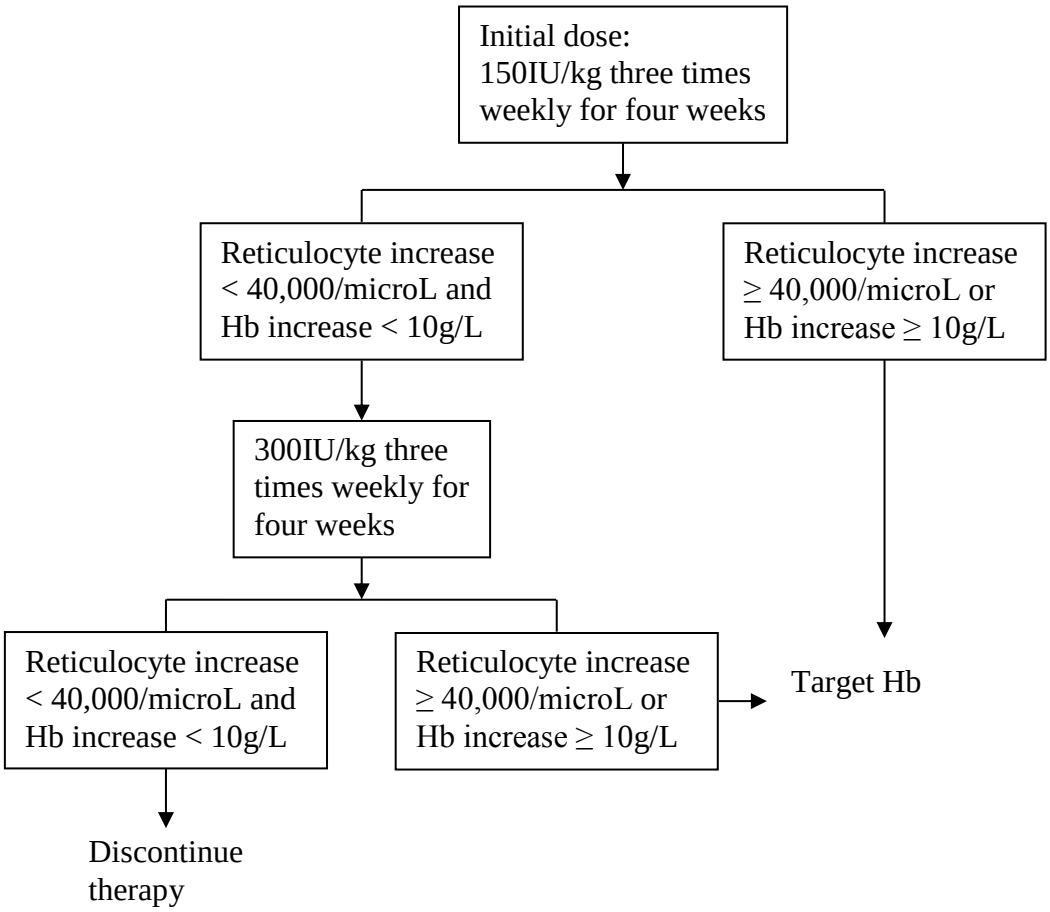
Adult patients with cancer

Treatment should not be commenced unless haemoglobin falls below 100 to 110g/L. The target haemoglobin concentration should be up to 120g/L in men and women and it should not be exceeded.

The initial dose is 150IU/kg given subcutaneously three times/week. If the haemoglobin has increased by at least 10g/L (0.62mmol/L) or the reticulocyte count has increased ≥ 40,000 cells/microliter above baseline after four weeks of treatment, the dose should remain at 150IU/kg. If the haemoglobin increase is < 10g/L (< 0.62mmol/L) and the reticulocyte count has increased < 40,000 cells/microliter above baseline, increase the dose to 300IU/kg. If after an additional four weeks of therapy at 300IU/kg, the haemoglobin has increased ≥ 10g/L (≥ 0.62mmol/L) or the reticulocyte count has increased ≥ 40,000 cells/microliter the dose should remain at 300IU/kg. However, if the haemoglobin has increased < 10g/L (< 0.62mmol/L) and the reticulocyte count has increased < 40,000 cells/microliter above baseline, response is unlikely and treatment should be discontinued.

The recommended dosing regimen is described in Figure 1.

Figure1: Novicrit – Recommended dosage regimen, adult patients with cancer



Patients should be monitored closely to ensure that the lowest approved dose of epoetin lambda (rch) is used to provide adequate control of the symptoms of anaemia.

Dose adjustment:

In oncology patients, rapid increases in haemoglobin concentrations or the use of erythropoietins in subjects with normal haemoglobin concentrations, may result in an increased risk of thrombotic adverse events (see PRECAUTIONS, Thrombotic events).

Therefore, a rate of rise in haemoglobin of greater than 10g/L per two week period or 20g/L per month, or haemoglobin levels of > 120g/L should be avoided.

If the haemoglobin is rising by more than 10g/L per two week period or 20g/L per month, or haemoglobin is approaching 120g/L, reduce Novicrit dose by about 25 to 50%. If the haemoglobin exceeds 120g/L, discontinue therapy until it falls to below 120g/L and then reinstitute Novicrit at a dose 25% below the previous dose.

Evaluation of iron status

Iron status should be assessed in all patients prior to therapy. See PRECAUTIONS – Iron Supplementation for further information.

Delayed or diminished response

Delayed or diminished response to Novicrit therapy should prompt a search for causative factors such as iron, folate or cyanocobalamin (vitamin B12) deficiency; aluminium intoxication; intercurrent infections; inflammatory or traumatic episodes; occult blood loss; haemolysis; and bone marrow fibrosis of any origin.

Administration

Parenteral drug products should be visually inspected for particulate matter and discolouration prior to administration. Product exhibiting particulate matter or discolouration must not be used. Do not shake; shaking may denature the glycoprotein, rendering it inactive.

Syringes are embossed with graduation rings in order to enable partial use if required. Each graduation ring corresponds to a volume of 0.1mL. Novicrit pre-filled syringes contain no preservatives. The pre-filled syringes are for single use in one patient only. Discard any unused portion.

Administer as an intravenous or subcutaneous injection over one to two minutes. In patients on dialysis the injection should follow the dialysis procedure. Slow injection over five minutes may be beneficial to those who experience flu-like symptoms.

Do not dilute or transfer to any other container. Do not administer by intravenous infusion or in conjunction with other medicine solutions.

For the subcutaneous route, a maximum volume of 1mL at one injection site should generally not be exceeded. In case of larger volumes, more than one site should be chosen for the injection. Subcutaneous injections are given in the limbs or the anterior abdominal wall.

In those situations in which the physician determines that a patient or caregiver can safely and effectively administer Novicrit subcutaneously, instruction as to the proper dose and administration should be provided.

Novicrit is for single use in one patient only. Discard any remaining contents.

OVERDOSAGE

Contact the Poisons Information Centre on 13 11 26 for advice on management of an overdose.

The maximum amount of epoetin lambda (rch) that can be safely administered in single or multiple doses has not been determined with respect to the direct effect of epoetin lambda (rch) as distinct from its effect on red cell mass.

The response to epoetin lambda (rch) is dose related and individual. With excessive erythropoietic response to Novicrit, dosing should be stopped and treatment begun as described above (see PRECAUTIONS, Hypertension and Seizures). Phlebotomy may be performed if excessively high haemoglobin levels occur. Additional supportive care should be provided as necessary.

PRESENTATION AND STORAGE CONDITIONS

Novicrit is supplied as a clear, colourless solution in a single-dose, pre-filled syringe. The pre-filled syringes are ready-to-use. The pre-filled syringes are fitted with a needle shield device.

Packs of 1 syringe or 6 syringes in the following presentations:

Novicrit Solution for Injection 1,000/0.5mL pre-filled syringe
Novicrit Solution for Injection 2,000/1.0mL pre-filled syringe
Novicrit Solution for Injection 3,000/0.3mL pre-filled syringe
Novicrit Solution for Injection 4,000/0.4mL pre-filled syringe
Novicrit Solution for Injection 5,000/0.5mL pre-filled syringe
Novicrit Solution for Injection 6,000/0.6mL pre-filled syringe
Novicrit Solution for Injection 7,000/0.7mL pre-filled syringe
Novicrit Solution for Injection 8,000/0.8mL pre-filled syringe
Novicrit Solution for Injection 9,000/0.9mL pre-filled syringe
Novicrit Solution for Injection 10,000/1.0mL pre-filled syringe

Not all presentations are marketed in Australia.

Store and transport refrigerated (2°C - 8°C). Do not freeze.

Keep the pre-filled syringe in the outer carton in order to protect from light.

For the purpose of ambulatory use, the patient may remove Novicrit from the refrigerator and store it not above 25°C for one single period of up to 3 days.

NAME AND ADDRESS OF THE SPONSOR

Sandoz Pty Ltd
ABN 60 075 449 553
54 Waterloo Road
Macquarie Park
NSW 2113

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POISON SCHEDULE OF THE MEDICINE

Schedule 4 – Prescription Medicine

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (ARTG)

27 January 2010

DATE OF MOST RECENT AMENDMENT

17 March 2017