SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicine is subject to additional monitoring. This triangle will enable the rapid identification of new safety information.

1 NAME OF THE MEDICINAL PRODUCT

Dropoetin Containing 3000 IU/ 0.3 ml SC/IV Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITIONS

Active Pharmaceutical Ingredient:

Epoetin alpha * (recombinant human erythropoietin) 80 - 88 µg / ml (10000 IU / ml)

* Epoetin alpha is a biosimilar produced using the culture of ovarian cells of the Chinese Hamster, genetically modified with recombinant DNA technology.

Excipients:

Sodium chloride 5.5 mg / ml

Monobasic sodium phosphate monohydrate 0.425 mg / ml

Dibasic sodium phosphate heptahydrate 1.85 mg / ml

For other excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Injectable solution in ready-to-use injector

Clear, colorless or yellowish solution

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

- Antianemic
- Treatment of renal anemia related to chronic renal failure in patients undergoing dialysis
- Treatment of symptomatic renal anemia in predialysis patients
- Treatment in patients with Hb ≤ 10 g / dl and subgroup of myelodysplastic syndromes (MDS) RA (refractory anemia), RARS (refractory anemia in ringed-ring sideroblasts) and RCMD (refractory cytopenia multilineage-multiple dysplasia), the use of ESA

agents is indicated in patients with basal EPO levels ≤ 500 MU / ml and blast count <5% in the bone marrow before treatment.

- The target hemoglobin (Hb) level is 10-12 g / dl in the use of DROPOETIN and other ESA (Erythropoiesis Stimulating Agents). The target hemoglobin should not be increased above Hb> 12 g / dl. ESAs should be discontinued when Hb = 12 g / dl.

4.2 Posology and method of administration

Posology / application frequency and duration:

All other causes of anemia (iron, folic acid or vitamin B12 deficiency, aluminum intoxication, infection or inflammation, blood loss, hemolysis, and bone marrow fibrosis due to any cause) should be evaluated and treated before starting treatment of epoetin alpha and when dose increase is decided. To ensure the optimum response of the epoetin to alpha, sufficient iron storage should be provided and iron supplements should be applied if necessary (see section 4.4).

Treatment of symptomatic anemia in adult chronic kidney failure patients

Anemia symptoms and sequelae may differ depending on age, gender, and concomitant medical conditions; The clinical course and condition of each patient should be evaluated by a physician.

The recommended desired hemoglobin concentration range is from 10 g / dl to 12 g / dl (6.2 to 7.4 mmol / l). DROPOETIN should be used to increase hemoglobin to a maximum level of 12 g / dl (7.4 mmol / l). An increase in hemoglobin level above 2 g / dl (1.25 mmol / l) over a four-week period should be avoided. If this happens, appropriate dose adjustment should be made as indicated.

Due to variability in the same patient, individual hemoglobin values may be observed from time to time above and below the desired hemoglobin concentration range for a patient. Hemoglobin variability should be addressed through dose management, taking into account the hemoglobin concentration ranges from 10 g / dl (6.2 mmol / l) to 12 g / dl (7.4 mmol / l).

It should be avoided that the hemoglobin level is constantly above 12 g / dl (6.8 mmol / l). If hemoglobin rises above 2 g / dl (1.25 mmol / l) per month, or if hemoglobin continuously exceeds 12 g / dl (7.4 mmol / l), the dose of DROPOETIN should be reduced by 25%. If hemoglobin exceeds 12 g / dl (7.4 mmol / l), treatment should be discontinued until it falls between 10 g / dl (6.2 mmol / l) to 12 g / dl (7.4 mmol / l) and then DROPOETIN treatment should be restarted at a dose 25% below the previous dose.

Patients should be closely monitored to ensure that the lowest approved dose of DROPOETIN is used to provide adequate control of anemia and anemia symptoms.

Treatment with DROPOETIN is divided into two stages - the initial phase (dose) and the maintenance phase (dose).

Adult hemodialysis patients

In hemodialysis patients with easy intravenous access, intravenous administration is preferred.

Initial phase:

The starting dose is 50 IU / kg 3 times a week.

If necessary, the dose should be increased or decreased by 25 IU / kg (3 times a week) until the desired hemoglobin concentration range from 10 g / dl to 12 g / dl (6.2 to 7.4 mmol / l) is achieved (this should be done at least four weeks apart).

Maintenance phase:

The recommended total weekly dose is between 75 IU / kg - 300 IU / kg.

Appropriate dose adjustments should be made to maintain hemoglobin values within the desired hemoglobin concentration range from 10 g / dl to 12 g / dl (6.2 to 7.4 mmol / l).

Patients with very low baseline hemoglobin levels (<6 g / dl or <3.75 mmol / l) may require higher maintenance doses than patients with an initial anemia less severe (> 8 g / dl or> 5 mmol / l).

Adult kidney failure patients who have not yet been on dialysis

In cases where easy intravenous access cannot be provided, DROPOETIN can be administered subcutaneously.

Initial phase:

Following an initial dose of 50 IU / kg 3 times a week, if necessary, dosage increase in increments of 25 IU / kg 3 times a week until the desired goal is achieved (this should be done in at least four weeks steps).

Maintenance phase:

In the maintenance phase, DROPOETIN can be administered either 3 times a week or once a week or once every 2 weeks in case of subcutaneous administration.

To keep the hemoglobin values at the desired level, appropriate dose and dose ranges should be adjusted: hemoglobin from 10 g / dl to 12 g / dl (6.2 to 7.4 mmol / l). Extending the dose intervals may require an increase in the dose.

The maximum dosage should not exceed 150 IU / kg 3 times a week, 240 IU / kg once a week (up to a maximum of 20,000 IU), or 480 IU / kg every 2 weeks (up to a maximum 40,000 IU).

Adult peritoneal dialysis patients

In cases where easy intravenous access cannot be provided, DROPOETIN can be administered subcutaneously.

Initial phase:

The starting dose is 50 IU / kg 2 times a week.

Maintenance phase:

The recommended maintenance dose is 25 IU / kg - 50 IU / kg in 2 equal injections twice a week. Appropriate dose adjustments should be made to keep hemoglobin values between 10 g / dl and 12 g / dl (6.2 to 7.4 mmol / l) at the desired level.

Pediatric population

Treatment of symptomatic anemia in patients with chronic renal failure undergoing hemodialysis

Anemia symptoms and sequelae may differ depending on age, gender and concomitant medical conditions; The clinical course and condition of each patient should be evaluated by a physician.

The recommended hemoglobin concentration range is between 9.5 g / dl to 11 g / dl (5.9 to 6.8 mmol / l) in pediatric patients. DROPOETIN should be used to increase the hemoglobin to a maximum level of 11 g / dl (6.8 mmol / l). An increase in hemoglobin level over 2 g / dl (1.25 mmol / l) should be avoided over a four-week period. If this happens, appropriate dose adjustment should be made as indicated.

Patients should be closely monitored to ensure that the lowest approved dose of DROPOETIN is used to provide adequate control of anemia and anemia symptoms.

Treatment with DROPOETIN is divided into two stages - the initial phase (dose) and the maintenance phase (dose).

In pediatric hemodialysis patients with easy intravenous access, intravenous administration is preferred.

Initial phase:

The starting dose is 50 IU / kg intravenously 3 times a week.

If necessary, increase or decrease the dose by 25 IU / kg 3 times a week until the desired hemoglobin concentration range from 9.5 g / dl to 11 g / dl (5.9 to 6.8 mmol / l) is achieved (this should be done in at least four weeks steps).

Maintenance phase:

Appropriate dose adjustments should be made to maintain hemoglobin values within the desired hemoglobin concentration range from 9.5 g / dl to 11 g / dl (5.9 to 6.8 mmol / l).

Generally, children under 30 kg require higher maintenance doses than children over 30 kg and adults.

Pediatric patients with initial hemoglobin levels too low (<6.8 g / dl or <4.25 mmol / l) may require higher maintenance doses than patients with higher initial hemoglobin (> 6.8 g / dl or> 4.25 mmol / l).

Route of Administration

Precautions to be taken before using or applying the medicinal product. Wait until it reaches room temperature (15-30 minutes) before use.

Treatment of symptomatic anemia in adult chronic kidney failure patients

In chronic renal failure patients (hemodialysis patients), where intravenous access is routinely available, DROPOETIN is preferred to be administered intravenously.

In cases where intravenous access cannot be easily achieved (patients who have not yet been dialyzed and patients with peritoneal dialysis), DROPOETIN can be administered via subcutaneous injection.

Treatment of symptomatic anemia in pediatric chronic renal failure patients undergoing hemodialysis

In pediatric chronic renal failure patients (hemodialysis patients), where intravenous access is routinely available, DROPOETIN is preferred to be administered intravenously.

Intravenous administration

Apply for at least one to five minutes, depending on the total dose. In hemodialysis patients, a bolus injection can be administered through an appropriate venous access in the dialysis line

during the dialysis session. Alternatively, the injection can be administered through the fistula needle tube at the end of the dialysis session, after which 10 ml of isotonic saline is administered, the tube is washed and the product is injected into the circulation sufficiently.

Slower administration is preferred in patients who respond to treatment with "flu-like" symptoms (see section 4.8).

Do not apply DROPOETIN with intravenous infusion or other drug solutions.

Subcutaneous application

The maximum volume of 1 ml in an injection site should generally not be exceeded. In case of larger volumes, multiple injection sites should be selected.

Injections should be applied to the extremities or anterior abdominal wall.

Where the physician decides that DROPOETIN can be administered safely and effectively by the patient or caregiver, instructions for appropriate dosage and administration should be provided.

As with any other injectable product, check that no particles or color change in the solution.

Additional information on special populations

Kidney failure:

DROPOETIN can be used for the treatment of anemia associated with chronic renal failure in pediatric and adult patients undergoing hemodialysis treatment and in adult patients undergoing peritoneal dialysis.

Liver failure:

DROPOETIN should be used with caution in patients with chronic liver failure.

The safety of DROPOETIN in patients with impaired liver function has not been established.

Pediatric population:

For use in the pediatric population, see the " Posology / application frequency and duration " section.

Geriatric population:

757 of 882 patients recorded in 3 studies conducted in chronic renal failure patients undergoing dialysis were administered epoetin alpha and 125 of them received placebo. 361 (47%) of 757 patients who received alpha in the epoetinine were 65 years and older, and 100 (13%) were 75

years and older. No differences in safety or efficacy were observed between geriatric patients and younger patients. Dosage selection and dose adjustment for elderly patients should be individualized according to the hemoglobin concentration range to be obtained and maintained (See Section 4.2).

4.3 Contraindications

• Hypersensitivity to any of the active ingredients or excipients.

• Patients who develop Pure Red Cell Aplasia (SKHA) mediated by antibodies following treatment with any erythropoietin should not take DROPOETIN or any other erythropoietin (see section 4.4).

• Uncontrolled hypertension.

• Attention should be paid to all contraindications related to the programs before autologous blood donation in patients given DROPOETIN.

• The use of DROPOETIN is contraindicated in patients with severe coronary, peripheral arterial, carotid or cerebral vascular disease, including patients undergoing major elective orthopedic surgery and not participating in the program before an autologous blood donation, including patients who have recently had myocardial infarction or cerebrovascular event.

• Surgical patients who cannot receive adequate antithrombotic prophylaxis for any reason.

• It has been observed that the use of ESA (Erythropoiesis Stimulating Agents) in cancer and cancer-related anemias and cancer-related anemias increases morbidity and mortality. Therefore, ESA (epoetin alpha, epoetin beta, darbepoietin alpha and similar agents) is contraindicated in cancer, cancer-related and cancer chemotherapy-related anemias.

4.4 Special warnings and special precautions for use

WARNING: ESAs INCREASE DEATH, MYOCARD INFARCTION, STROKE, VENOUS TROMBOEMBOLISM, VASCULAR ENTRANCE PATH TROMBOZE AND TUMOR PROGRAM OR RELAPSE RISK.

In chronic kidney patients, erythropoiesis-stimulated agents should be considered to start treatment with hemoglobin levels below 10 g / dl and treatment over 12 g / dl should be discontinued.

The dose should be individualized and the lowest dose sufficient to reduce the need for red blood cell transfusion.

In particular, care should be taken in increasing the dose to reach the target hemoglobin level (10-12 g / dl) in patients who do not respond adequately to treatment.

As with all other therapeutic proteins, there is a potential risk of immunogenicity for DROPOETIN.

General:

Blood pressure should be closely follow-up and monitored in all patients using DROPOETIN. DROPOETIN should be used with caution in the presence of untreated, inadequate or poorly controlled hypertension.

It may be necessary to start or increase antihypertensive therapy during DROPOETIN treatment. If blood pressure cannot be controlled, DROPOETIN treatment should be discontinued.

In patients with previously normal or low blood pressure, hypertensive crisis also occurred during the treatment of epoetin alpha, which immediately followed the attention of a physician and encephalopathy and seizures requiring intensive medical care. Particular attention should be paid as a possible warning sign to a sudden migraine-like headache that sticks like a knife.

Epoetin alpha should also be used with caution in patients with medical conditions associated with a predisposition to seizure activity such as epilepsy, epileptic seizure history or central nervous system infection and brain metastasis.

Increased frequency of thrombotic vascular events (TVE) has been observed in patients using ESA (See Section 4.8). These include venous and arterial thromboses such as deep vein thrombosis, pulmonary embolism, retinal thrombosis, myocardial infarction, and emboli (some

of which have fatal consequences). In addition, cerebrovascular events (including cerebral infarction, cerebral hemorrhage and transient ischemic attacks) have been reported.

The reported risk for TVE should be carefully calculated against the benefits of epoetin alpha treatment, especially in patients who previously had a risk factor for TVE, including a history of obesity and previous TVE (e.g. deep vein thrombosis, pulmonary embolism and cerebrovascular accident).

When treated at hemoglobin concentrations above the target range in the indication for use, hemoglobin levels should be closely monitored in all patients due to fatal outcomes and a potential increase in the risk of thromboembolic events.

The safety and efficacy of epoetin alpha treatment have not been established in patients with underlying hematological disease (e.g. hemolytic anemia, sickle cell anemia, thalassemia).

The safety and efficacy of epoetin alpha treatment have not been established in patients with underlying hematological disease (e.g. hemolytic anemia, sickle cell anemia, thalassemia).

During treatment with DROPOETIN, there may be a moderate dose-dependent increase in platelet count within normal limits. This regresses during ongoing treatment. In addition, thrombocytosis has been reported above normal limits. During the first 8 weeks of treatment, regular monitoring of platelet count is recommended.

In chronic renal failure patients treated with epoetin alphine, hemoglobin levels should be measured regularly until reaching a stable level and periodically after reaching these levels.

In chronic renal failure patients, the rate of increase in hemoglobin should be approximately 1 g / dl (0.62 mmol / l) per month and should not exceed 2 g / dl (1.25 mmol / l) per month to minimize the risk of increased hypertension. When the hemoglobin level approaches 12 g / dl, the dose should be reduced.

Severe cutaneous adverse reactions that can be life-threatening or fatal (SCARs) have been reported in relation to epoetin therapy, including Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN) (see section 4.8). More severe cases have been observed with long-acting epoethins.

During prescribing, patients should be informed about signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of these reactions occur,

DROPOETIN treatment should be terminated immediately and an alternative treatment should be considered.

If a severe cutaneous skin reaction such as SJS or TEN develops due to the use of DROPOETIN, ESA (erythropoietin stimulating agent) therapy should not be restarted in these patients. In patients with chronic renal failure, the maintenance hemoglobin concentration should not exceed the upper limit of the hemoglobin concentration range, as recommended in the section titled "**4.2 Posology and method of administration**".

In chronic kidney patients, ESA (erythropoiesis-stimulating agent) therapy should be considered when the hemoglobin level is below 10 g / dl. The dose should be individualized and used at the lowest dose sufficient to reduce the need for red blood cells transfusion. The target hemoglobin level is between 10-12 g / dl. In particular, care should be taken in increasing the dose to reach the target hemoglobin level in patients who do not respond adequately to treatment.

Patients with chronic kidney failure and an inadequate hemoglobin response to ESA therapy may be more at risk for cardiovascular events and death than other patients. Patients with chronic renal failure treated with epoetin alpha subcutaneously should be regularly monitored for loss of efficacy, defined as no response or reduced response to epoetin alpha treatment in patients who previously responded to this treatment. This is characterized by a continuous decrease in hemoglobin level despite an increase in the dose of epoetin alpha (see section 4.8).

Some patients whose epoetin alpha dosage ranges are extended longer (longer than once a week) may not maintain adequate hemoglobin levels (see section 5.1) and may require an increase in the dose of epoetin alpha. Hemoglobin levels should be monitored regularly.

According to information obtained to date, the use of epoetin alpha in predialysis (end-stage renal failure) patients does not increase the rate of progression of kidney failure.

Shunt thrombosis has occurred in hemodialysis patients, especially in patients with a tendency to hypotension or complications of arterio-venous fistulas (e.g. stenosis, aneurysm, etc.). In these patients, early shunt revision, for example, thrombosis prophylaxis with the application of acetylsalicylic acid is recommended.

Although there is no causal relationship in individual cases, hyperkalaemia has been observed. Serum electrolytes should be monitored in patients with chronic renal failure.

If high or rising serum potassium levels are noticed, in addition to the appropriate treatment of hyperkalaemia, the administration of epoetin alpha should be considered until the serum potassium level is corrected.

As a result of the increase in hematocrit, hemodialysis patients using epoetin alpha need to increase the heparin dose frequently during dialysis. If heparinization is not optimal, the dialysis system may be blocked.

All other causes of anemia (iron, folic acid or vitamin B12 deficiency, aluminum intoxication, infection or inflammation, blood loss, hemolysis, and bone marrow fibrosis due to any cause) should be evaluated and treated before starting treatment with epoetin alpha and when deciding on an increase in dose.

In many cases, ferritin values in serum decrease simultaneously with an increase in hematocrit. It should be ensured that sufficient stock of iron is available to ensure that the epoetin has the most appropriate response to alpha; iron supplements should be applied when it is necessary.

• If serum ferritin levels are below 100 ng / ml in patients with chronic renal failure, iron supplementation (200-300 mg / day orally for adults; elementary iron 100-200 mg / day orally for children) is recommended.

Very rarely, it has been observed that porphyria first appears or intensifies in patients treated with epoetin alpha. Epoetin alpha should be used with caution in patients with porphyria.

In order to improve traceability of erythropoiesis-stimulating agents (ESA), the trade name of the administered ESA should be clearly recorded (or specified) in the patient file. Patients should be passed from one ESA to another only under appropriate supervision.

ESAs are mainly growth factors that stimulate red blood cell production. Erythropoietin receptor can be found on the surface of various tumor cells. As with all growth factors, there is concern that ESAs can stimulate tumor growth.

In patients planning major elective orthopedic surgery, iron supplements (elemental iron 200 mg / day by mouth) should be administered during the treatment of epoetin alpha. If possible, iron supplements should be initiated prior to treatment of epoetin alpha to reach adequate iron stores.

Pure Red Cell Aplasia (SKHA)

Antibody-mediated SKHA has been rarely reported months to years after the subcutaneous epoetin therapy in patients with chronic renal failure.

When used with ESAs, cases have also been rarely reported in patients with hepatitis C treated with interferon and ribavirin. ESAs are not approved for the treatment of hepatitis C-related anemia.

Reticulocyte counts should be performed in patients with chronic kidney failure who develop sudden loss of efficacy, defined as a decrease in hemoglobin (1 to 2 g / dl per month) with increased need for blood transfusion, and typical causes of non-response (e.g. iron, folate or vitamin B12 deficiency, aluminum intoxication, infection or inflammation, blood loss, hemolysis and bone marrow fibrosis due to any cause) should be investigated.

A paradoxical decrease in hemoglobin level and the development of severe anemia associated with low reticulocyte counts require immediate cessation of epoetin alpha treatment and an anti-erythropoietin antibody test. Bone marrow examination should also be considered for the diagnosis of SCHA.

In order to ensure the traceability of biosimilar products, the trade name and serial number of the applied product must be recorded in the patient file.

No other ESA therapy should be initiated due to the risk of cross-reaction.

This medicinal product contains less than 1 mmol (23 mg) sodium per dose; that is, it is considered essentially free of sodium.

4.5. Interactions with other medicinal products and other forms of interaction

There is no evidence that treatment with epoetin alpha changes the metabolism of other drugs.

Since cyclosporine is bound to erythrocytes, it has the potential to interact with epoetin alpha.

If DROPOETIN is given simultaneously with cyclosporine, blood cyclosporine levels should be monitored and the dose of cyclosporine adjusted as hematocrit rises.

There is no evidence of interaction between epoetin alpha and Granulocyte Colony Stimulating Factor (G-CSF) or Granulocyte Macrophage Colony Stimulating Factor (GM-CSF) in terms of proliferation or hematological differentiation of tumor cells in biopsy samples in vitro.

The use of 40000 IU / ml epoetin alpha and trastuzumab (6 mg / kg) with subcutaneous route in adult female patients with metastatic breast cancer did not affect the pharmacokinetics of trastuzumab.

The effect of epoetin alpha can be enhanced by simultaneous therapeutic application of a hematinic agent such as ferro sulfate when there is a deficiency.

Drugs that reduce erythropoiesis can reduce the response to DROPOETIN.

Additional information on special populations

No interaction research has been conducted on special populations.

Additional information on pediatric populations

No interaction research has been conducted on the pediatric population.

4.6. Pregnancy and lactation

General advice

Pregnancy category: C

Women with childbearing potential / Contraception

In some female patients with chronic kidney failure, menstrual bleeding has resumed following the treatment of epoetin alpha; potential pregnancy probability should be discussed and the need to prevent pregnancy should be evaluated.

Pregnancy period:

There are no adequate and controlled studies in pregnant women.

Reproductive toxicity has been demonstrated in animal studies (see section 5.3). The potential risk for humans is unknown.

DROPOETIN should not be used during pregnancy unless clearly necessary. In chronic kidney failure patients, DROPOETIN should be used during pregnancy only if the potential benefit to be obtained is more important than the potential risk for the fetus.

Lactation period:

It is not known whether exogenous epoetin alpha passes into breast milk in humans. Epoetin alpha should be used with caution in women who are breastfeeding their baby. The decision to continue / discontinue breastfeeding or to continue / discontinue treatment of epoetin alpha should be made taking into account the benefit of breast milk for the child and the benefit of the epoetin alpha treatment for the mother.

Reproductive ability / Fertility

It is not known whether DROPOETIN treatment affects fertility in humans.

4.7. Effects on the ability to drive and use machines

No studies on the effect of epoetin on alpha's ability to drive and use machines have been performed. However, patients may be advised to be careful when performing such activities.

4.8 Undesirable effects

Security Profile Summary

The most common adverse drug reaction during treatment with epoetin alpha is a dose-dependent increase in blood pressure or worsening of existing hypertension. Especially at the beginning of treatment, blood pressure monitoring should be done (see section 4.4).

The most common adverse drug reactions observed in clinical trials with epoetin alpha are hyperpotasemia, diarrhea, nausea, headache, venous and arterial thrombosis, rash, arthralgia, extremity pain, shaking and reactions at the injection site. A flu-like illness can occur especially at the start of treatment.

In studies in which the dosage range is extended in adult renal failure patients who have not yet received dialysis, respiratory tract congestion including upper respiratory tract congestion, nasal congestion and nasopharyngitis events has been reported.

An increase in the incidence of thrombotic vascular event (TVO) has been observed in patients undergoing ESA (see section 4.4).

Adverse reactions table

DROPOETIN's overall safety profile was evaluated in 228 patients treated with epoetin alpha in four kidney failure studies (2 studies were performed before dialysis [N = 131 patients with CKF] and 2 studies were performed during dialysis [N = 97 patients with CKF]) and with

chronic kidney failure (CKF). Adverse drug reactions reported by patients treated with ≥ 1% of epoetin alpha in this study are shown in the following table.

Frequencies are defined as follows:

Very common (≥1 / 10); common (≥1 / 100 to <1/10); uncommon (≥1 / 1.000 to <1/100); rare (≥1 / 10,000 to <1 / 1,000); very rare (<1 / 10,000); unknown (cannot be estimated from the available data).

Blood and lymphatic system disorders

Rare: Pure red cell aplasia[3] mediated by erythropoietin antibodies, thrombocytopenia

Metabolism and nutritional diseases

Uncommon: Hyperpotasemia[1]

Immune system diseases

Uncommon: Hypersensitivity[3]

Rare: Anaphylactic reaction

Nervous system disorders

Common: Headache

Uncommon: Convulsions

Vascular diseases

Common: Hypertension, venous and arterial thrombosis[2]

Not known: hypertensive crisis[3]

Respiratory, thoracic and mediastinal disorders

Common: Cough

Uncommon: congestion in the respiratory tract

Gastrointestinal diseases

Very common: Diarrhea, nausea, vomiting

Skin and subcutaneous tissue disorders

Common: Rash

Uncommon: Urticaria[3]

Not known: angioneurotic edema[3]

Musculoskeletal system, connective tissue and bone diseases

Common: Arthralgia, bone pain, myalgia, pain in extremities

Congenital and hereditary / genetic diseases

Rare: Acute porfiria[3]

General disorders and diseases related to the application site

Very common: Pyrexia

Common: Tremors, flu-like illness, reaction at the injection site, peripheral edema

Not known: drug ineffectiveness[3]

Research

Rare: Positive Anti-erythropoetin antibody

[1] Common in dialysis patients

[2] Arterial and venous, lethal and non-lethal events (e.g. deep vein thrombosis, pulmonary embolism, retinal thrombosis, arterial thrombosis [including myocardial infarction], cerebrovascular events [cerebral infarction and cerebral hemorrhage], transient ischemic attacks, shunt thrombosis [diarrheal hardware] including] and thrombosis in arteriovenous shunt aneurysms).

[3] It is discussed in the following subsection and section 4.4.

Definition of selected adverse reactions

Hypersensitivity reactions, including rash cases (including urticaria), anaphylactic reactions, and angioneurotic edema have been reported.

Violent cutaneous adverse reactions have been reported in relation to epoetin therapy, including Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN) (see section 4.4).

Life threatening or fatal violent cutaneous adverse reactions have been reported in relation to epoetin therapy, including Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN) (see section 4.4).

In patients with normal or low blood pressure, hypertensive crisis that accompanied by encephalopathy and seizure and requiring emergency doctor intervention and intensive medical care, was observed during treatment of epoetin alpha. As a possible warning sign, attention should be paid to migraine-like headaches in the form of sudden stubs (see section 4.4).

Pure red cell aplasia mediated by antibodies has been reported very rarely after months-years of treatment with DROPOETIN (<1/10000 cases per patient year) (see section 4.4).

Pediatric patients with chronic renal failure undergoing hemodialysis treatment

In clinical trials and experience gained after the drug is placed on the market, exposure to the drug is limited in pediatric patients with chronic renal failure and hemodialysis. In this patient population, pediatric-specific adverse reactions or adverse reactions not attributable to the underlying disease have not been reported in the table above.

Reporting of suspected adverse reactions

It is very important to report suspected adverse reactions after registration. Reporting allows continuous monitoring of the drug's benefit / risk balance.

4.9. Overdose and treatment

The therapeutic range of DROPOETIN is very wide. Overdose of epoetin alpha can lead to effects that increase the pharmacological effects of the hormone. If excessively high hemoglobin levels occur, phlebotomy can be performed. Supplementary treatment methods should be applied when necessary.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Other antianemic preparations

ATC code: B03XA01

DROPOETIN is a biosimilar product.

5.1. Pharmacodynamics properties

Mechanism of action

Erythropoietin (EPO) is a glycoprotein hormone produced primarily in the kidney in response to hypoxia and is the key regulator of erythrocyte production. EPO plays a role in all stages of erythroid cell line development.

It shows its main effect at the level of erythroid serial precursor cells. Once the EPO binds to the cell surface receptor, it activates signal transduction pathways that interact with apoptosis and stimulates erythroid cell proliferation.

Recombinant human EPO (epoetin alpha) expressed in Chinese hamster ovarian cells has 165 amino acid sequences that are equivalent to human urinary EPO. Neither of these can be distinguished by functional measurement. The virtual molecular weight of erythropoietin is 32000-40000 waves.

Erythropoietin is mainly a growth factor that stimulates erythrocyte production. Erythropoietin receptors can be expressed on the surface of various tumor cells.

Pharmacodynamics effects

Healthy volunteers

A dose-dependent response was observed in pharmacodynamics indicators, including reticulocytes, erythrocytes, and hemoglobin, after alpha doses (subcutaneously between 20000-160000 IU) of single epoietin. A concentration-time profile defined with peak and return to basal values was observed in terms of reticulocyte change percentages. A less defined profile was observed for erythrocyte and hemoglobin. In general, all pharmacodynamics indicators increase linearly with dose, reaching maximum response at the highest dose levels.

In further pharmacodynamics studies, 40000 IU once a week was compared with 150 IU / kg 3 times a week. Despite differences in concentration-time profiles, the pharmacodynamics responses measured as changes in hemoglobin, total erythrocyte and reticulocyte percentage in these regimens were similar. Other studies have compared doses between 40000 IU epoetin alpha once a week and 80000 and 120000 IU administered subcutaneously once every two

weeks. In general, based on the results of the pharmacodynamics studies conducted in healthy subjects,

although reticulocyte production is similar in applications once a week and once every two weeks, once a week, 40000 IU dosing regimen has the impression that it is more effective for erythrocyte production.

Chronic renal failure

Epoetin alpha has been shown to induce erythropoiesis in patients with CRF, dialysis or anemia before dialysis. The first evidence of epoetin alpha response was an increase in reticulocyte count within 10 days; this is usually followed by an increase in erythrocyte count, hemoglobin and hematocrit within 2-6 weeks. The hemoglobin response varies from patient to patient; It can be affected by iron stores and the presence of other diseases.

Clinical efficacy and safety

Chronic renal failure

Epoetin alpha has been explored to treat anemia and to keep the hematocrit within the target concentration range of %30-%36, including patients with CKF and anemia, including those who received pre-dialysis and dialysis treatment.

In clinical trials, approximately 95% of patients responded with a clinically significant increase in hematocrit at baseline doses of 50-150 IU / kg three times a week. Almost all patients became independent from transfusion after approximately two months of treatment. After reaching the target hematocrit, the maintenance dose is individualized for each patient.

In the three largest clinical trials with adult patients in dialysis therapy, the average maintenance dose required to maintain hematocrit between 30-36% was approximately 75 IU / kg 3 times a week.

In a double-blind, placebo-controlled, multicenter quality of life study in patients with chronic renal failure undergoing hemodialysis treatment; patients treated with epoetin alpha have been shown to have clinical and statistically significant improvement in the criteria of weakness, physical symptoms, relationships, and depression (Kidney Disease Questionnaire) after six months of treatment compared to the placebo group. Patients treated with epoetin alpha participated in an open-label extension study; In this study, it was shown that the positive improvement in the quality of life continued for an additional 12 months.

Adult patients with kidney failure and have not yet received dialysis

In clinical trials in predialysis patients with chronic kidney failure and treated with epoetin alpha, the mean duration of treatment was approximately five months. These patients responded

to the treatment of epoetin alpha similar to that observed in patients on dialysis. In predialysis patients with chronic renal failure, hematocrit has been shown to have a dose-dependent and permanent increase in when epoetin alpha administered intravenously or subcutaneously. When epoetin alpha was administered by either of two ways, close increase rates in hematocrit were determined. In addition, epoetine alpha doses of 75-150 IU / kg per week have been shown to keep hematocrit between 36% and 38% for up to six months.

In two studies (3 times a week, once a week, once every 2 weeks and once every four weeks) where the dosage range of DROPOETIN was extended, some patients with longer dosage ranges could not maintain adequate hemoglobin levels and reached hemoglobin withdrawal symptoms or withdrawal symptoms defined in the protocol (0% once a week in the group, 3.7% once in a 2-week group, and 3.3% once in a 4-week group).

In a randomized prospective trial (CHOIR), 1432 patients with chronic anemia and anemia without dialysis were evaluated. The patients were divided into alpha treatment groups by targeting 13.5 g / dl (above the recommended hemoglobin concentration level) or 11.3 g / dl maintenance hemoglobin level. The major cardiovascular event (hospitalization due to death, myocardial infarction, stroke or congestive heart failure) occurred in 125 of 715 patients (18 %) in the higher hemoglobin group; in 97 (14 %) of 717 patients in the lower hemoglobin group (hazard ratio [HR] 1.3, 95% CI: 1.0, 1.7, p = 0.03).

Chronic kidney failure in pediatric patients

Epoetin alpha was evaluated in an open-label, non-randomized, open-dose, 52-week clinical study in pediatric patients undergoing hemodialysis and chronic renal failure. The average age in patients enrolled in the study is 11.6 (0.5 to 20.1 years old).

Epoetin alpha administered 75 IU / kg per week intravenously in doses divided into 2 or 3 after dialysis, with a 1 g / dl increase per month in hemoglobin; It was titrated with a dose of 75 IU / kg per week at 4-week intervals, with a maximum of 300 IU / kg per week. The desired hemoglobin concentration range was 9.6-11.2 g / dl. The desired level of hemoglobin concentration was achieved in 81% of patients. The average time to goal is 11 weeks, and the average dose when reaching the goal is 150 IU / kg / week. In 90% of the patients who achieve the target, the application regime is 3 times a week.

Fifty-two weeks later, 57% of patients who received an average weekly dose of 200 IU / kg continued to study.

5.2. PHARMACOKINETİC PROPERTIES

General Properties

Absorption

After subcutaneous injection, serum epoetin alpha levels reach their peak within 12-18 hours of dosing. No accumulation was observed subcutaneously weekly after multiple doses of 600 IU / kg.

The absolute bioavailability of subcutaneous injectable epoetin alpha is about 20% in healthy individuals.

Distribution

The average distribution volume after healthy doses of 50 and 100 IU / kg intravenously is 49.3 ml / kg. In patients with chronic renal failure, after intravenous administration of epoetin alpha, the volume of distribution is 57-107 ml / kg with a single dose of 12 IU / kg; It ranged from 42 to 64 ml / kg with multiple doses ranging from 48 to 192 IU / kg. Therefore, the volume of distribution is slightly larger than the plasma range.

Metabolism:

No data are available.

Elimination

Half-life of epoetin alpha is approximately 4 hours after multiple doses intravenously in healthy individuals. The half-life for the subcutaneous route was calculated to be approximately 24 hours in healthy subjects.

For healthy individuals, the average CL / F for the regimens of 150 IU / kg 3 times a week and 40000 IU once a week were 31.2 and 12.6 ml / hour / kg, respectively. The average CL / F was 45.8 and 11.3 ml / hour / kg, respectively, in groups with cancer anemia with 40000 IU once a week and 150 IU / kg three times a week. In most patients with anemia who had cancer and cyclic chemotherapy, CL / F was found to be lower than in healthy subjects after administration of 40000 IU once a week and 150 IU / kg 3 times a week.

Linearity / Nonlinear State:

In healthy individuals, a dose-proportional increase in serum epoetin alpha concentrations was observed after administration of doses of 150 and 300 IU / kg 3 times a week intravenously. Administration of single doses of epoetin alpha between 300-2400 IU / kg subcutaneously resulted in a linear relationship between the mean Cmax and dose, and the average AUC and

dose. In healthy volunteers, an inverse relationship was observed between virtual clearance and dose.

In studies for increasing the dose range (40000 IU once a week and 80000, 100000 and 120000 IU once every two weeks), a linear but not proportional relationship was observed between the mean Cmax and dose at steady state and between the mean AUC and dose.

Pharmacokinetic / Pharmacodynamics relationships:

Epoetin alpha has a dose-related effect on hematological parameters, regardless of the route of administration.

Characteristic features in patients

Pediatric patients:

In pediatric patients with chronic renal failure, a half-life of approximately 6.2-8.7 hours has been reported after multiple intravenous epoetin alpha administration. The impression is that the pharmacokinetic profile of epoetin alpha in children and adolescents is similar to that in adults.

Kidney dysfunction:

The half-life of epoetin alpha administered intravenously is slightly longer in chronic renal failure patients compared to healthy people, by approximately 5 hours.

5.3. Preclinical safety data

In some repeated dose toxicology studies on dogs and rats (except monkeys), treatment of epoetin alpha has been associated with subclinical bone marrow fibrosis.

Bone marrow fibrosis is a known complication of chronic kidney failure in humans; it may be associated with secondary hyperparathyroidism or unknown factors. In one study, there was no difference in the frequency of bone marrow fibrosis in hemodialysis patients treated with epoetin alpha for 3 years and hemodialysis patients not treated with epoetin alpha.

Long-term carcinogenicity studies have not been conducted. Conflicting reports in the literature state that erythropoietins may play a role like a tumor proliferator based on *in vitro* findings from human tumor samples. The significance of this in clinical conditions is uncertain.

It has been shown that epoetin alpha does not stimulate bacterial (Ames Test) and mammalian cell culture mutagenicity tests (chromosomal aberration) and does not cause any changes in the in vivo micronucleus test in mice.

In human bone marrow cell cultures, epoetin alpha specifically stimulates erythropoiesis and does not affect leukopoiesis. No cytotoxic effect of epoetin alpha on bone marrow cells was detected.

In experimental studies, epoetin alpha has been shown to reduce fetal body weight, delay ossification and increase fetal mortality when given weekly doses approximately 20 times the recommended weekly dose for humans. It has been interpreted that these changes are secondary to a decrease in maternal body weight, and their significance is uncertain for people given therapeutic dose levels.

6.PHARMACEUTICAL PROPERTIES

6.1. List of Excipient

Polysorbate 20

Propylene glycol

the Glycine

D-mannitol

Sodium chloride

Monobasic sodium phosphate monohydrate

Dibasic sodium phosphate heptahydrate

Water for Injection

6.2. Incompatibility

It should not be diluted or transferred to another container. It should not be given with other drug solutions or by intravenous infusion.

6.3. Shelf Life

24 months

6.4. Special precautions for storage

Stored between 2 °C- 8 °C. It should not be frozen and shaken. It should be protected from light.

6.5. The nature and content of the packaging

Ready-to-use glass injector with injection needle

Dropoetin 3000 IU / 0.3 ml SC / IV Ready-to-Use Syringe with Solution for Injection:

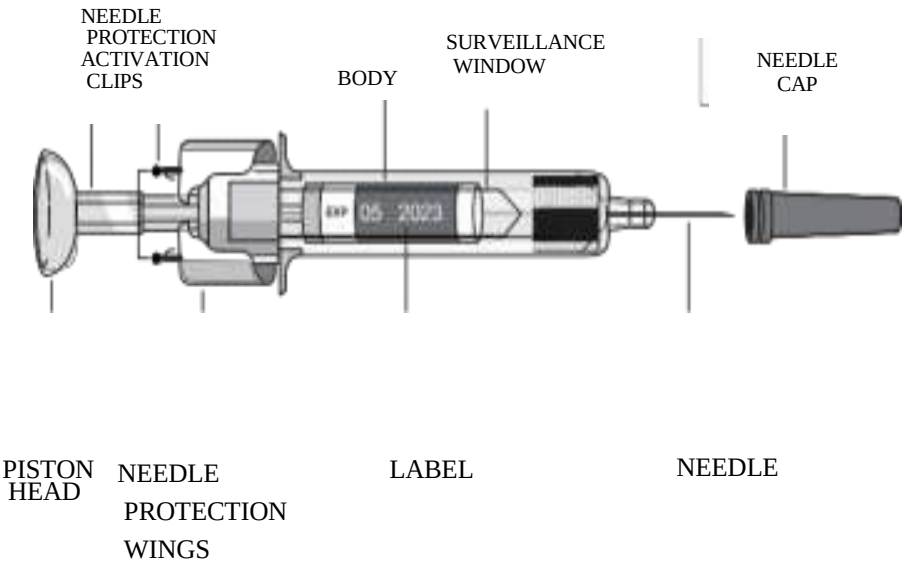
3000 IU / 0.3 ml Syringe; It is available in 6 syringes.

6.6. Disposal of residual substances from the medicinal product and other special precautions

Products or waste materials that have not been used must be disposed of in accordance with the "Medical Waste Control Regulation" and "Packaging and Packaging Waste Control Regulation".

Figure 1 shows the syringe ready for use.

PISTON



Instructions on how to inject DROPOETIN into yourself

Instructions on how to inject DROPOETIN into yourself

When treatment begins, DROPOETIN injection is usually administered by the medical treatment or care team. Your doctor may then advise you to learn how to inject DROPOETIN under the skin (subcutaneously) or your caregiver to learn.

- **Do not try to inject yourself until you know how to do this from your doctor or nurse.**
- **Always use DROPOETIN strictly according to the instructions of your doctor or nurse.**
- **Only use DROPOETIN if it has been stored correctly “5. See "Storing DROPOETIN".**
- **Allow the DROPOETIN syringe to stand until it reaches room temperature before use. It usually takes 15 to 30 minutes to reach this temperature.**

Take only one dose of DROPOETIN from each syringe.

If DROPOETIN is injected subcutaneously, the amount injected is normally at most one milliliter (1 ml) in a single injection.

DROPOETIN should be applied alone and not mixed with other injection liquids.

Do not shake the DROPOETIN syringe. Shaking quickly for a long time can damage the product.

This product should not be used if it is shaken rapidly.

How can you apply the injection to yourself using a ready-to-use syringe? :

Ready-to-use syringes are equipped with the PROTECS^{TM} needle protection device to help prevent needle-tip injuries after use. This is indicated on the packaging.

- **Take a syringe from the refrigerator.** The liquid should come to room temperature. Do not remove the syringe needle cap while waiting for it to reach room temperature.
- **Check the syringe** to make sure it is the correct dose, the expiration date has not passed, is not damaged, and the liquid is clear and not frozen.
- **Choose an injection site.** Suitable places are the upper part of the thigh and the abdomen; but it should be far from the navel. Change the injection site on each application day.
- **Wash your hands. Apply an antiseptic cotton or gauze bandage over the injection site** to disinfect.
- **Hold the filled syringe ready for use, with the capped needle facing up, from the body of the syringe.**
- **Do not hold the piston head, piston, needle guard flaps, or needle cap.**
- **Never withdraw the piston.**
- **Do not remove the needle cap from the ready-to-use syringe until you are ready to inject your DROPOETIN.**
- **Remove the cap** of the syringe by holding the syringe body and pulling the cap off carefully. Do not push the piston, touch the needle, or shake the syringe.
- **Do not touch the needle activation clips (shown in Figure 1) to prevent the needle from closing prematurely with the needle protector.**
- Hold a **layer of skin** between your thumb and forefinger. Do not squeeze.
- **Push the needle in fully.** Your doctor or nurse may have shown you how to do this.
- **Push the piston with your thumb until all liquid can be injected. While holding** the skin layer firmly, push it slowly and steadily**. The PROTECS^{TM} needle protection**

device will not activate unless the entire dose is administered. You may hear a clicking sound when the PROTECS™ needle guard is activated.

- **When the piston is pushed as far as it can go,** pull the needle out and release the skin.
- **Slowly pull your thumb out of the piston** and allow the syringe to move upward until the entire needle is surrounded by the PROTECSTM needle guard.
- **When the needle is pulled from your skin, there may be some bleeding at the injection site. It's normal.** You can press an antiseptic cotton or bandage over the injection site for a few seconds after the injection.
- **Throw the syringe you are using in a** safe container - "See "5.How to store DROPOETIN?".

7. MARKETING AUTHORIZATION HOLDER

LG Chem. Ltd. licensed with
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8.MARKETING LICENCE NUMBER

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9.FIRST MARKETING LICENCE DATE/ LICENCE RENEWAL DATE

First Marketing License Date: 24.09.2013
License Renewal Date:

10.RENEWAL DATE OF THIS DOCUMENT

06/03/2019