표시자재 표준화판 EV4PH-221027-T02_03

제 품 명	Epokine 4000IU Vial (필리핀) 인서트	본사 담당	등록팀	고아라 님 / 02-6477-0227		
규격(장 / 폭 / 고)	170 × 265 (mm)	인쇄소 담당	성지피앤씨	이창준 님 / 010-3752-3375		
인 쇄 도 수	1도 (Black)	원고 담당	로직앤매직	이현지 / 02-558-8970		
	Black		담당자 확인		팀장 확인	
수 정 내 역	0_개정번호 변경(변경전: EV4PH-210728-T01), 24 May 2019 -> 18 May 2021로 변경, 제품명 수정, 비주얼바	검토 및 승인	QA			
	이동, 4000 Units : 부분 20 October 2015, 18 May 2021 둘다 기재, store at 2~8 문안을 CONDITION 옆으로					
	표기, Foods~문안 For ~문안 밑에 표기, 12항 문구 추가, 2000과 4000은 아래 날짜 수정, Foods~ 문구 하단		QC			
	에 문구추가, Korea -> Republic of Korea 문구 변경 1_성지종합인쇄 -> 성지피앤씨 2_HEMATOGROWTH ~		제조부서			
	> Anti-anaemic 문안 수정, 10000IU 갱신 일자 업데이트 3_AVAILABILITY 문안 수정		생산관리			
			QA책임자			

에이치케이이노엔주식회사

EV4PH-221027-T02

EPOETIN ALFA

EPOKINE®

SOLUTION FOR INJECTION (IV/SC)

Anti-anaemic Preparations

EPOKINE is a recombinant human erythropoietin, type-α, which is produced by HK inno.N Corporation Korea. It is a glycoprotein hormone which stimulates the division and differentiation of committed erythroid progenitors in the bone marrow.

EPOKINE has the same biological and immunological effect as endogenous erythropoietin and contains the identical amino acid sequence of isolated natural erythropoietin.

• FORMULATION

Active Ingredient :

Recombinant human erythropoietin 1,000 Units/ 2,000 Units/ 3,000 Units/ 4,000 Units/6,000 Units/ 10,000 Units (Host : CHO cell, Vector : pSVEp2neo)

Excipients : Human serum albumin 2.5mg/ mL
Sodium chloride 5.84mg/mL
Sodium dihydrogen phosphate dihydrate 1.164mg/mL
Disodium phosphate dihydrate 2.225mg/mL
Water for Injection q.s.

• PRODUCT DESCRIPTION

EPOKINE is a sterile, clear, colorless aqueous solution in glass containers (vial or prefilled syringe).

• INDICATIONS

(Injection)

*Limited to EPOKINE prefilled injection and EPOKINE injection

1. Treatment of Anemia of Chronic Renal Failure Patients

1) symptomatic anemia
2) anemia requiring blood transfusion

2. Treatment of Anemia in Cancer Patients on Chemotherapy

3. Patients participating in autologous blood donation program : EPOKINE is indicated to elevate the red blood cell level to donate autologous blood. EPOKINE is also indicated to prevent from reducing of hemoglobin for the patients scheduled to major surgery who are not able to participate in an autologous blood donation program.

Case :

1) low hemoglobin concentration
2) when the scheduled major surgery requires a large volume of blood (4 or more units of blood for females or 5 or more units for males).
3) in case of short time before surgery to donate autologous blood

• DOSAGE & MODE OF ADMINISTRATION

(Injection)

* Limited to EPOKINE prefilled injection and EPOKINE injection

Other causes of anaemia, such as vitamin deficiency, metabolic or chronic inflammatory conditions, bleeding, should be excluded before instituting therapy with epoetin alfa.

1) Chronic Renal Failure (CRF) Patients

EPOKINE is administered intravenously or subcutaneously at an initial dose of 50units/kg three times a week. In adult patients with CRF not on dialysis, EPOKINE may be given either as an intravenous or subcutaneous injection. The dose increase is dependent upon the initial response. The dose can be increased, if necessary, by 25units/kg in 4-weeks period. If hemoglobin is increased greater than 2g/dL at a dose of 50units/kg, the frequency should be reduced to two times a week. To correct the anemia, the target concentration of hemoglobin is 10g/dL (30% as hematocrit). When the anemia is corrected, EPOKINE is given as a maintenance dose of 25~50 units/kg two times a week or three times a week. The target range of hemoglobin is known to be 10~11 g/dL. The patients whose initial hemoglobin is low (<6g/dL) require higher maintenance dose than the patients whose initial hemoglobin is > 8g/dL, and the dose may be adjusted according to the age of patients. The unit dose of EPOKINE should not exceed 200units/kg, and the frequency should not be more than three times a week. Iron status should be evaluated prior to and during treatment and iron supplementation administered if necessary. If the patients are in aluminum intoxication or infected, delayed or diminished responses may be occurred. In patients with CRF not on dialysis, the maintenance dose must also be individualized according to the severity of anemia or age, however, the dose of 70~150 units/kg per week have been shown to maintain 36~38% of hematocrit for more than six months. During the maintenance phase in the case of subcutaneous administration, EPOKINE, can be administered either 2 ~ 3 times per week, and once weekly by physician's judgment.

2) Cancer Patients on Chemotherapy

The initial dose is 150 units/kg given subcutaneously 3 times per week. If the response is unsatisfactory after 8 weeks of therapy, the dose of EPOKINE can be increased up to 300 units/kg three times a week. If patients have not responded satisfactorily to an EPOKINE dose of 300units/kg three times a week, it is unlikely that they will respond to higher doses of EPOKINE. If the hematocrit exceeds 36%, discontinue therapy until it falls to 36%. The dose of EPOKINE should be reduced by 25% when treatment is resumed or the dose is titrated to maintain the desired hematocrit level. If the initial dose of EPOKINE includes a very rapid hemotocrit response (e.g. an increase of greater than 4% points in any 2- week period), the dose should be reduced. From the clinical study results, in general, patients with lower baseline serum erythropoietin levels responded more vigorously to EPOKINE than patients with higher erythropoietin levels. Although no specific serum erythropoietin level can be stipulated above which patients would be unlikely to respond to EPOKINE therapy, treatment of patients with grossly elevated serum erythropoietin levels higher than 200 mU/mL is not recommended. The hematocrit should be monitored on a weekly basis in patients receiving EPOKINE therapy until hematocrit becomes stable.

3) Patients to be Participated in an Autologous Blood Donation Program

Prior to major surgery, it is recommended to take autologous blood two times a week for 3 weeks. Based on previous studies, EPOKINE can be given intravenously at a dose of 150~300units/kg, two times a week for 3 weeks to elevate the red blood cell levels. The recommended maximum dose to promote erythropoiesis is 600 units/kg, two times a week for 3 weeks intravenously; for example, the patients who are expected to require ≥ 4 units of blood with pretreatment of hemoglobin ≤ 11 g/dL (Hb ≤ 6.8 mmol/L), or the patients require ≥ 5 units of blood with pretreatment hemoglobin ≥ 11 g/dL (Hb ≥ 6.8 mmol/L), or the patients to be scheduled to surgery within 1~3 weeks.

The concentration of hemoglobin should be controlled on a weekly basis.

Iron supplementation : All surgery patients being treated with EPOKINE should receive adequate iron supplementation (e.g., 200mg of iron preparations per day, P.O) throughout the course of therapy. Iron supplementation should be initiated as soon as possible, several weeks before taking blood for the purpose of sufficient iron stores

• PRECAUTION

(Injection)

1. Warnings

1) Use the lowest dose of EPOKINE that will maintain the minimum hemoglobin concentration to avoid red blood cell transfusions.
2) EPOKINE increase the risk for death and for serious cardiovascular events when administered this drug to target the hemoglobin of greater than 12g/dL(11g/dL in case of the patients with chronic renal failure)
3) EPOKINE increase the risk for death and shorten the time to tumor progression when administered to target a hemoglobin of greater than 12g/dL in patients with advanced head and neck cancer receiving radiation therapy, metastatic breast cancer receiving chemotherapy, and active tumor disease receiving neither chemotherapy nor radiation therapy.
4) A higher incidence of deep venous thrombosis was observed in patients with receiving epoetin pre-operatively for reduction of allogeneic red blood cell transfusion.

2. Contraindications

1) Patients who develop pure red cell aplasia (PRCA) following treatment with erythropoietin should not receive this drug or any other erythropoietin.
2) Hypersensitivity to the active substance or to any of the excipients
3) Uncontrolled hypertension.
4) Known hypersensitivity to mammalian cell-derived products or human serum albumin.

3. EPOKINE should be administered with caution to the following patients

1) Patients with hypertension (Blood pressure may rise or hypertensive encephalopathy may occur during EPOKINE therapy.)
2) Patients with known history of a hypersensitivity to drugs
3) Patients with known history of allergic reactions to drugs
4) Patients with myocardial infarction, pulmonary infarction, cerebral infarction, or history of those diseases (It may reportedly increase blood viscosity and aggravate or cause thromboembolism. If particularly used for self-blood deposit or postoperative, it may increase blood coagulability, which requires sufficient observation.).
5) Patients with intraventricular hemorrhage or premature infant with intraventricular hemorrhage (cerebral hemorrhage may become worse).
6) Patients with ischaemic cardiovascular disease
7) Patients with history of paroxysm
8) Patients with epilepsy
9) Patients with thrombocytosis
10) Patients with chronic hepatic failure

4. Adverse reactions

1) Shock : Rarely shock and anaphylactic hypersensitivity(urticaria, dyspnoea, lip edema, pharynx edema and etc) may occur, patients should be monitored closely. If the symptoms appear, the administration should be discontinued and an appropriate treatment should be taken.
2) Cardiovascularsystem
   (1) High blood pressure, thrombosis at the contact site of blood vessel such as fistula, and tachycardia may occur.
   (2) Hypertensive encephalopathy, cerebral hemorrhage: As hypertensive encephalopathy such as headache, conscious disorder and seizures by sudden increase of high blood pressure have been reported and relapse to cerebral hemorrhage occasionally when epoetin treated, EPOKINE should be administered cautiously with observation of the trends of blood pressure and hematocrit during the therapy.
   (3) Cerebral infarction, myocardial infarction, pulmonary infarction : As cerebral infarction, myocardial infarction, pulmonary infarction may occur, patients should be monitored closely. If the symptoms appear, the administration should be discontinued and an appropriate treatment should be taken.
3) Seizure : In clinical studies, seizures were observed in patients receiving erythropoietin. Among adult dialysis patients, seizure incidence was higher in initial administration of 90 days than later stage (almost 2.5% of patients). In early 90 days of administration, monitor patients closely for blood pressure and neurologic symptoms. Patients should be refrained from driving or handling heavy equipment. Relationship between seizure and hematocrit value is unsure but if hematocrit value is increased over 4% in 2 weeks, dosage should be reduced.
4) Liver : Dyshepatia accompanied by elevation in AST, ALT, γ-GTP, LDH, ALP, bilirubin, and icterus have been reported, patients should be monitored closely. If the symptoms appear, the administration should be discontinued and an appropriate treatment should be taken.
5) Skin : Itching, skin rash and acne may occur occasionally.
6) G.I. : Nausea, retching, vomiting, anorexia, and diarrhea may occur occasionally.
7) Blood :
   (1) On occasion, increase of white blood cell, eosinophil and platelet may occur.
   (2) On occasion, granulocytopenia and richekts may be occurred in premature infant.
   (3) Cases of PRCA have been reported rarely in CRF patients after treatment of erythropoietin for a few months or years.
8) CNS and Sensory system: Dizziness, bitter taste in the mouth, headache, migraine, fatigue, chills, fever, hot flashes, burning feeling, general malaise, arthralgia, myalgia, and insomnia may occur occasionally.
9) Others : Retinal hemorrhage (retinal thrombosis in veins and arteries), nasal congestion, epistaxis, occasionally elevation in serum potassium level, BUN, creatinine, and uric acid, edema, convulsion, palpebral edema may occur.
10) Studies analyzed to date indicate that epoetin is generally well-tolerated. The adverse reactions reported are frequent sequelae from patient's disease and are not necessarily attributable to epoetin therapy.

① Patients with Chronic Renal Failure

In double-blind, placebo-controlled studies involving over 300 patients with CRF, the reactions reported in greater than 5% of patients treated with epoetin during the blinded phase were :

Adverse Reaction	Patients-Treated with epoetin(N=200)	PLACEBO-Treated Patients(N=135)
Hypertension	24.0%	18.5%
Headache	16.0%	11.9%
Arthralgias	11.0%	5.9%
Nausea	10.5%	8.9%
Edema	9.0%	10.4%
Fatigue	9.0%	14.1%
Diarrhea	8.5%	5.9%
Vomiting	8.0%	5.2%
Chest Pain	7.0%	8.8%
Skin Reaction (Administration site)	7.0%	11.9%
Asthenia	7.0%	11.9%
Dizziness	7.0%	12.6%
Clotted Access	6.8%	2.3%

Significant adverse reactions of concern in patients with CRF treated with in double-blinded, placebo-controlled trials occurred in the following percent of patients during the blinded phase of the studies :

Adverse Reaction	Patients-Treated with epoetin(N=200)	PLACEBO-Treated Patients(N=135)
Seizure	1.1%	1.1%
CVA/TIA	0.4%	0.6%
MI	0.4%	1.1%
Death	0%	1.7%

In the epoetin studies in patients on dialysis(N =567), the incidence of the most frequently reported adverse reactions were : hypertension(0.75%), headache(0.40%), tachycardia(0.31%), nausea/vomiting(0.26%), clotted vascular access(0.25%), shortness of breath(0.14%), hyperkalemia(0.11%), and diarrhea(0.11%). Other reported reactions occurred at a rate of less than 0.10% of reactions per patient per year. Reactions reported to have occurred within several hours after administration of epoetin were rare, mild, and transient, and included stab at injection site in patients on dialysis and flu-like symptoms such as arthralgias and myalgias. In all studies analyzed to date, epoetin administration was generally well-tolerated, irrespective of the route of administration.

② Cancer patients on chemotherapy

In double-blind, placebo-controlled studies of up to 3-month duration involving 131 cancer patients, adverse reactions with an incidence ≥ 10% in either patients treated with epoetin or placebo-treated patients were as indicated below.

Adverse Reaction	Patients-Treated with epoetin(N=200)	PLACEBO-Treated Patients(N=135)
Pyrexia	29%	19%
Diarrhea	21%	7%
Nausea	17%	32%
Vomiting	17%	15%
Edema	17%	1%
Asthenia	13%	16%
Fatigue	13%	15%
Shortness of breath	13%	9%
Paresthesia	11%	6%
Upper respiratory infection	11%	4%
Dizziness	5%	12%
Trunk pain	3%	16%

Although some statistically significant differences between patients treated with epoetin and placebo-treated patients were noted, the overall safety profile of epoetin appeared to be consistent with the disease process of advanced cancer. In clinical studies of patients (N=72)treated with dose as high as 927 units/kg of EPOKINE for 32 weeks, the adverse reaction profile of epoetin was consistent with the progression of advanced cancer. Based on comparable survival data and on the percentage of patients treated with epoetin and placebo-treated patients who discontinued therapy due to death, disease progression or adverse reactions (22% and 13%, respectively ; p=0.25), the clinical outcome in patients treated with epoetin and placebo-treated patients appeared to be similar. Available data from animal tumor models and measurement of proliferation of solid tumor cells from clinical biopsy specimens in response to epoetin suggest that epoetin does not potentiate tumor growth. Nevertheless, as a growth factor, the possibility that epoetin may potentiate growth of some tumors, particularly myeloid tumors, cannot be excluded. There was no change in peripheral white blood cells in patients treated with this drug compared to the placebo group.

11) (Excluding EPOKINE prefilled injection) In Korea, post-marketing surveillance was conducted with total 2064 patients, and adverse reactions were reported from 75 patients(3.6%). The most frequent adverse reaction was elevation of blood pressure (28 cases), and dyspnea, thrombosis, headache, elevation of serum potassium, itching, nausea, and etc were reported. Each 1 case of arteriovenous graft occlusion, cerebral hemorrhage were reported as serious adverse reactions. Mild exfoliative dermatitis (unknown causality), cough, hematuria were reported as unexpected adverse reactions.
12) (For 'EPOKINE prefilled injection' only) From post-marketing surveillance of this drug for 4 years with total of 637 patients in Korea, 55 cases (8.63%) of adverse reactions were reported in 35 patients.23 cases (5.9%) of adverse reactions were reported in 13 patients.Unknown symptoms in adverse reactions that have not been reported are cough and insomnia.

5. General precautions

1) EPOKINE treatment should be limited to anemic patients with CRF or cancer (it is limited only to EPOKINE indicated for patients with cancer) who are interfered with their daily lives. Moreover, initiate EPOKINE treatment in renal anemic patients when the hemoglobin is less than 10 g/dL (30% as hematocrit value) and in cancer patients when serum erythropoietin is less than 200mUnit/mL.
2) Effect on tumor growth: erythropoietin is a primary growth factor to facilitate erythropoiesis. Erythropoietin acceptor may appear on surface of tumor cells. Like all growth factor, erythropoietin may promote growth of malignant tumor. With other erythropoietin drug, unexpected death was observed with head and neck cancer patients and breast cancer patients in controlled two clinical studies.
3) In the clinical study (targeted to maintain hematocrit value 42±3% or 30±3%) of 1265 patients with cardiovascular disease (ischemic heart disease, congestive heart failure) on dialysis, the test group targeted to maintain hematocrit value 42% (221 out of 634 patients died, death rate 35%) had higher death rate than the test group targeted to maintain hematocrit value 30% (185 out of 631 patients died, death rate 29%). The reason for increased death rate is unknown, however, myocardial infarction (3.1% ; 2.3%), vascular thrombosis(39% ; 29%) and other thrombosis(22% ; 18%) showed higher rate for test group of 42% hematocrit value.
   In placebo-controlled study of adult patient undergoing coronary artery bypass graft surgery (CABG) not having CRF, 7 patients died in erythropoietin treatment group of 126 patients, while no patients died in placebo group.4 death cases out of the death cases were related to thrombosis. The risk should be carefully weighed against the benefit to be derived from treatment with epoetin alfa particularly in patients with risk of thrombosis.
4) In EPOKINE treatment, confirm renal anemia and do not administer EPOKINE in case of other types of anemia (e.g. anemia due to blood loss, pancytopenia, aluminum accumulation, vitamin B12 or folic acid deficiency anemia). Caution should be taken because vitamin B12 or folate deficiencies may reduce efficacy of EPOKINE.
5) Ask a sufficient amount of detailed questions to predict such reactions as shock. Moreover, Before initiation EPOKINE therapy or administration the first dose after the withdrawal period, it is desirable to give intravenous injection of a small dose to confirm that no abnormal reaction is observed before administering the whole dose.
6) During EPOKINE treatment, hemoglobin concentration or hematocrit should be periodically monitored (once a week at the early stage of treatment; every two weeks in maintenance period). Special cautions should be taken not to result in excessive erythropoiesis (hemoglobin concentration higher than 12g/dL or hematocrit value higher than 36%). If more erythropoiesis than necessary is recognized, the administration should be discontinued and an appropriate treatment should be taken.
7) As EPOKINE treatment may lead to increase in blood pressure and to hypertensive encephalopathy, blood pressure, hematocrit, hemoglobin concentration should be monitored carefully and administer. In particular, cautions should be taken so that hematocrit and hemoglobin concentration shall rise slowly. Hematocrit may rise after EPOKINE treatment is discontinued, monitoring should be performed carefully. Accordingly, blood pressure should be carefully monitored in patients, especially patients with cardiovascular disease or patients who have possibility of hypertension. Excessive rise of hematocrit may aggravate hypertension in patients whose hematocrit rises rapidly (greater than 4% increase over 2 weeks) due to EPOKINE therapy. Consideration should be given to appropriate dose adjustment such as reducing the dose of EPOKINE.
8) Seizure was observed in CRF patients participating in clinical study of EPOKINE. In patients on dialysis, there was a higher incidence of seizure during the first 90 days of therapy (occurring in approximately 2.5% of patients) as compared with later time points. In double blind, placebo-controlled trials, 3.2% (N=2/63) of patients treated with epoetin and 2.9% (N=2/68) of placebo-treated patients had seizure. Seizures in 1.6% (N=1/63) of patients treated with epoetin occurred in the context of a significant increase in blood pressure and hematocrit from baseline values. However, both patients treated with epoetin also had underlying CNS pathology which may have been related to seizure activity. Given the potential for an increased risk of seizures during the therapy, blood pressure and the presence of premonitory neurologic symptoms should be monitored closely.
9) Since hyperkalemia in CRF patients may be occurred due to EPOKINE therapy, the concentration of potassium in blood should be monitored regularly along with proper diet during EPOKINE therapy. If hyperkalemia is occurred, discontinue the administration until the serum potassium level has been corrected.
10) Care should be taken with shunt and flow rate of dialysis equipment since shunt occlusion and residual blood in dialysis equipment may occur by EPOKINE therapy. In those cases, take appropriate treatment including revision of shunt and increasing dose of anticoagulant.
11) Since iron status may affect the efficacy of EPOKINE, iron status should be evaluated prior to and during treatment and iron supplementation administered if necessary.
12) EPOKINE is a growth factor to stimulate erythropoiesis. However, the possibility that EPOKINE can act as a growth factor for any tumor type, particularly myeloid malignancies, cannot be excluded.
13) Antibody-mediated pure red cell aplasia (PRCA) has been rarely reported after months to years of epoetin treatment mainly in chronic renal failure patients. The intravenous (IV) route is recommended in patients with CRF where intravenous access is readily available, since PRCA has been reported predominantly in patients receiving ESAs by subcutaneous administration. Anti-erythropoietin antibodies were observed predominately in patients who developed PRCA. In patients developing sudden lack of efficacy, typical causes of non-response (e.g. iron, folate or Vitamin B12 deficiency, aluminium intoxication, infection or inflammation, blood loss and haemolysis) should be investigated. A bone marrow examination should also be considered if it is failed to find out causes. Discontinue treatment with EPOKINE in patients with who are diagnosed with PRCA, and anti-erythropoietin antibody testing should be considered. No other erythropoietin therapy should be switched because anti-erythropoietin antibodies cross-react with other erythropoietin drugs.

6. Interaction with other medicinal products and other forms of interaction

1) No evidence exists that indicates that treatment with epoetin alfa alters the metabolism of other drugs. However, since cyclosporin is bound by RBCs there is potential for a drug interaction. If epoetin alfa is given concomitantly with cyclosporin, blood levels of cyclosporin should be monitored and the dose of cyclosporin adjusted as the haematocrit rises.
2) If epoetin alfa is give concomitantly with hematopoietics, the efficacy of EPOKINE may be increased.
3) If epoetin alfa is give concomitantly with antihypertensive drugs, EPOKINE may lower the hypotensive effect.

7. Pregnancy and lactation

1) In the animal test with rats, when a dose 20 times more than the one-week dose for human beings was administered as a one-week dose, the decrease in fetal weight loss, delayed ossification, and the increase in mortality showed.
2) In the animal test with rabbits, when a high dose in 500 units per kg of body weight was administered between 6 and 18 days of pregnancy, there were no adverse reaction.
3) Since the safety of epoetin in pregnancy has not been established, it is desirable not to administer it to pregnant women or those likely to become pregnant. But if required, administer it only if therapeutic benefits exceed risks.
4) Since it is uncertain if epoetin are transferrable to milk, it is desirable not to administer EPOKINE to nursing mother.
5) There is no appropriate clinical experience of administering epoetin to human beings in pregnancy or nursing conditions.

8. Pediatric Use

No safety of epoetin in children have not been established.

9. Geriatric Use

When epoetin are administered, dosage and frequency should be controlled on the basis of observed blood pressure and hemoglobin concentration or hematocrit for several times since geriatric patients have declined physiological functions on the average and complication with circulatory diseases such as hypertension.

10. Overdose & Treatment

The dose response of EPOKINE depends upon the conditions of patient. In case of overdosage, hypertension and erythrocytosis may be occurred. If polycythemia (excessive increase in hemoglobin value) is of concern, phlebotomy may be indicated.

11. Precautions in administration

1) Do not dilute. Do not mix with other drug solutions
2) Administer EPOKINE after dialysis in patients on dialysis and a slower injection longer than 5 minutes is preferable in patients who react to the treatment with "flu-like" symptoms.
3) Do not administer by intravenous infusion.
4) Let the drug reaches room temperaturebefore use. Usually takes 15~30 minutes.

12. CLINICAL PHARMACOLOGY

1) Pharmacodynamics

Epokine increases the reticulocyte count within 10 days of initiation, followed by increases in the RBC count, hemoglobin, and hematocrit, usually within 2 to 6 weeks. The rate of hemoglobin increase varies among patients and is dependent upon the dose of Epokine administered. For correction of anemia in hemodialysis patients, a greater biologic response is not observed at doses exceeding 300 Units/kg 3 times weekly.

2) Pharmacokinetics

In adult and pediatric patients with CKD, the elimination half-life (t1/2) of plasma erythropoietin after intravenous administration of Epogen ranged from 4 to 13 hours. After subcutaneous administration, Cmax was achieved within 5 to 24 hours. The t1/2 in adult patients with serum creatinine greater than 3 mg/dL was similar between those not on dialysis and those maintained on dialysis. The pharmacokinetic data indicate no apparent difference in Epogen t1/2 among adult patients above or below 65 years of age.

A pharmacokinetic study comparing 150 Units/kg subcutaneous 3 times weekly to 40,000 Units subcutaneous weekly dosing regimen was conducted for 4 weeks in healthy subjects (n = 12) and for 6 weeks in anemic cancer patients (n = 32) receiving cyclic chemotherapy. There was no accumulation of serum erythropoietin after the 2 dosing regimens during the study period. The 40,000 Units weekly regimen had a higher Cmax (3-to 7-fold), longer Tmax (2-to 3-fold), higher AUC0-168 h (2-to 3-fold) of erythropoietin and lower clearance (CL)(50%) than the 150 Units/kg 3 times weekly regimen. In anemic cancer patients, the average t1/2 was similar (40 hours with range of 16 to 67 hours) after both dosing regimens. After the 150 Units/kg 3 times weekly dosing, the values of Tmax and CL were similar (13.3 ± 12.4 vs. 14.2 ± 6.7 hours, and 20.2 ± 15.9 vs. 23.6 ± 9.5 mL/hr/kg) between week 1 when patients were receiving chemotherapy (n = 14) and week 3 when patients were not receiving chemotherapy (n = 4). Differences were observed after the 40,000 Units weekly dosing with longer Tmax (38 ± 18 hours) and lower CL (9.2 ± 4.7 mL/hr/kg) during week 1 when patients were receiving chemotherapy (n = 18) compared with those (22 ± 4.5 hours, 13.9 ± 7.6 mL/hr/kg, respectively) during week 3 when patients were not receiving chemotherapy (n = 7).

• STORAGE CONDITION

Store at temperatures not exceeding 2-8°C.
Shelf Life: 24 months

• AVAILABILITY

Epokine is supplied in prefilled-syringes (Box of 6's) or vials (Box of 10's).

FDA Reg. No.:	*Renewal of the Authorization:*
EPOKINE (Prefilled - Inj.)	**EPOKINE (Prefilled - Inj.)**
- 2000 IU/ 0.5mL : BRP-104	- 2000 IU/ 0.5mL : 06 July, 2022
- 4000 IU/ 0.4mL : BRP-103	- 4000 IU/ 0.4mL : 06 July, 2022
- 10,000 IU/ mL : BRP-102	- 10,000 IU/ mL : 23 November, 2022
EPOKINE (Inj.-Vials)	**EPOKINE (Inj.-Vials)**
- 4000 IU/ mL : BRP-101	- 4000 IU/ mL : 07 January 2022

For suspected adverse drug reaction, report to FDA: www.fda.gov.ph
Seek medical attention immediately at the first sign of any adverse drug reaction.
Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.
Date of Revision of Package Insert: November 2022

Manufactured by : HK inno.N Corporation
811, Deokpyeong-ro, Majang-myeon, Icheon-si, Gyeonggi-Do, Republic of Korea
Imported and Distributed by : MACROPHARMA CORPORATION
90 Upper Gondola, San Francisco Village, Muzon, Taytay, Rizal

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