Patient Information Leaflet

EFESA
Efepoetin alfa 0,3mg / 0,3mL ; Efepoetin alfa 0,6mg/ 0,6mL

Injeksi subkutan

Baca seluruh isi *leaflet* dengan cermat sebelum Anda menggunakan obat ini karena di dalam *leaflet* ini terdapat informasi penting untuk Anda.

- Simpan *leaflet* ini, mungkin suatu saat Anda perlu membacanya kembali.
- Apabila Anda memiliki pertanyaan lebih lanjut, tanyakan pada dokter atau apoteker.
- Obat ini hanya diresepkan untuk Anda. Tidak boleh memberikan obat ini pada orang lain karena akan membahayakan, meskipun orang tersebut memiliki gejala yang sama seperti Anda.
- Apabila muncul efek samping, segera hubungi dokter atau apoteker. Termasuk efek samping yang tidak tercantum di dalam *leaflet* ini.

Apa saja yang terdapat pada *leaflet* ini?

1. Apa itu EFESA dan apa kegunannya

EFESA merupakan cairan jernih dan tidak berwarna untuk injeksi yang dikemas dalam pre-filled syringe dosis tunggal. EFESA mengandung Efepoetin alfa sebagai zat aktif yang merupakan *recombinant human erythropoietin-hybrid Fc fusion protein*, yang berasal dari sel *Chinese Hamster Ovary* (CHO) dengan teknik rekombinan DNA. EFESA injeksi *prefilled syringe* digunakan sebagai terapi anemia pada penyakit ginjal kronik (PGK) tanpa dialisis. Anemia adalah kondisi kekurangan sel darah merah atau hemoglobin (zat yang mengangkut oksigen di dalam sel darah merah) dengan gejala yang umum berupa kelelahan, lemah dan napas yang pendek. Pada PGK, ginjal tidak dapat memproduksi hormon *erythropoietin* yang cukup sehingga menyebabkan anemia.

2. Apa yang perlu anda ketahui sebelum menggunakan EFESA

Bagian berikut berisi informasi yang Anda, dokter dan apoteker harus pertimbangkan sebelum Anda menggunakan EFESA.

EFESA tidak boleh digunakan pada pasien dengan kondisi berikut:

- Hipertensi yang tidak terkontrol

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- Hipersensitivitas terhadap kandungan EFESA atau obat lain yang mengandung *erythropoietin*
- Hipersensitivitas terhadap produk yang berasal dari sel mamalia atau pembawanya
- Pasien yang mengalami kejadian *Pure Red Cell Aplasia (PRCA)* setelah pengobatan dengan eritropoietin, pasien yang karena alasan apa pun tidak dapat menerima profilaksis antitrombotik yang memadai

Peringatan:

- Dosis yang diberikan adalah dosis terkecil yang mampu mempertahankan kadar hemoglobin (Hb) dan tidak memerlukan transfusi darah.
- Setelah pemberian obat, jika kadar Hb darah melebihi 12 g/dL, akan meningkatkan risiko terjadi efek samping berat pada sistem jantung dan pembuluh darah serta risiko kematian.
- Penggunaan terapi eritropoietin (EPO) yang diberikan sebelum operasi untuk tujuan mengurangi transfusi sel darah merah, cukup sering menyebabkan kejadian penyumbatan pembuluh darah vena dalam.
- Setelah beberapa bulan hingga tahun setelah pemberian EPO secara subkutan untuk pasien penyakit gagal ginjal kronik (PGK), kejadian terbentuknya antibodi terhadap PRCA jarang terjadi. Namun jika dicurigai antibodi terhadap PRCA terbentuk, maka penggunaan EFESA harus segera dihentikan. Terapi erythropoiesis stimulating agent (ESA) lain tidak boleh diberikan karena risiko terjadinya reaksi silang. Pada kondisi ini, terapi transfusi darah dapat diberikan apabila diperlukan.
- Pada semua pasien, pemantauan konsentrasi Hb harus dipantau secara ketat karena terdapat potensi peningkatan risiko kejadian penyumbatan pembuluh darah dan kejadian fatal pada pasien dengan konsentrasi Hb diatas nilai target.

Perhatian khusus:

Penggunaan harus diberikan dengan hati – hati kepada setiap pasien dengan:

- Anemia ginjal yang menerima terapi EPO
- Hipertensi (beberapa laporan kejadian peningkatan tekanan darah setelah pemberian EPO, oleh karena itu pasien dengan hipertensi harus mengikuti pengobatan antihipertensi dan kontrol pola hidup sehat selama menggunakan obat ini)
- Riwayat alergi terhadap obat – obatan
- Memiliki kecenderungan alergi
- Penyakit penyumbatan pembuluh darah jantung, paru, dan otak (terdapat laporan mengenai kejadian penyumbatan pembuluh darah akibat pemberian obat ini, obat ini berisiko menyebabkan atau memperburuk kondisi penyumbatan pembuluh darah
- Penyakit hati (obat ini akan dieliminasi melalui organ hati, sehingga pasien dengan gangguan hati yang aktif dapat dipertimbangkan untuk tidak menggunakan obat ini)
- Keamanan dan khasiat EFESA belum diketahui pada pasien dengan penyakit kelainan darah (seperti anemia hemolitik, anemia sel sabit, talasemia)
- Pasien dengan kondisi kejang – kejang (epilepsi)
- Jika Anda sedang hamil atau merencanakan kehamilan, mintalah saran dokter atau apoteker Anda sebelum menggunakan obat ini.
- Jika Anda sedang menyusui atau berencana untuk menyusui, mintalah saran dokter atau apoteker Anda sebelum menggunakan obat ini. Tidak diketahui apakah EFESA diekskresikan dalam air susu.

Interaksi Obat lain dengan EFESA

Informasikan kepada dokter atau apoteker Anda mengenai obat lain yang sedang Anda gunakan, belum lama digunakan, atau yang mungkin akan digunakan, baik obat yang diresepkan, vitamin dan suplemen herbal.

3. Bagaimana cara penggunaan EFESA

Selalu gunakan EFESA sesuai dengan petunjuk dokter atau apoteker Anda. Diskusikan dengan dokter atau apoteker Anda jika Anda merasa ragu.

Setelah melakukan pemeriksaan darah, dokter Anda akan memutuskan untuk memberikan EFESA karena kadar hemoglobin Anda adalah 10 g/dL atau kurang dari 10 g/dL.

Jika Anda adalah pasien dengan penyakit ginjal kronik tanpa dialisis

Dosis awal EFESA yang umumnya diberikan adalah 4 mcg/kgBB, secara injeksi tunggal subkutan setiap 2 minggu sekali. Target Hb yang ingin dicapai adalah 10-12 g/dL.

Dosis EFESA akan dinaikan sebesar 25% bila peningkatan kadar Hb kurang dari 1 g/dL dalam 4 minggu. Dosis maksimal yang dapat diberikan adalah 8 mcg/kgBB, jika diperlukan.

Jika peningkatan kadar Hb lebih besar dari 1 g/dL dalam 2 minggu atau peningkatan kadar Hb lebih besar dari 2 g/dL dalam 4 minggu atau kadar Hb meningkat melebihi 11,5 g/dL, maka dosis EFESA harus dikurangi 25%.

Jika kadar Hb melebihi 12 g/dL maka pemberian EFESA akan dihentikan sementara dan mulai kembali diberikan saat kadar Hb ≤ 11,5 g/dL, dengan dosis EFESA dikurangi 25% dari dosis sebelumnya.

Untuk dosis pemeliharaan, setelah tercapai target kadar Hb 10-12 g/dL dapat menggunakan dosis yang sama seperti pada dosis setiap 2 minggu, atau menjadi setiap 4 minggu dengan menggandakan dosis setiap 2 minggu.

Dokter akan melakukan pengecekan darah secara teratur untuk mengetahui bagaimana kondisi anemia Anda dan untuk melakukan penyesuaian dosis jika diperlukan.

Pastikan tekanan darah Anda sudah diperiksa sesuai dengan petunjuk dokter, terutama pada saat memulai terapi.

Selama terapi menggunakan EFESA, ikuti petunjuk dokter atau apoteker Anda terkait pola makan dan obat-obatan yang digunakan.

Jika Anda menggunakan EFESA lebih dari yang seharusnya

- Jika Anda menggunakan EFESA lebih dari yang diinstruksikan oleh dokter, segera hubungi dokter Anda.

Jika Anda lupa menggunakan EFESA

- Jika Anda melewatkan dosis EFESA, segera hubungi dokter Anda dan diskusikan kapan Anda harus menggunakan dosis berikutnya.

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4. Apa saja efek samping yang mungkin terjadi

Seperti obat-obatan lainnya, obat ini dapat menyebabkan efek samping, meskipun tidak terjadi pada setiap orang.

EFESA dapat menyebabkan efek samping:

- Sistem saraf pusat: sakit kepala, pusing, kesemutan hingga mati rasa dan kecemasan.
- Secara umum dan pada tempat suntikan: nyeri tempat suntikan, menggigil, merasa kedinginan atau kepanasan.
- Kulit: bibir melepuh, kemerahan, urtikaria, gatal di tempat suntikan, papul (permukaan kulit yang menonjol), dermatitis seboroik (gangguan kulit kepala yang menyebabkan kulit bersisik, berketombe dan berwarna kemerahan).
- Sistem saluran cerna: rasa tidak nyaman di ulu hati, dispepsia, rasa tidak nyaman di bagian perut, diare, mual, muntah, nyeri rongga perut, nyeri pada gusi, sariawan, sakit gigi dan konstipasi.
- Sistem pernapasan: sesak, sesak pada posisi tertentu, efusi pleura (adanya penumpukan cairan di pleura paru), edema paru (pembengkakan paru), infeksi saluran napas atas, batuk, sumbatan di hidung, nyeri orofaring, rhinorrhea (keluarnya lendir dari lubang hidung yang berlebihan), iritasi tenggorokan.
- Kelainan metabolisme dan nutrisi: hiperkalsemia (kadar kalsium darah di atas nilai normal), hiperglikemia (kadar gula darah di atas nilai normal), hipoglikemia (kadar gula darah di bawah nilai normal).
- Sistem muskuloskeletal: patah tulang pergelangan kaki, arthralgia (nyeri sendi), peradangan jaringan bawah kaki, nyeri otot, leher dan lutut serta peradangan tulang rawan
- Pembuluh darah: mimisan, perdarahan gusi, hipertensi, hipotensi akibat posisi tertentu
- Ginjal: poliuria (sering buang air kecil), disuria (nyeri pada saat buang air kecil)
- Sistem reproduksi: peradangan prostat

Efek samping yang telah disebutkan bukan merupakan semua efek samping yang mungkin terjadi dari penggunaan EFESA. Informasikan kepada dokter atau apoteker bila Anda mengalami efek samping yang mungkin terkait dengan pemberian EFESA.

5. Bagaimana cara penyimpanan EFESA

EFESA disimpan pada kulkas suhu 2-8^{o}C, telindung dari cahaya, tidak dibekukan, dan hindari pengocokkan.

6. Apa yang terkandung dalam EFESA

Zat aktif	: Efepoetin alfa
Zat tambahan	: Sodium klorida, asam sitrat anhidrat, sodium sitrat dihidrat, glisin, polisorbat 20, dan cairan injeksi.

7. Informasi lainnya

Kemasan

- Dus, 1 pre-filled syringe @ 0,3 mL
- Dus, 1 pre-filled syringe @ 0.6 mL

Reg No. DKL2358500143A1

HARUS DENGAN RESEP DOKTER

Diproduksi dan didaftarkan oleh:

PT Kalbio Global Medika

Jl. Soka Delta Silicon 3, Lippo Cikarang Blok F-19 No.002

Kelurahan Cicau, Kabupaten Bekasi

Jawa Barat, Indonesia 17530

EFESA

Subcutaneous injection

DRUG NAME

Common Name : Efepoetin alfa

Product Name : EFESA

Dosage forms : sterile liquid, injection, single dose pre-filled syringe

CHARACTERISTIC/ PRESENTATION

EFESA is a clear and colorless solution

COMPOSITIONS

Active Ingredients: Efepoetin alfa, a recombinant human erythropoietin-hybrid Fc fusion protein, prepared from Chinese Hamster Ovary (CHO) cells by DNA recombinant technique.

Excipients: sodium chloride, citric acid anhydrate, sodium citrate dihydrate, glycine, polysorbate 20, and water for injection.

Prepared in 2 strengths:

Efepoetin alfa 0.3 mg (0.3 mL)

Efepoetin alfa 0.6 mg (0.6 mL)

INDICATION

EFESA is indicated for the treatment of anemia in non-dialysis Chronic Kidney Disease (CKD) patients.

DOSAGE AND ADMINISTRATION

In adult patients, EFESA is administered with recommended starting dose for anemia in CKD not on dialysis;

- 4 mcg/kg body weight administered subcutaneously, subsequent doses will be titrated to optimal hemoglobin target and will be administered once every two weeks.
- When initiating or adjusting therapy, monitor hemoglobin levels at least biweekly until stable, then monitor at least monthly. Administer Efesa subcutaneously in the abdomen, arm or thigh.
- If the increase in Hb is less than 1.0 g/dL over 4 weeks and iron stores are adequate, the dose may be increased by approximately 25% of the previous dose. Further increases may be made at 4-week intervals when the Hb is in the specified target Hb range. The maximum dose of Efepoetin alfa is 8 mcg/kg BW, which may be given when it is necessary.
- If the rate of rise in Hb is greater than 2 g/dL in one month or the Hb increases by more than 1.0 g/dL in a 2-week period, the dose should be decreased by approximately 25%.
- If the Hb is increasing and exceeds 11.5 g/dL, the dose should be reduced by approximately 25%.
- If the Hb continues to increase and exceeds 12 g/dL, dosing should be temporarily withheld until the Hb begins to decrease and restart dosing when Hb level falls back to the predetermined Hb level for restarting (ie ≤11.5 g/dL) based on the next scheduled Hb test results, at which point therapy should be reinitiated at a dose approximately 25% below the previous dose.
- During maintenance period, dosage of Efesa should be adjusted to maintain the Hb within the target range (10 g/dL to 12 g/dL). Efesa could be administered using the same every-two-week dose. It could also be administered every-four-week at double the two weekly dosage ***(see Clinical Studies section - study GXE4KGbio-001)***.

Instruction for use and handling

- Do not inject EFESA with other products.
- Before using EFESA prefilled-syringe injection, remove the tip cap.
- Be sure to discard the used residual solution.

CONTRAINDICATION

EFESA is contraindicated for use in patients with:

- Uncontrolled hypertension
- Known hypersensitivity to this drug or other erythropoietin (EPO)
- Known hypersensitivity to mammalian cell-derived product or excipient
- Patients who develop Pure Red Cell Aplasia (PRCA) following treatment with erythropoietin, patients who for any reason cannot receive adequate antithrombotic prophylaxis

WARNINGS AND PRECAUTIONS

Warnings

- A dose capable of maintaining the least blood Hb level not requiring RBC transfusion shall be administered.
- After the drug administration, if the blood Hb level exceeds 12 g/dL, risks of SAEs of the cardiovascular system and death will increase.
- The frequency of deep vein thrombosis was high in patients who used EPOs preoperatively to reduce the transfusion of homologous RBCs.
- Antibody-mediated PRCA has been rarely reported after months to years of subcutaneous epoetin treatment in Chronic Renal Failure patients. If anti-erythropoietin, antibody-mediated PRCA is suspected, therapy with EFESA should be discontinued immediately. No other ESA therapy should be commenced because of the risk of cross-reaction. Appropriate therapy, such as blood transfusions, may be given to patients when indicated.
- In all patients, haemoglobin concentrations should be closely monitored due to a potential increased risk of thromboembolic events and fatal outcomes when patients are treated at haemoglobin concentrations above the range for the indication of use.

Precautions

This product must be carefully administered to any patients with:

- Renal anemia who are receiving EPOs.
- Hypertension (increased blood pressure has been reported after administering Efepoetin alfa, therefore, hypertensive patients must follow antihypertensive treatment and dietary control during treatment with this drug).
- History of drug hypersensitivity.
- Predisposition to allergy.
- Myocardial infarction, pulmonary infarction, and cerebral infarction (since thromboembolism resulting from administration of this drug was reported, this drug has a risk of aggravating or causing thromboembolism).
- Liver disease (Efepoetin alfa is eliminated through the liver, so patients with active liver disease shall be excluded).
- The safety and efficacy of EFESA have not been established in patients with the underlying haematologic disease (e.g haemolytic anemia, sickle cell anemia, thalassemia).
- Epilepsy.

Special cautions for drug administration:

- Avoid co-administering this drug with any other drug.
- Visually inspect to confirm absence of foreign matter or discoloration, if any, before administration, and do not use any syringe where foreign matter is found or if the contents are discolored.
- Do not use any drugs with insoluble matter seen, or if the solution is turbid.
- Never use any drugs that have been opened previously or whose primary package has been damaged.
- Do not attempt to use any fluids that have been frozen.
- To avoid injection site pains, gently inject this drug at different sites at every administration.

INTERACTIONS

Any interactions of other medications with this product have not been studied.

USE IN SPECIAL POPULATION

The safety of this product in pregnant women, infants, and children has not yet been established.

Geriatric use of this product has not been studied, yet. However, according to the literature review, there are many cases of physiological dysfunction and complications of circulatory disorders such as hypertension in elderly people, so it is recommended that during treatment with this product, blood pressure, blood Hb level, or HCT level shall be measured several times, and the dosage shall be properly adjusted.

ADVERSE REACTIONS

Injection site pain was reported as an attributable to treatment in clinical studies where Efepoetin alfa was administered via SC injection. The injection site discomfort was generally mild and transient in nature and occurred predominantly after the first injection. Some of the reported AEs that may occur after the administration of Efepoetin alfa are as follows:

1. Central nervous system: headache, dizziness, paraesthesia, anxiety.
2. General and administration site conditions: chills, feeling cold, feeling hot.
3. Skin: lip blister, rash, urticaria, injection site pruritus, papule, seborrheic dermatitis.
4. Gastrointestinal system: epigastric discomfort, dyspepsia, abdominal discomfort, diarrhea, vomiting, nausea, abdominal pain, gingival pain, stomatitis, toothache, constipation.
5. Respiratory system: dyspnea, orthopnoea, pleural effusion, pulmonary oedema, upper respiratory tract infection, cough, nasal congestion, oropharyngeal pain, rhinorrhea, throat irritation.

6. Metabolism and nutrition disorders: hypercalcaemia, hyperglycaemia, hypoglycaemia.
7. Musculoskeletal system: ankle fracture, arthralgia, plantar fasciitis, myalgia, neck pain, knee pain, costochondritis.
8. Vascular: epistaxis, gingival bleeding, hypertension, orthostatic hypotension.
9. Renal: polyuria, dysuria.
10. Reproductive system: prostatitis.

NON-CLINICAL STUDIES

Reproductive Toxicity

1. Fertility and early embryonic development study

   Study in Rats

Toxicity: Based on the results of toxicological observations and examinations for Efepoetin alfa in rats, the NOAELs (no observed adverse effect level) were at least 50 µg/kg BW/week in both sexes for fertility and 5 µg/kg BW/week for early embryonic development. The approximate HED (human equivalent dose) determined was 8-32 µg/kg BW.

Fertility: There were no treatment-related changes in fertility.

Early embryonic development toxicity: Increased fetal death and post-implantation loss with a decreased live fetus in females at 20 and 50 µg/kg BW were observed.

2. Embryo-fetal development study

a. Study in Rats

Toxicity: Based on the results of toxicological observations and examinations for Efepoetin alfa in rats, the NOAEL for maternal toxicity was observed at 24 µg/kg BW/dose (HED: ~38 µg/kg BW), and for embryo-fetal development, NOAEL was 3 µg/kg BW/dose (HED: ~5 µg/kg BW). Early embryonic development toxicity observed includes decreased fetal weight and skeletal retardation at 8 and 24 µg/kg BW.

b. Study in New Zealand Rabbits

Maternal toxicity observed includes premature delivery/abortion, decreased body weight gain, food consumption, and net body weight change, and embryo-fetal development toxicity including abdominal distension and fluid-filled abdomen were observed at 72 µg/kg BW dose. Based on the results of toxicological observations and examinations for Efepoetin alfa in rabbits, the NOAEL for maternal and embryo-fetal development was considered to be 24 µg/kg BW/dose.

3. Pre/Post-natal development and maternal function study

   Studies in Rats

No treatment-related maternal toxicity was observed. Based on the results of toxicological observations and examinations for Efepoetin alfa in rats, the NOAELs for maternal toxicity and F1 animals were considered to be 24 µg/kg BW/dose (HED: ~38 µg/kg BW) and 8 µg/kg BW/dose (HED: 13 µg/kg BW), respectively.

CLINICAL STUDIES

Phase 1 study (GC1113P1)

A Phase 1, Dose-Block Randomized, Double-blind Placebo controlled, Open-label Active controlled, Dose-escalation Study to investigate the safety, tolerability, and Pharmacokinetics/Pharmacodynamics of GC1113 after Single Intravenous/Subcutaneous Administration in Healthy Male Subjects.

Part A: intravenous

Ten (10) subjects are randomized into 4 dose groups, from group A – group D (8 subjects for the study drug, 2 subjects for placebo). According to each dose group, the study drug or placebo drug are intravenously administered. Dose group X was an open-label trial along with the process of dose group A–D, and 8 subjects were intravenously administered with 30 µg of NESP (Darbepoetin-alfa).

Part B: subcutaneous

Ten (10) subjects (8 study drugs, 2 placebos) were randomized into 4 dose groups, from H – group K, and were subcutaneously administered with the study drug or placebo accordingly. A clinical trial of dose group Y was also spontaneously carried out during the process of groups H–K as an open-label subcutaneous NESP (Darbepoetin-alfa) 30 µg administration in 8 subjects.

Efficacy

Reticulocyte count increased with the intravenous and subcutaneous administration of GC1113 or NESP and was recovered to the baseline. Maximum reticulocyte count was reached at 109– 204 (median) hours after GC1113 0.3, 1, 3, 5 µg/kg groups and at 121 hours (median) in the NESP 30 µg group via intravenous administration. Maximum reticulocyte count was reached at 168–240 hours (median) after GC1113 1, 3, 5, 8 µg/kg groups; and at 168 hours (median) in the NESP 30 µg group via subcutaneous administration. Reticulocyte count slowly increased then decreased in both the GC1113and NESP administration groups, which are greater in the subcutaneous administration group than in the intravenous administration group. Looking at the reticulocyte count calibrated per individual baseline, no big difference was seen from the placebo group baseline. However, the difference in the change was seen to increase according to the administration dose for the GC1113 administration groups.

Hemoglobin generally increased 112 hours after GC1113 administration, but no definite tendency was observed. The average maximum hemoglobin (Emax) range in the GC1113 0.3, 1, 3, 5 µg/kg intravenous administration groups were 15.34–15.83 g/dL and 15.76 g/dL in the NESP 30 µg intravenous administration group. The average maximum hemoglobin (Emax) range in the GC1113 0.3, 1, 3, 5 µg/kg subcutaneous administration groups were 15.36–16.04 g/dL, and 15.39 g/dL in the NESP 30 µg subcutaneous administration group.

No definite tendency was observed in the reticulocyte hemoglobin after GC1113 and NESP administration. The time when the minimum reticulocyte hemoglobin was observed was between 60.01 – 240.03 hours (mean value) for the GC1113 0.3, 1, 3, 5 µg/kg groups and at

66.8 hours (mean value) for the NESP 30 µg group, which were all via intravenous administration. The time was at 18 –168.19 hours (mean value) for the GC1113 1, 3, 5, 8 µg/kg groups and 36.01 hours (mean value) for the NESP 30 µg group of the subcutaneous administration.

Phase 3 Study (GXE4KGbio-001)

This is an open-label, randomized, multicenter, Mircera–controlled, parallel group, Phase 3 study to determine whether subcutaneously administered Efepoetin alfa is as effective and well tolerated as subcutaneous Mircera for anaemia correction and maintenance in erythropoiesis stimulating agent (ESA)-naïve subjects who have CKD and are not on dialysis. This report provides results from a primary analysis performed on data when all subjects completed the correction and evaluation phase, while the extension period was ongoing.

For the primary analysis conducted in the PP population, 76.44% subjects (95% CI: 69.60, 82.13) in the Efepoetin alfa Q2W group and 68.93% subjects (95% CI: 61.77, 75.28) in the Mircera Q2W group achieved ≥ 1 g/dL Hb increase with mean Hb within 10-12 g/dL without RBC transfusion during the evaluation period with a treatment difference of 7.51% (95% CI: -1.82, 16.66). The lower limit of the 95% CI was above the prespecified non-inferiority margin of -9%, demonstrating non-inferiority of Efepoetin alfa Q2W to Mircera Q2W in the primary efficacy endpoint.

In the PP population, the Least Squares (LS) mean change in Hb levels from baseline to evaluation period (mean of Hb levels from week 22 to week 28) was 1.61 g/dL for the Efepoetin alfa Q2W group and 1.78 g/dL for the Mircera Q2W group with a LS mean difference of -0.18 g/dL (95% CI: -0.35, -0.002). The lower limit of the 95% CI was above the prespecified non-inferiority margin of -0.75 g/dL, demonstrating non-inferiority of Efepoetin alfa Q2W to Mircera Q2W in this endpoint.

In the EXT-PP population, the LS mean change in Hb levels from end of evaluation period to end of extension period was -0.07 g/dL in the Efepoetin alfa Q2W group, -0.35 g/dL in the Efepoetin alfa Q4W group, and -0.49 g/dL in the Mircera Q4W group. The LS mean difference

between the Efepoetin alfa Q2W and Mircera Q4W groups was 0.42 g/dL (95% CI: 0.19, 0.66) and between the Efepoetin alfa Q4W and Mircera Q4W groups was 0.14 g/dL (95% CI: -0.10, 0.38). The lower limits of the 95% CIs were above the prespecified non-inferiority margin of -0.75 g/dL, demonstrating non-inferiority of Efepoetin alfa Q2W and Efepoetin alfa Q4W to Mircera Q4W in this endpoint.

In the PP population, majority of subjects in both treatment groups (91.38% in Efepoetin alfa Q2W and 86.44% in Mircera Q2W) maintained Hb levels within ± 1 g/dL of the mean Hb value at each visit during week 22 to week 28 with a difference of 4.94% (95% CI: -1.73, 11.65).

PHARMACOLOGY

Pharmacodynamics

RET count: Reticulocyte count increased with the IV and SC administration of Efepoetin alfa and was recovered to the baseline. In the IV dose groups, maximum RET count was reached at median 109-204 hrs after Efepoetin alfa (0.3, 1, 3, 5 µg/kg BW). In the SC dose groups, maximum RET count was reached at median 168-240 hrs after Efepoetin alfa (1, 3, 5, 8 µg/kg BW) administration. Reticulocyte count slowly increased then decreased in both dose groups, but were greater in the SC dose groups than in the IV dose groups.

Compared to IV administration in Efepoetin alfa dose groups, higher average ΔAUEC was observed in the SC dose groups. The AUEC values revised with individual baseline was calculated at 240 hrs, 336 hrs, 504 hrs, and 672 hrs. The $\Delta AUEC_{0\text{-}240h}$ revised with baseline showed an increase, along with dose increase until 240 hrs, and relatively similar AUEC value per dose until 672 hrs with time accumulation for SC Efepoetin alfa dose group. Considering AUEC change per cumulative time zone and RET-time profile, the maximum effect of RET increase in the low dose groups (1 and 3 µg/kg BW group) were lower and slower compared to the Darbepoetin alfa 30 µg dose group, while the maximum effect of RET increase in the higher dose groups (5 and 8 µg/kg BW group) were similar to the Darbepoetin alfa 30 µg dose group and were continuous.

Hemoglobin: Hemoglobin generally increased 112 hrs after Efepoetin alfa administration, but no definite tendency was observed. The mean Emax range in the Efepoetin alfa IV dose groups was 15.34–15.83 g/dL and 15.76 g/dL in the Darbepoetin alfa 30 µg IV dose group. The mean Emax range in the Efepoetin alfa SC dose groups were 15.36–16.04 g/dL, and 15.39 g/dL in the Darbepoetin alfa 30 µg SC dose group.

RET haemoglobin: The median time when the minimum RET Hb (Emin) was observed was between 60.01 – 240.03 hrs for the Efepoetin alfa 0.3, 1, 3, 5 µg/kg BW IV dose groups and at 66.8 hrs for the Darbepoetin alfa 30 µg IV dose group. The median Tmin was 18-168.19 hrs for the Efepoetin alfa 1, 3, 5, 8 µg/kg BW SC dose groups and 36.01 hrs for the Darbepoetin alfa 30 µg SC dose group.

Pharmacokinetics

The PK of Efepoetin alfa was determined in one Phase I study wherein a single dose of Efepoetin alfa was administered IV/SC to 100 healthy Korean male subjects. Blood and urine sample collection for PK evaluation of Efepoetin alfa and Darbepoetin alfa were carried out until 672 hrs after IV/SC administration of the study drug.

The mean serum concentration-time profiles of Efepoetin alfa after single IV administration showed a dose dependent relationship and progressively decreasing over time. The lowest dose group of Efepoetin alfa (0.3 µg/kg) reached an almost 0 serum concentration after 12 hours. The highest dose of Efepoetin alfa 5 µg/kg reached an almost 0 µg/L serum concentration after 72 hours, while the rest of the doses and Darbepoetin alfa 30 µg did so after 48 hours.

The mean serum concentration-time profiles of Efepoetin alfa after SC administration reached Tmax at 0-12 hrs post-dose and declined in apparently bi-phasic manner. The highest dose group (8 µg/kg) was still quantifiable after 120 hours.

STORAGE

Store at temperature between 2 – 8°C

Protect from light

Do not freeze

Avoid shaking

PACKAGING

Box, 1 pre-filled syringe @ 0.3 mL

Box, 1 pre-filled syringe @ 0.6 mL

Reg No. DKL2358500143A1

ON MEDICAL PRESCRIPTION ONLY

HARUS DENGAN RESEP DOKTER

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