CKD OTTO Pharma

Nesbell
20, 30, 40, 60, dan 120 µg

No. : FPT10/016F/00

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Artwork for Registration

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LEAFLET

Nama Bahan Kemas Packaging Material Name	Leaflet Nesbell
Kode Registrasi Registration Code	REG/DAA-BI01/LE-000
Menggantikan Kode Superseded Code	NA

Keterangan Dasar
Basic Information

Ukuran : 280 x 210 mm
Size

Bahan : Due to principal specification
Material

Warna : Hitam (cetak 2 muka / bolak-balik)
Color Black (print 2 faces / front and back print)

Font :
NESBELL (English) : Helvetica Neue 77 Bold Condensed - 8 pt
Prefilled-syringe injection (English) : Helvetica Neue 77 Bold Condensed - 8 pt
NESBELL (Indonesia) : Helvetica Neue 77 Bold Condensed - 7 pt
Injeksi (Indonesia) : Helvetica Neue 77 Bold Condensed - 7 pt
prefilled syringe : Helvetica Neue 77 Bold Condensed Oblique - 7 pt
Teks / *Text* : Myriad Pro Bold dan Regular - 4,5 pt dan 5 pt

NESBELL

Prefilled-syringe injection

Compositions:
NESBELL 20
Each **NESBELL 20** prefilled syringe injection contains:
Darbepoetin alfa 20 µg/0.5 ml
NESBELL 30
Each **NESBELL 30** prefilled syringe injection contains:
Darbepoetin alfa 30 µg/0.5 ml
NESBELL 40
Each **NESBELL 40** prefilled syringe injection contains:
Darbepoetin alfa 40 µg/0.5 ml
NESBELL 60
Each **NESBELL 60** prefilled syringe injection contains:
Darbepoetin alfa 60 µg/0.5 ml
NESBELL 120
Each **NESBELL 120** prefilled syringe injection contains:
Darbepoetin alfa 120 µg/0.5 ml
Excipients:
Sodium dihydrogen phosphate monohydrate, disodium phosphate dihydrate, sodium chloride, polysorbate 80, water for injection
Pharmacology:
Darbepoetin alfa exerts an erythropoietic effect by acting on erythroid progenitor cells directly.
1. Erythropoietic action
When intravenously administered darbepoetin alfa showed an erythropoietic effect (increasing the hemoglobin concentration and the reticulocyte count) more sustained than that of epoetin alfa. Moreover, when intravenously or subcutaneously administered, darbepoetin alfa brought about a marked improvement in anemia. Darbepoetin alfa showed an effect of improving anemia equivalent to that of epoetin alfa in a lower administration frequency.
2. Mechanism of action
By binding with erythropoietin receptors, darbepoetin alfa acted on human hemapoietic progenitor cells to promote colony formation of late erythroid progenitor cells (CFU-E) and early erythroid progenitor cells (BFU-E) in a concentration-dependent manner (in vitro)
Pharmacokinetics
Serum Concentration
• Single administration
- Intravenous administration
Following a single intravenous administration of darbepoetin alfa at a dose of 10 – 180 µg to patients with renal anemia receiving hemodialysis, the serum concentration increased almost dose proportionally and its time-course changes showed biphasic elimination. AUC also increased almost in proportion to the dose
- Subcutaneous administration
Following a single subcutaneous administration of darbepoetin alfa at a dose of 20 – 180 µg to patients with chronic kidney not on dialysis, the serum concentration increased almost dose proportionally. AUC also increased almost in proportion to the dose
• Repeated administration
Following repeated intravenous administration of darbepoetin alfa at a dose of 10 – 60 µg to patients with renal anemia receiving hemodialysis for 28 weeks, no change was found in the pharmacokinetics at the final administration when compared to the initial administration. Following repeated intravenous administration of darbepoetin alfa at a dose 10 – 180 µg to patients with renal anemia receiving hemodialysis, no major change was found in the serum through concentration.
Following repeated subcutaneous administration of darbepoetin alfa at a dose 15 – 180 µg to patients with chronic kidney disease not on dialysis, no major change was found in the serum through concentration.
Preclinical safety study
Repeat dose toxicity study of NESBELL in rats, showed mortality of 15% with intravenous administration once a week for 90 days at the dose of 30 µg/kg. The cause of death in the animal for which it could determined, was renal thrombosis or renal infarct attributable to an exacerbated polycythemia, secondary to the expected pharmacological activity of darbepoetin alfa, which are erythropoiesis stimulating hormones.
Hematology study in male rats showed higher white blood cell count, neutrophil, platelet values and reticulocyte count treated with NESBELL and reference darbepoetin alfa. Enlargement of the speen was observed on most of animals and irregular surface of the kidneys was observed in practically all the male rats treated with NESBELL or reference darbepoetin alfa.
In the clinical biochemistry studies, it showed higher urea triglyceride, ASAT and potassium, and lower albumin and protein levels in plasma. After intravenously administration once a week over a period of 13-weeks to rats, NESBELL showed no immunogenic potential. Based on pathology examination in animal studies, no relevant differences were observed between Nesbell or reference darbepoetin alfa at same dose level.
In the toxicokinetics study between NESBELL and reference darbepeotin alfa, it showed that exposure tended to be dose proportionally increasing at incrementing low and high dose, and there is no gender difference AUC ratio between female and male rats.
There is similarities of Cmax, AUC, and half life between NESBELL and reference darbepoetin alfa in the absorption studies of intravenous and subcutaneous administration.
The minimum lethal dose of darbepoetin alfa after single intravenous administration was >1000 µg/kg in rats and >150 µg/kg in dogs.
Repeat dose toxicity studies of darbepoetin alfa were conducted in rats and dogs. Darbepoetin alfa was administered up to 26 weeks in rats (NOAEL: <1.8 µg/kg) and up to 39 weeks in dogs (NOAEL: 0.1 µg/kg) at intervals of once or 3 times weekly via an intravenous or subcutaneous route. Also, the changes observed in the toxicity studies of darbepoetin alfa were secondary to the erythropoietic activity, excess hematopoietic activity and persistent polycythemia and were similar to those observed for recombinant human erythropoietin.
In the general and safety pharmacology studies (in current regulation "Safety Pharmacology"), darbepoetin alfa, like recombinant human erythropoietin, had no clinically significant effects on the central nervous system, cardiovascular or respiratory system.
No genotoxicity of darbepoetin alfa was observed. In the reproductive and developmental toxicity studies, darbepoetin alfa had no effect on the reproductive function of parent animals and had no teratogenic potential.
Description of Clinical Studies
Phase I Clinical Studies
Intravenous administration
A randomized, double blind, active control, single dosing, crossover clinical trial to investigate the pharmacokinetics of NESBELL and darbepoetin alfa after intravenous administration in healthy male volunteers. Safety, tolerability and pharmacokinetics were evaluated in 26 subjects of Nesbell.
Immunogenocity studies was performed before and after NESBELL administration tested, and the antibody test for NESBELL were negative in every serum sample.
The pharmacokinetic in the healthy subject is the terminal half life is 90.21 hours, clearance 0.15 L/hr, volume distribution (Vz) 16.23 L.
Subcutaneous administration
A randomized, double blind, active control, single dosing, crossover clinical trial to investigate the pharmacokinetics of Nesbell and darbepoetin alfa after subcutaneous administration in healthy male volunteers. Safety, tolerability and pharmacokinetics were evaluated in 33 subjects of Nesbell.
Immunogenocity studies was performed before and after NESBELL administration tested, and the antibody test for NESBELL were negative in every serum sample.
The pharmacokinetic in the healthy subject is the terminal half life is 214.69 hours, clearance 0.24 L/hr, volume distribution (Vz) 58.15 L.
Phase III Clinical Studies
Intravenous administration
NESBELL was evaluated in 401 subjects in patients with chronic kidney disease receiving hemodialysis clinical trials. The safety and efficacy of NESBELL was evaluated in a randomized, double blind, multicenter clinical study. In this clinical study, the changes in mean Hb levels and the mean dose during the evaluation period after intravenous administration for 24 weeks were evaluate. This clinical study demonstrated that NESBELL is effective in maintaining Hb levels within the range of 10 to 12g/dl and in correcting anemia by maintaining Hb levels within a narrow range in patients with chronic kidney disease.
Subcutaneous administration
NESBELL was evaluated in 287 subjects in patients with chronic renal failure of stage 3 or greater not receiving hemodialysis or peritoneal dialysis.
The safety and efficacy of NESBELL was evaluated in a randomized, double blind and multi center clinical study. In this clinical study, the changes in mean Hb levels and the mean dose during the evaluation period after intravenous administration for 24 weeks were evaluate. The result of this study is NESBELL can achieve the target Hb level of 10 – 12 g/dl during the evaluation period with the time required to reach the target Hb level was 30.36±19.48 days from 85.19% of subjects.
Indication
Anemia associated with chronic kidney disease (CKD) in patients on hemodialysis or not on dialysis.
Contraindication
- Patients with a history of hypersensitivity to any of ingredients in the product or to other erythropoietin preparations
- Uncontrolled hypertension
Dosage and administration:
• Hemodialysis patients
- Initial dose
The usual dose of darbepoetin alfa in adult patients is 20 µg as darbepoetin alfa (genetical recombination), to be administered as single intravenous injection once weekly.
- Initial dose at the switching from erythropoietin preparations (epoetin alfa (genetical recombination), epoetin beta (genetical recombination), etc).
The usual dose of darbepoetin alfa in adult patients is 15 – 60 µg as darbepoetin alfa (genetical recombination), to be administered as a single intravenous injection once weekly.
- Maintenance dose
When correction of anemia is achieved, the usual dose of darbepoetin alfa in adult patients is 15 – 60 µg as darbepoetin alfa (genetical recombination), to be administered as a single intravenous injection once weekly. If alleviation of anemia is maintained by once weekly injection, the frequency of administration can be changed to once every two weeks with an initial dose set to be two-fold of the dose in the once weekly injection. In this case, the usual dose in adult patients is 30 – 120 µg administered as a single intravenous injection once every two weeks.
In all cases, the dose should be adjusted in view of the degree of anemic symptoms and the patients's age, and should not exceed 180 µg as a single injection.
Initiate treatment when the hemoglobin level is less than 10 g/dl. If the hemoglobin level approaches or exceeds 11 g/dl, reduce or interrupt the dose of darbepoetin alfa (genetical recombinant).
• Patients with chronic kidney disease not on dialysis
- Initial dose
The usual dose of darbepoetin alfa in adult patients is 30 µg as darbepoetin alfa (genetical recombination), to be administered as a single injection once every two weeks subcutaneously or intravenously.
- Initial dose at the switching from erythropoietin preparations (epoetin alfa (genetical recombination), epoetin beta (genetical recombination), etc).
The usual dose of darbepoetin alfa in adult patients is 30 – 120 µg as darbepoetin alfa (genetical recombination), to be administered as a single injection once every two weeks subcutaneously or intravenously.
- Maintenance dose
When correction of anemia is achieved, the usual dose of darbepoetin alfa in adult patients is 30 – 120 µg as darbepoetin alfa (genetical recombination), to be administered as single injection once every two weeks subcutaneously or intravenously. If allevation of anemia is maintained by once every two weeks injection, the frequency of administration can be changed to once every four weeks with an initial dose set to be two-fold of the dose in the once every two weeks injection. In this case, the usual dose in adult patients is 60 – 180 µg administered as a single injection once every four weeks subcutaneously or intravenously.
In all cases, the dose should be adjusted in view of the degree of anemic symptoms and the patient's age, and should not exceed 180 µg as a single injection.
Consider initiating darbepoetin alfa treatment only when the hemoglobin level is less than 10 g/dl and the following consideration apply: (1) the rate of hemoglobin decline indicates the likelihood of requiring a RBC transfusion and (2) reducing the risk of alloimmunization and/or other RBC transfusion-related risks is a goal. If the hemoglobin level exceeds 10 g/dl, reduce or interrupt the dose of darbepoetin alfa, and use the lowest dose of darbepoetin alfa sufficient to reduce the need for RBC transfusions.
• Precautions related to Dosage and Administration
- Initial dose at the switching from an erythropoietin preparation
When darbepoetin alfa is started in substitution for an erythropoietin preparation, the dose and the frequency of administration should be determined on the basis of the dose of the erythropoietin preparation that has been used. See table below.
(1) Patients who have been treated with an erythropoietin preparation twice weekly or three times weekly
Calculate the total dose of the erythropoietin preparation administered during the week before the switching, and then determine the initial dose of darbepoetin alfa according to the table below. The treatment should be started on once weekly basis.
(2) Patients who have been treated with an erythropoietin preparation once weekly or once every two weeks
Calculate the total dose of the erythropoietin preparation administered during the two weeks before switching and then determine the initial dose of darbepoetin alfa according to the table below.
The treatment should be started on once every two weeks basis.

Total dose of the erythropoietin preparation administered during the week or two weeks before the switching	Dose of Darbepoetin Alfa
3,000 IU or less	15 *µg*
4,500 IU	20 *µg*
6,000 IU	30 *µg*
9,000 IU	40 *µg*
12,000 IU	60 *µg*

- Dose adjustment
If dose adjustment is required (for example, when the appropriate increase in the hemoglobin concentration or the hematocrit levels can not be achieved in correction phase, or when the hemoglobin concentration or the hematocrit level deviates from the target range for successive two weeks in maintenance phase), the dose should be increased or decreased according to the table below. Any dose increase should be performed stage by stage in principle

Table for dose adjustment in the intravenous administration (hemodialysis patients and patients with chronic kidney disease not on dialysis)

Stage	Dose of Darbepoetin Alfa
1	10 *µg*
2	15 *µg*
3	20 *µg*
4	30 *µg*
5	40 *µg*
6	50 *µg*
7	60 *µg*
8	80 *µg*
9	100 *µg*
10	120 *µg*
11	140 *µg*
12	160 *µg*
13	180 *µg*

Table for dose adjustment in the subcutaneous administration (patients with chronic kidney disease not on dialysis)

Stage	Dose of Darbepoetin Alfa
1	15 *µg*
2	30 *µg*
3	60 *µg*
4	90 *µg*
5	120 *µg*
6	180 *µg*

- Change of the frequency of administration
(1) When changing the frequency of administration, the hemoglobin concentration or the hematocrit level should be sufficiently monitored before expanding the interval of administration. Be sure that the hemoglobin concentration or the hematocrit level have been kept stable at a certain dose of darbepoetin alfa and then change the frequency of administration from once weekly to once every two weeks, or from once every two weeks to once every four weeks. The hemoglobin concentration or the hematocrit level should be monitored after the change as well, and adjustment should be made as needed.
(2) If the hemoglobin concentration or the hematocrit level fails to reach the target range even with the dose of 180 *µg*, the dose should be reduced by half and the frequency of administration should be changed from once every two weeks to once weekly, or from once every four weeks to once every two weeks.

NESBELL
Injeksi *prefilled syringe*

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 NESBELL dan kegunaannya
NESBELL injeksi *prefilled syringe* digunakan untuk mengobati anemia yang berhubungan dengan penyakit ginjal kronik (gagal ginjal) pada pasien dengan hemodialisis atau tanpa dialisis. Anemia adalah keadaan dimana darah Anda kekurangan kandungan sel darah merah dengan gejala yang umum berupa kelelahan, lemah dan napas yang pendek. Pada gagal ginjal, ginjal tidak dapat memproduksi hormon *erythropoietin* yang cukup, sehingga menyebabkan anemia.

NESBELL injeksi *prefilled syringe* mengandung *darbepoetin alfa* sebagai zat aktif yang bekerja seperti hormon *erythropoietin*, yaitu protein di dalam tubuh yang membantu untuk memproduksi sel darah merah

2. Apa yang perlu Anda ketahui sebelum menggunakan NESBELL
Bagian berikut berisi informasi yang Anda, dokter dan apoteker harus pertimbangkan sebelum Anda menggunakan NESBELL.

NESBELL tidak boleh digunakan:
• Jika Anda alergi (hipersensitif) terhadap *darbepoetin alfa* atau komponen dalam obat ini (lihat **bagian 6**)
• Jika Anda memiliki tekanan darah tinggi (hipertensi) yang tidak dapat dikontrol.

Peringatan dan perhatian:
Diskusikan dengan dokter atau apoteker sebelum menggunakan NESBELL bila Anda:
• Memiliki riwayat penyakit jantung
• Memiliki tekanan darah tinggi, yang dapat dikontrol dengan obat yang diresepkan oleh dokter Anda
• Pernah mengalami kejang, kejang epilepsi atau stroke
• Memiliki kecenderungan alergi atau hipersensitif terhadap suatu obat
• Memiliki riwayat medis lainnya
• Dapat meningkatkan perkembangan atau kekambuhan tumor pada pasien kanker
• Dapat meningkatkan terjadinya kejang pada pasien dengan penyakit ginjal kronik

Perhatian khusus:
• Sebelum menggunakan NESBELL, pastikan Anda mendapatkan diagnosis yang tepat dari dokter Anda. NESBELL digunakan untuk pasien yang mengalami anemia terkait penyakit ginjal. NESBELL tidak boleh digunakan pada pasien dengan tipe anemia lain (seperti anemia hemoragi, pansitopenia, dan lainnya)
• Jika Anda mengalami gejala termasuk kelelahan yang tidak biasa dan kurang berenergi, dapat berarti Anda memiliki aplasia sel darah merah murni (*pure red cell aplasia*/PRCA). Aplasia sel darah merah murni menunjukkan bahwa tubuh telah menghentikan atau mengurangi produksi sel darah merah sehingga menyebabkan penyakit anemia berat. Jika Anda mengalami gejala – gejala tersebut, Anda harus menghubungi dokter Anda yang akan menentukan tindakan yang tepat untuk pengobatan anemia Anda.
• Hati - hati pada produk yang menstimulasi produksi sel darah merah: NESBELL merupakan salah satu di dalam kelompok obat yang dapat menstimulasi produksi sel darah merah seperti yang dilakukan oleh protein *erythropoietin* manusia. Tenaga kesehatan Anda harus selalu mencatat produk yang Anda gunakan secara tepat
• Jika Anda pasien dengan gagal ginjal kronis dan tidak merespons terhadap NESBELL, dokter Anda akan memeriksa dosis NESBELL Anda, karena peningkatan dosis NESBELL berulang kali jika Anda tidak merespons NESBELL dapat meningkatkan risiko masalah jantung atau pembuluh darah dan dapat meningkatkan risiko terjadinya kematian jaringan karena kekurangan pasokan darah pada otot jantung (infark miokardium), *stroke* dan kematian.
• Dokter Anda harus menjaga kadar hemoglobin Anda antara 10 dan 12 g/dl. Dokter Anda akan melakukan pemeriksaan hemoglobin Anda agar tidak melebihi kadar tertentu, karena tingginya kadar hemoglobin dapat membuat Anda berisiko mengalami masalah jantung atau pembuluh darah dan dapat meningkatkan risiko terjadinya kematian jaringan karena kekurangan pasokan darah pada otot jantung (infark miokardium), stroke dan kematian
• Jika Anda memiliki gejala, termasuk sakit kepala berat, mengantuk, kebingungan, masalah dengan penglihatan, mual, muntah atau kejang, hal itu bisa berarti bahwa Anda memiliki tekanan darah yang sangat tinggi. Jika Anda mengalami gejala – gejala tersebut, Anda harus menghubungi dokter Anda.
• Penyalahgunaan obat oleh orang yang sehat dapat menyebabkan masalah yang mengancam jiwa terkait dengan jantung atau pembuluh darah
• Reaksi kulit yang serius termasuk sindrom Stevens-Johnson (SJS) dan nekrolisis epidermal toksik (*toxic epidermal necrolysis*/TEN) telah dilaporkan berhubungan dengan penggunaan *epoetin*. SJS atau TEN awalnya dapat muncul berupa kemerahan seperti titik atau bentuk melingkar yang sering disertai dengan lepuhan terpusat. Ulkus atau luka terbuka pada bagian mulut, tenggorokan, hidung , alat kelamin dan mata (mata merah dan bengkak) juga dapat terjadi. Ruam kulit yang serius ini sering didahului dengan demam dan/atau gejala yang mirip flu. Ruam dapat berkembang menjadi pengelupasan kulit yang luas dan komplikasi yang mengancam jiwa. Jika ruam atau gejala kulit lain yang serius berkembang, hentikan penggunaan NESBELL dan hubungi dokter Anda atau segera dapatkan bantuan medis.

Obat lain dan NESBELL:
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.

Kehamilan, menyusui, dan fertilitas
Beritahukan kepada dokter atau apoteker Anda sebelum menggunakan NESBELL
• 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 NESBELL diekskresikan dalam air susu

3. Bagaimana cara menggunakan NESBELL
Selalu gunakan NESBELL 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 NESBELL karena kadar hemoglobin Anda adalah 10 g/dl atau kurang dari 10 g/dl

Jika Anda atau orang yang merawat Anda telah terlatih untuk memberikan suntikan NESBELL (injeksi) di rumah:
• Dokter Anda akan menunjukkan seberapa banyak NESBELL yang Anda gunakan, bagaimana cara menyuntikkannya, seberapa sering harus disuntikkan, serta bagaimana cara membuang syringe, dan jarum suntik bekas secara aman
• Jangan menyuntikkan sendiri NESBELL ke dalam vena jika Anda belum terlatih dengan baik
• Tidak boleh menyuntikkan NESBELL bersama dengan produk lain
• Sebelum menggunakan NESBELL injeksi prefilled syringe, lepas bagian tip cap. Pasangkan jarum yang sesuai, jika diperlukan, dan kemudian berikan obatnya.

Jika Anda adalah pasien yang menjalani hemodialisis
Dosis awal NESBELL yang umumnya diberikan pada pasien dewasa yang menjalani hemodialisis adalah 20 µg, diberikan secara injeksi tunggal intravena sekali seminggu.

Jika Anda adalah pasien dengan penyakit ginjal kronis tanpa dialisis
Dosis awal NESBELL yang umunya diberikan adalah 30 µg, diberikan secara injeksi tunggal intravena atau subkutan setiap dua minggu sekali.

Prepared by :	Reviewed by :						Approved by :
Packdev, QA Staff/Spv	QA Head Dept.	RA Head Dept.	QC Head Dept.	PPWH Head Dept.	Production Head Dept.	Marketing Head Dept.	Quality Management General Manager
Date :	Date :	Date :	Date :	Date :	Date :	Date :	Date :

Verified by :

Dokter Anda 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 petunjuk dokter, terutama pada saat memulai terapi.

Selama terapi mengunakan NESBELL, lakukan sesuai petunjuk dokter atau apoteker Anda terkait pola makan dan obat – obatan yang digunakan.

Mengemudi dan menggunakan mesin
NESBELL tidak berpengaruh pada kemampuan mengemudi dan menggunakan mesin

Jika Anda menggunakan NESBELL lebih dari yang seharusnya Anda gunakan
Jika Anda mengunakan NESBELL lebih dari yang diinstruksikan oleh dokter, segera hubungi dokter Anda

Jika Anda lupa mengunakan NESBELL
Jika Anda melewatkan dosis NESBELL, segera hubungi dokter Anda dan diskusikan kapan Anda harus menggunakan dosis berikutnya

4. Efek samping yang mungkin terjadi
Seperti obat – obatan lainnya, obat ini dapat menyebabkan efek samping, meskipun tidak terjadi pada setiap orang

NESBELL dapat menyebabkan efek samping serius berikut:

- **Tekanan darah tinggi**
  Tekanan darah tinggi merupakan efek samping yang umum dari darbepoetin alfa pada pasien dengan penyakit ginjal kronis. Ketika menggunakan darbepoetin alfa, tekanan darah Anda mungkin akan meningkat atau sulit dikontrol dengan obat tekanan darah. Hal ini dapat terjadi, bahkan jika Anda tidak pernah memiliki tekanan darah tinggi sebelumnya. Dokter, apoteker atau perawat Anda akan sering memeriksa tekanan darah Anda. Jika tekanan darah Anda meningkat, dokter mungkin akan meresepkan obat tekanan darah yang baru atau tambahan
- **Kejang**
  Jika Anda mengalami kejang ketika menggunakan darbepoetin alfa, segera dapatkan pertolongan medis dan beritahukan ke dokter Anda
- **Pembentukan antibodi terhadap darbepoetin alfa**
  Tubuh Anda mungkin akan membentuk antibodi terhadap darbepoetin alfa. Antibodi tersebut dapat menghambat atau mengurangi kemampuan tubuh Anda dalam membentuk sel darah merah dan menyebabkan Anda mengalami anemia yang berat. Hubungi dokter Anda jika terjadi kelelahan yang tidak seperti biasanya, kurang berenergi, pusing atau pingsan. Anda mungkin perlu menghentikan penggunaan darbepoetin alfa.
- **Reaksi alergi serius**
  Reaksi alergi yang serius dapat menyebabkan kemerahan di seluruh tubuh, napas pendek, bersin, pusing dan pingsan dikarenakan turunnya tekanan darah, pembengkakan di area sekitar mulut atau mata, denyut nadi yang cepat, atau berkeringat. Jika Anda mengalami reaksi alergi yang serius, hentikan penggunaan darbepoetin alfa dan hubungi dokter Anda atau segera dapatkan pertolongan medis.
- **Gangguan fungsi hati, ikterus**
  Gangguan fungsi hati dan/atau ikterus (keadaan dimana kulit, jaringan, dan cairan tubuh berwarna kekuningan akibat tingginya kadarnya bilirubin) yang disertai dengan peningkatan enzim hati mungkin terjadi. Anda mungkin perlu menghentikan darbepoetin alfa
- **Infark**
  Infark atau kematian jaringan karena kekurangan pasokan darah dapat terjadi pada bagian otot jantung (miokardium), paru – paru atau bagain pada otak (serebral). Anda mungkin perlu menghentikan penggunaan darbepoetin alfa.

Efek samping umum dari NESBELL meliputi:

- Napas pendek
- Batuk
- Tekanan darah rendah selama dialisis
- Nyeri perut (abdominal)
- Pembengkakan (edema) pada bagian lengan dan kaki

Efek samping lainnya:

- Sakit kepala, pusing
- Demam
- Detak jantung cepat, irama jantung yang tidak normal
- Gatal, kemerahan pada kulit
- Mual atau muntah
- Radang usus, radang lambung
- Urin berdarah
- Penurunan fungsi ginjal
- Nyeri pada tulang (muskuloskeletal)
- Gangguan pendengaran
- Rasa tidak enak badan (*malaise*)
- Nafsu makan menurun
- Rasa tidak nyaman di dada
- Ditemukan darah residu pada alat hemodialisis (*hemodialyzers*)
- Ketidaknyamanan epigastric
- Nyeri dada
- Edema
- *Dyspnea*

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

5. Bagaimana cara penyimpanan NESBELL
Jangan menggunakan obat melewati tanggal kedaluwarsa yang telah tercantum pada kemasan karton dan *prefilled syringe*

- Jangan mengocok NESBELL
- Simpan NESBELL di dalam lemari pendingin pada suhu 2°C sampai 8°C
- **Jangan membekukan NESBELL**. Jangan gunakan NESBELL yang telah dibekukan
- Simpan *prefilled syringe* di dalam kemasan karton untuk melindungi dari cahaya
- Jauhkan dari jangkauan anak – anak
- Buang *prefilled syringe* setelah satu kali penggunaan. Jangan menggunakan kembali meskipun terdapat obat yang tertinggal

6. Bagaimanakah isi kemasan NESBELL dan informasi lainnya
Apa isi kandungan NESBELL

Zat aktif:
Darbepoetin alfa

Bahan lainnya:
Sodium dihydrogen phosphate monohydrate, disodium phosphate dihydrate, sodium chloride, polysorbate 80, water for injection

Seperti apa NESBELL dan isi kemasannya
NESBELL berupa cairan jernih, tidak berwarna di dalam *prefilled syringe*

Kemasan dan nomor izin edar
NESBELL 20. Kotak, 1 prefilled-syringe NESBELL 20 µg/0.5 ml + 1 jarum steril; DKI2284401143A1
NESBELL 30. Kotak, 1 prefilled-syringe NESBELL 30 µg/0.5 ml + 1 jarum steril; DKI2284401143B1
NESBELL 40. Kotak, 1 prefilled-syringe NESBELL 40 µg/0.5 ml + 1 jarum steril; DKI2284401143C1
NESBELL 60. Kotak, 1 prefilled-syringe NESBELL 60 µg/0.5 ml + 1 jarum steril; DKI2284401143D1
NESBELL 120. Kotak, 1 prefilled-syringe NESBELL 120 µg/0.5 ml + 1 jarum steril; DKI2284401143E1

HARUS DENGAN RESEP DOKTER

Diproduksi oleh:
Chong Kun Dang Pharmaceutical Corp.
Cheonan – Korea

Diimpor oleh:
PT CKD OTTO Pharmaceuticals
Bekasi – Indonesia

Instruction for use and handling:
1) Do not inject NESBELL with other products
2) Before using NESBELL prefilled-syringe injection, remove the tip cap. Attach an appropriate needle, if necessary, and then administer the drug
3) Be sure to discard residual solution after use

Warning and Precautions:

- **Darbepoetin alfa should be administered with care in the following patients :**
  - Patients with myocardial infarction, pulmonary infarction, cerebral infarction, or those with history of these conditions who may experience thromboembolism. The administration of erythropoietic proteins increased the viscosity of the blood, and may potentially aggravate or induce thromboembolism. Therefore, if darbepoetin alfa is used in these patients, sufficient monitoring is required.
  - Patients with hypertension. As administration of darbepoetin alfa may increase blood pressure and induce hypertensive encephalopathy, sufficient monitoring is required
  - Patients with a history of hypersensitivity to any drug
  - Patients with an allergic predisposition
  - Patients with cancer. As administration of darbepoetin alfa may increase risk of tumor progression or recurrence
  - Patients with chronic kidney disease. As administration of darbepoetin alfa may increase risk for seizures.
- **Important Precautions**
  - This product is intended for use in patients with renal anemia who have anemia-associated problems in their daily activities. An approximate hemoglobin concentration to start the therapy with this product is less than 10 g/dl (30% as hematocrit level)
  - Prior to use of darbepoetin alfa, the diagnosis of renal anemia should be confirmed. Darbepoetin alfa should not be used in patients with other types of anemia (hemorrhagic anemia, pancytopenia, etc.)
  - Patients should be carefully interviewed to assess the risk of reactions such as shock. Instruments and medicines for emergency treatment should be prepared beforehand in case of shock, etc. Patients should be kept calm and sufficiently monitored from the start through the end of administration. Especially, careful monitoring is required immediately after the start of administration. When treatment with darbepoetin alfa is started for the first time or restarted after temporary discontinuation, it is recommended to inject intravenously or intradermally a small amount of darbepoetin alfa and then administer the remaining portion only after confirming that patients do not develop any abnormal reactions.
  - During treatment with darbepoetin alfa, the hemoglobin concentration or the hematocrit level should be carefully monitored at regular intervals. Attention should be paid to prevent excessive hemopoiesis (hemoglobin concentration ≥ 12 g/dl, or hematocrit level ≥ 36 g/dl for hemodialysis patients) with making reference to the guidelines and other relevant updates.
    1) In hemodialysis patients with ischemic heart disease or heart failure, mortality tended to be higher in patients targeted to a maintenance hemoglobin of 14 g/dl (42% as hematocrit level) than in patients targeted to a maintenance hemoglobin of 10 g/dl (30% as hematocrit level)
    2) In treatment with erythropoiesis stimulating agents for renal anemia in patients with chronic kidney disease not on dialysis, significantly higher incidences of death and cardiovascular disorder have been reported in patients with the target hemoglobin concentration set at 13.5 g/dl than in those with the target hemoglobin concentration set at 11.3 g/dl. In patients with renal anemia, type 2 diabetes, and chronic kidney diseases who were not on dialysis, event rate of stroke was high in patients receiving an erythropoiesis stimulating agent targeted to a hemoglobin level 13 g/dl.
  - When starting darbepoetin alfa or changing the dose of darbepoetin alfa, measure hemoglobin concentration or hematocrit level once a week or once every two weeks, until hemoglobin concentration or hematocrit level reach the target range and get stable. If response of excessive hemopoiesis develops, appropriate measures such as temporary discontinuation of darbepoetin alfa should be taken
  - Since administration of darbepoetin alfa may increase blood pressure and has been reported to case hypersensitive encephalopathy, parameters such as blood pressure, hemoglobin concentration, hematocrit level, etc. should be closely monitored during the treatment. In particular, caution should be exercised to ensure that the hemoglobin concentration or the hematocrit level increases gradually. As darbepoetin alfa is a long-acting drug, its hematopoietic action lasts longer than that of erythropoietin preparation. It took long time for the hemoglobin concentration or the hematocrit level to decrease even after discontinuation of the treatment in some cases. Therefore, patients should be carefully monitored until the hemoglobin concentration or the hematocrit level recovers.
  - **Pure red cell aplasia** associated with production of antierythropoietin antibodies may occur. Its occurrence should be suspected if anemia is not improved or rather exacerbated during the treatment. When pure red cell aplasia is diagnosed, the treatment with darbepoetin alfa should be discontinued and appropriate measures, excluding switching to erythropoietin preparations, should be taken.
  - Since the administration of darbepoetin alfa may cause hyperkalemia, appropriate dietary control is required.
  - Iron is an important element for exertion of the pharmacological effect of darbepoetin alfa. Therefore, iron should be administrated to patients with iron deficiency.
  - Since the administration of darbepoetin alfa may cause shunt occlusion or residual blood in hemodialyzers, the flow of blood through shunts and hemodialyzers should be carefully monitored in hemodialysis patients. If such problems occur, appropriate measures, such as reconstruction a shunt or increasing the dose of an anticoagulant, should be taken.
  - Special attention should be paid to the following points when the product is used in patients with chronic kidney disease not on dialysis.
    1) Body fluid balance is difficult to control in patients with chronic kidney disease not on dialysis. Therefore, closely monitor body fluid and electrolyte balance, renal function, and blood pressure.
    2) The effect of this product in improving anemia may weaken with progress of chronic kidney disease. Serum creatinine concentrations and creatinine clearance must be monitored during treatment with this product, and appropriate measures such as increasing the dose or temporary discontinuation of darbepoetin alfa should be taken.

Elderly
When darbepoetin alfa is used in elderly patients, parameters such as the blood pressure, hemoglobin concentration and hematocrit level should be frequently measured so that the dosage and the frequency of administration can be appropriately adjusted. The elderly generally have reduced physiological function and are likely to have cardiovascular complications such as hypertension.

Pregnancy
Use of darbepoetin alfa in pregnant women or women who may possibly be pregnant is not recommended. When the use is necessary in such women, it should be limited to cases where expected therapeutic benefits outweigh possible risks associated with the treatment. The safety of darbepoetin alfa in pregnant women has not been established.

Lactation
Use of darbepoetin alfa in lactating women is not recommended. When the use is necessary in such women, the patients should avoid lactation during the treatment. The safety of darbepoetin alfa in lactating women has not been established.

Pediatric
The safety of darbepoetin alfa in babies with low birthweight, neonates, suckling babies, infants or children has not been established.

Adverse reactions
Adverse reactions were reported in 472 (32.3%) of 1,462 patients treated with darbepoetin alfa. The major adverse reactions were increased blood pressure in 248 cases (17.0%), shunt thrombosis/occlusion in 44 cases (3.0%), headache in 29 cases (2.0%) and malaise in 20 cases (1.4%).
Adverse reactions were reported in 10 (2.49%) of 401 patients treated with NESBELL in the intravenous administration. The most common adverse reactions were blood pressure increased in 5 cases (0.75%), hypertension 3 cases (0.75%), 1 case (0.25%) each of epigastric discomfort, nausea, palpitations, deafness neurosensory, chest pain, and myalgia.
Adverse reactions were reported in 12 (4.86%) of 287 patients treated with NESBELL in the subcutaneous administration. The adverse reaction were hypertension in 3 cases (1.21%), hepatic disorders in 2 cases (0.8%), myalgia in 2 cases (0.81%), hematologic disorders in 2 cases (0.8%), 1 case (0.4%) each of kidney disorder, blood pressure increased, oedema, headache, dyspnea, and pruritus.

- **Clinically significant adverse reactions**
  - **Cerebral infarction:** Since cerebral infarction may occur, patients should be closely monitored. If any abnormalities are observed, appropriate measures such as discontinuation of darbepoetin alfa should be taken.
  - **Cerebral hemorrhage:** Since cerebral hemorrhage may occur, patients should be closely monitored. If any abnormalities are observed, appropriate measures such as discontinuation of darbepoetin alfa should be taken
  - **Hepatic function disorder, jaundice:** Since hepatic function disorder and/or jaundice accompanied by increase ALT (GPT), γ-GTP, etc. may occur, patients should be closely monitored. If any abnormalities are observed, darbepoetin alfa should be discontinued and appropriate measures should be taken
  - **Hypertensive encephalopathy:** Since hypertensive encephalopathy may occur, patients should be closely monitored for changes in the blood pressure, etc. during the treatment.
  - **Shock and anaphylactoid reactions:** Since shock and/or anaphylactoid reactions (urticarial, dyspnea, lip edema, pharyngeal edema, etc.) may occur, patients should be cclosely monitored. If any abnormalities are observed, darbepoetin alfa should be discontinued and appropriate measures should be taken.
  - **Pure red cell aplasia:** Pure red aplasia accompanied by production of anti-erythropoietin antibodies may occur. If such a problem is observed, darbepoetin alfa should be discontinued and appropriate measures should be taken
  - **Myocardial infarction, pulmonary infarction:** Since myocardial infarction and/or pulmonary infarction may occur, patients should be closely monitored. If any abnormalities are observed, appropriate measures such as discontinuation of darbepoetin alfa should be taken.
- **Other adverse reactions**

Incidence of adverse reactions is listed by frequency. Frequencies are defined as: very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥ 1/10,000, <1/1,000); very rare (<1/10,000), not known (cannot be estimated).

System organ class	Incidence (%)					
	Very common	Common	Uncommon	Rare	Very rare	Not known
Cardio-vascular	Increased blood pressure		Arrhythmia, hypotension during dialysis, palpitations, angina pectoris/cardiac muscle ischemia, arteriosclerosis obliterans, hypertension			
Dermatologic			Pruritus, rash			
Hepatic			Abnormal hepatic function, increased Al-P, increased γ-GTP, increased AST (GOT), increased ALT (GTP) gallbladder polyp			
Metabolic			Decreased iron storage, increased serum potassium, increased blood phosphate, increased uric acid, decreased appetite, secondary hyperparathyroidism			
Hematologic		Increased eosinophils	Decreased platelets, decreased white blood cells, increased white blood cells, decreased lymphocytes			
Kidney/urinary			Decreased in renal function (increased BUN, increased creatinine, etc). hematuria			
Gastro intestinal			Nausea/vomiting, abdominal pain, gastritis, duodenitis, epigastric discomfort			
Sensory		Headache, malaise	Dizziness, neurosensory deafness			
Ophthalmologic			Vitreous hemorrhage, conjunctivitis			
Others		Shunt thrombosis/ occlusion, increased LDH	Residual blood in hemodialyzers, chest discomfort pain at the site of shunt, poor hemostasis, diabetic gangrene, fever, musculoskeletal pain, feeling hot/hot flushes, chest pain, oedema, dyspnea			

Interaction with other medicinal products and other forms of interaction
The clinical results obtained so far do not indicate any interaction of darbepoetin alfa with other substances. However, there is potential for an interaction with substances that are highly bound to red cells e.g. cyclosporine and tacrolimus. If darbepoetin alfa is given concomitantly with any of these treatments, blood levels of these substances should be monitored and the dosage adjusted as the haemoglobin rises.

Effects on ability to drive and use machines:
Darbepoetin alfa has no or negligible influence on the ability to drive and use machines. There are no reports of adverse effects that would have effects on ability to drive or operate machinery or that would impair mental ability.

Overdosage
In clinical pharmacology studies, there is no clinical experience of use at higher doses
The maximum amount of darbepoetin alfa that can be safely administered in single or mutiple doses has not been determined. Therapy with darbepoetin alfa can result in polycythemia if the hemoglobin is not carefully monitored and the dose appropriately adjusted. Cases of severe hypertension have been observed following overdose with darbepoetin alfa.
In the event of polycythemia, darbepoetin alfa should be temporarily withheld. If clinically indicated, phlebotomy may be performed.

Presentations and registration numbers:
NESBELL 20. Box @ 1 prefilled syringe Nesbell 20 µg/0.5 ml + 1 sterile needle; DKI2284401143A1
NESBELL 30. Box @ 1 prefilled syringe Nesbell 30 µg/0.5 ml + 1 sterile needle; DKI2284401143B1
NESBELL 40. Box @ 1 prefilled syringe Nesbell 40 µg/0.5 ml + 1 sterile needle; DKI2284401143C1
NESBELL 60. Box @ 1 prefilled syringe Nesbell 60 µg/0.5 ml + 1 sterile needle; DKI2284401143D1
NESBELL 120. Box @ 1 prefilled syringe Nesbell 120 µg/0.5 ml + 1 sterile needle; DKI2284401143E1

ON MEDICAL PRESCRIPTION ONLY

STORE AT TEMPERATURE BETWEEN 2-8°C
PROTECT FROM LIGHT
DO NOT FREEZE
AVOID SHAKING
KEEP OUT OF REACH OF THE CHILDREN

Shelf-life: 36 months
Manufactured by:
Chong Kun Dang Pharmaceutical Corp.
Cheonan – Korea

Imported by:
PT CKD OTTO Pharmaceuticals
Bekasi – Indonesia

material code

Verified by :

DISETUJUI OLEH BPOM : 06/01/2025

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