Informasi Produk untuk Pasien
HEMOFE 250 IU and 1000 IU Lyophilized Powder for Injection
Omfiloctocog alfa
(Recombinant Human Coagulation Factor VIII)

A. Nama Obat
Nama dagang : **HEMOFE 250 IU and 1000 IU Lyophilized Powder for Injection**
Nama generik : Omfiloctocog alfa (Recombinant Human Coagulation Factor VIII)

B. Bentuk Sediaan
Serbuk injeksi liofilisasi + pelarut

C. **Komposisi Zat Aktif/Apa yang terkandung dalam HEMOFE?**
HEMOFE mengandung zat aktif B-domain deleted human coagulation factor VIII (Omfiloctocog alfa). Faktor VIII adalah protein alami yang ditemukan dalam darah manusia yang membantu mencegah dan menghentikan pendarahan.

D. Kekuatan Obat/Berapa kekuatan HEMOFE?
HEMOFE 250 IU lyophilized powder for injection
Setiap vial serbuk mengandung 250 IU omfiloctocog alfa.

HEMOFE 1000 IU powder and solvent for solution for injection
Setiap vial serbuk mengandung 1000 IU omfiloctocog alfa.

E. Pemerian Obat/Bagaimana penampakan HEMOFE?
HEMOFE disediakan sebagai serbuk liofilisasi untuk injeksi. Serbuknya kering, dan putih hingga putih pudar. Setelah rekonstitusi cairannya jernih.

F. Indikasi/Untuk apa HEMOFE digunakan?
Hemofe diindikasikan untuk digunakan pada orang dewasa dan anak-anak dengan hemofilia A (defisiensi faktor VIII kongenital) untuk pengobatan sesuai kebutuhan dan profilaksis episode perdarahan.
Karena tidak ada data yang tersedia, Hemofe tidak diindikasikan untuk profilaksis perdarahan pada kondisi perioperatif.
Hemofe tidak diindikasikan untuk pengobatan penyakit von Willebrand (vWD).
Pada orang dengan hemofilia A, faktor VIII hilang atau tidak berfungsi dengan baik. HEMOFE menggantikan faktor VIII yang cacat atau hilang ini dan membantu darah membentuk gumpalan di lokasi perdarahan.

G. Posologi dan Cara Pemberian/Berapa banyak dan seberapa sering HEMOFE boleh digunakan? Apa yang harus dilakukan bila lupa menggunakan HEMOFE?
Pengobatan dengan HEMOFE akan dimulai oleh dokter yang berpengalaman dalam perawatan pasien dengan hemofilia A. Setelah pelatihan yang sesuai, pasien mungkin dapat diberikan HEMOFE di rumah.
Selalu gunakan obat ini persis seperti yang dijelaskan dalam brosur ini dan seperti yang dikatakan dokter atau apoteker kepada Anda. Periksakan kepada dokter atau apoteker Anda jika Anda tidak yakin.

Pengobatan perdarahan
Dokter Anda akan menghitung dosis obat ini dan seberapa sering Anda harus menggunakannya untuk mendapatkan tingkat aktivitas faktor VIII yang diperlukan dalam darah Anda. Dokter harus selalu menyesuaikan dosis dan frekuensi pemberian sesuai dengan kebutuhan pribadi Anda. Jika Anda mengalami efek HEMOFE yang tidak mencukupi, konsultasikan kepada dokter Anda. Berapa banyak HEMOFE yang harus Anda gunakan dan seberapa sering Anda harus menggunakannya tergantung pada banyak faktor seperti:

- Berat badan Anda
- Tingkat keparahan hemofilia Anda

- Di mana pendarahan itu dan seberapa seriusnya
- Apakah Anda memiliki inhibitor dan seberapa tinggi tingkat inhibitor
- Tingkat faktor VIII yang dibutuhkan.

Pencegahan perdarahan
Jika Anda menggunakan HEMOFE untuk mencegah perdarahan (profilaksis), dokter Anda akan menghitung dosis untuk Anda. Biasanya akan berada di kisaran 25 hingga 50 IU HEMOFE per kg berat badan, disuntikkan setiap hari atau 3 kali seminggu (2-3 hari antara dosis). Namun dalam beberapa kasus, terutama untuk pasien yang lebih muda, interval dosis yang lebih pendek atau dosis yang lebih tinggi mungkin diperlukan.

Penggunaan pada anak-anak dan remaja
HEMOFE hanya dapat digunakan pada dewasa dan anak-anak. Dosis pada remaja juga dihitung berdasarkan berat badan dan dosis yang sama seperti untuk orang dewasa.

Tes laboratorium
Sangat disarankan agar tes laboratorium yang sesuai dilakukan pada plasma Anda pada interval yang sesuai untuk memastikan bahwa aktivitas faktor VIII yang memadai telah tercapai dan dapat dipertahankan.

Pasien dengan inhibitor
Jika Anda telah diberitahu oleh dokter Anda bahwa Anda telah mengalami pembentukan Inhibitor faktor VIII, Anda mungkin perlu menggunakan dosis yang lebih tinggi dari HEMOFE untuk mengontrol perdarahan. Jika dosis ini tidak mengontrol pendarahan Anda, dokter Anda mungkin mempertimbangkan untuk memberikan produk lain.
Konsultasikan dengan dokter Anda jika Anda ingin informasi lebih lanjut tentang ini.
Jangan meningkatkan dosis HEMOFE untuk mengontrol perdarahan Anda tanpa memeriksa dengan dokter Anda.

Lama pengobatan
Biasanya, pengobatan HFMOFE untuk hemofilia dibutuhkan seumur hidup.

Bagaimana HEMOFE diberikan
HEMOFE biasanya disuntikkan ke dalam vena (intravena) oleh dokter atau perawat Anda. Anda atau orang lain mungkin juga dapat memberikan HEMOFE sebagai suntikan, tetapi hanya setelah menerima pelatihan yang memadai. Instruksi terperinci untuk pemberian secara mandiri diberikan pada akhir brosur kemasan ini.

Jika Anda lupa menggunakan HEMOFE
Suntikkan dosis Anda berikutnya dengan segera dan lanjutkan secara berkala seperti yang disarankan oleh dokter Anda.
Jangan gunakan dosis ganda untuk mengganti dosis yang terlupakan.

Jika Anda berhenti menggunakan HEMOFE
Jangan berhenti menggunakan HEMOFE tanpa memeriksa dengan dokter Anda.
Jika Anda memiliki pertanyaan lebih lanjut tentang penggunaan HEMOFE, konsultasikan kepada dokter atau apoteker Anda.

H. Kontraindikasi/Pada keadaan apa Anda tidak diperbolehkan menggunakan HEMOFE?

Jangan gunakan HEMOFE jika Anda:
- Alergi terhadap Omfiloctocog alfa atau bahan lain dari obat ini (tercantum dalam bagian 6).
- Alergi terhadap protein tikus atau hamster.

Jangan gunakan HEMOFE jika salah satu dari hal di atas berlaku untuk Anda. Jika Anda tidak yakin, konsultasikan dengan dokter Anda sebelum menggunakan obat ini.

I. Peringatan dan Perhatian/Apa yang perlu diperhatikan bila menggunakan obat ini?

Penggunaan obat faktor VIII sebelumnya
Beri tahu dokter Anda jika Anda telah menggunakan obat-obatan faktor VIII sebelumnya, terutama jika Anda mengalami pembentukan *Inhibitor* (antibodi) terhadap obat, karena mungkin ada risiko untuk terjadi lagi.
Berhati-hatilah dengan HEMOFE dan konsultasikan dengan dokter atau apoteker Anda sebelum menggunakan HEMOFE:

Reaksi Alergi
Ada risiko yang jarang bahwa Anda mungkin mengalami reaksi anafilaksis (reaksi alergi yang berat dan tiba-tiba) terhadap HEMOFE. Anda harus menyadari tanda-tanda awal reaksi alergi seperti ruam, gatal-gatal, biduran, gatal seluruh tubuh, pembengkakan bibir dan lidah, kesulitan bernapas, mengi, sesak di dada, merasa tidak sehat, dan pusing. Hal ini bisa menjadi gejala awal syok anafilaksis; gejala tambahan mungkin termasuk pusing ekstrim, kehilangan kesadaran, dan kesulitan bernapas yang ekstrim.
Jika salah satu dari gejala-gejala ini terjadi, segera hentikan suntikan dan hubungi dokter Anda. Gejala yang berat, termasuk kesulitan bernapas dan (hampir) pingsan, memerlukan perawatan darurat yang cepat.

Pembentukan '*Inhibitor* FVIII' (antibodi)
Inhibitor (antibodi) dapat berkembang selama perawatan dengan semua obat faktor VIII.
- *Inhibitor* ini, terutama pada tingkat tinggi, menghentikan terapi untuk bekerja dengan baik.
- Anda akan dipantau dengan cermat untuk terjadinya pembentukan *Inhibitor* ini.
- Jika pendarahan Anda tidak terkontrol dengan HEMOFE, segera beri tahu dokter Anda.
- Jangan meningkatkan dosis total HEMOFE untuk mengontrol pendarahan Anda tanpa berkonsultasi dengan dokter Anda.

Masalah terkait kateter
Jika Anda memerlukan perangkat akses vena sentral (CVAD), harap diberi tahu tentang risiko komplikasi terkait CVAD, yang meliputi infeksi lokal, adanya bakteri dalam darah dan pembentukan gumpalan darah di pembuluh darah (thrombosis) tempat kateter dimasukkan.

Penyakit jantung
Konsultasikan dengan dokter atau apoteker Anda jika Anda memiliki penyakit jantung atau Anda berisiko terkena penyakit jantung.

J. Interaksi Obat/Obat dan makanan apa yang harus dihindari jika menggunakan obat ini?
HEMOFE tidak diketahui mempengaruhi atau dipengaruhi olah obat-obatan lain. Beri tahu dokter atau apoteker Anda jika Anda menggunakan, akhir-akhir ini menggunakan atau mungkin akan menggunakan obat-obatan lain.

K. Kehamilan dan Menyusui/Apakah obat boleh digunakan pada wanita hamil dan menyusui?
Jika Anda sedang hamil atau menyusui, berasumsi Anda mungkin hamil atau berencana untuk memiliki bayi, mintalah saran dari dokter Anda sebelum menggunakan obat ini. HEMOFE harus diberikan hanya jika jelas diperlukan. Hemofilia A jarang terjadi pada Wanita. Oleh karena itu, tidak ada pengalaman mengenai penggunaan HEMOFE selama kehamilan dan menyusui yang tersedia.

L. Efek pada Pengendara dan Menjalankan Mesin/Apakah boleh mengendarai dan menjalankan mesin selama menggunakan obat ini?
HEMOFE tidak memiliki pengaruh pada kemampuan Anda untuk mengemudi dan menggunakan mesin.

M. Efek Samping/Apa efek yang tidak diinginkan yang mungkin terjadi jika menggunakan obat ini?

Seperti semua obat-obatan, obat ini dapat menyebabkan efek samping, meskipun tidak semua orang mendapatkannya.

Reaksi alergi (hipersensitivitas)

Hentikan injeksi segera jika Anda mengalami reaksi alergi yang berat dan tiba-tiba (reaksi anafilaksis). Anda harus segera menghubungi dokter atau Unit Gawat Darurat jika Anda memiliki tanda-tanda reaksi alergi seperti:

- Ruam, gatal-gatal, biduran, gatal seluruh tubuh,
- Pembengkakan bibir dan lidah,
- Kesulitan bernapas, mengi, sesak di dada,
- Perasaan umum tidak sehat,
- Pusing dan kehilangan kesadaran.

Pengembangan '*Inhibitor* FVIII' (antibodi)

Untuk pasien yang telah menerima perawatan sebelumnya dengan faktor VIII (lebih dari 150 hari pengobatan) antibodi *Inhibitor* dapat terbentuk secara tidak biasa (kurang dari 1 dari 100 pasien). Jika ini terjadi, obat Anda mungkin berhenti bekerja dengan baik dan Anda mungkin mengalami pendarahan terus-menerus. Jika ini terjadi, Anda harus segera menghubungi dokter Anda.

Efek samping berikut dapat terjadi dengan HEMOFE:

Umum (dapat terjadi hingga 1 dari 10 orang):

- Diare

Tidak umum (dapat terjadi hingga 1 dari 100 orang):

- Peningkatan Aspartat Aminotransferase
- Tekanan darah meningkat
- Ekstrasistol Venrikel
- *Somnolence*

Pelaporan efek samping

Jika Anda mendapatkan efek samping, berbicara dengan dokter Anda. Termasuk kemungkinan efek samping yang tidak tercantum dalam brosur ini. Dengan melaporkan efek samping, Anda dapat membantu memberikan informasi lebih lanjut tentang keamanan obat ini.

Anda juga dapat melaporkan efek samping secara langsung melalui:

Kontak Industri Farmasi:

PT ETANA BIOTECHNOLOGIES INDONESIA

Kawasan Industri Pulogadung, Jl. Rawa Gelam V, Blok. L, Kav. 11-13, Jakarta

Email: pv@id.etanabiotech.com

Website: https://ebi-pharmacovigilance.azurewebsites.net/

N. Overdosis dan Penanganannya/Apa tanda dan gejala kelebihan dosis? Apa yang harus dilakukan bila menggunakan HEMOFE melebihi dosis yang dianjurkan?

Tidak ada informasi mengenai overdosis faktor koagulasi rekombinan VIII. Selalu gunakan HEMOFE persis seperti yang dikatakan dokter Anda. Anda harus memeriksakan diri ke dokter Anda jika Anda tidak yakin. Jika Anda menyuntikkan lebih banyak HEMOFE daripada yang direkomendasikan, beri tahu dokter Anda sesegera mungkin.

O. Cara Penyimpanan/Bagaimana cara menyimpan HEMOFE?

Jauhkan obat ini dari pandangan dan jangkauan anak-anak.

Jangan gunakan obat ini setelah tanggal kadaluwarsa yang tertera pada label dan karton.

Simpan di lemari pendingin (2°C - 8°C). Jangan dibekukan.

Sebelum rekonstitusi (sebelum serbuk dicampur dengan pelarut):
Simpan di lemari pendingin (2°C - 8°C).
Jangan dibekukan. Simpan dalam kemasan asli untuk melindungi dari cahaya.
Serbuk dalam vial tersedia sebagai serbuk putih hingga putih pudar. Jangan gunakan serbuk jika warnanya telah berubah.

Setelah rekonstitusi (setelah serbuk dicampur dengan pelarut):
Setelah Anda melakukan rekonstitusi HEMOFE, harus segera digunakan. Jika Ada tidak dapat menggunakan cairan yang direkonstitusi degan segera, cairan ini harus digunakan dalam waktu 3 jam setelah rekonstitusi Ketika disimpan pada suhu kamar.
Cairan yang direkonsistusi harus jernih dan tidak berwarna.
Jangan gunakan cairan yang direkonstitusi jika Anda melihat adanya partikel atau perubahan warna.

Jangan membuang obat apa pun melalui air limbah atau limbah rumah tangga. Tanyakan kepada apoteker Anda bagaimana cara membuang obat-obatan yang tidak lagi Anda gunakan. Langkah-langkah ini akan membantu melindungi lingkungan.

P. Informasi Lain/Informasi apa yang harus diketahui dari obat ini?

Apa yang terkandung di dalam HEMOFE
Zat **aktifnya** adalah Omfiloctocog alfa (recombinant human coagulation factor VIII). Setiap vial HEMOFE mengandung sebanyak 250 atau 1000 IU Omfiloctocog alfa.
Bahan **lainnya** adalah natrium klorida, arginin hidroklorida, sukrosa, histidin, kalsium klorida, polisorbat 80.

HEMOFE mengandung natrium
Obat ini mengandung kurang dari 1 mmol (0,06 mg) natrium per dosis setelah rekonstitusi, dan karena itu dianggap pada dasarnya ‘bebas natrium’. Namun, tergantung pada berat badan Anda dan dosis HEMOFE Anda, Anda bisa menerima lebih dari satu vial. Hal ini harus dipertimbangkan jika Anda melakukan diet natrium terkontrol.

Seperti apa HEMOFE dan isi kemasan
HEMOFE disediakan sebagai serbuk liofilisasi untuk injeksi. Serbuknya kering, dan putih hingga putih pudar. Setelah rekonstitusi cairannya jernih.
Setiap kemasan HEMOFE berisi:
1 vial recombinant human coagulation factor VIII serbuk liofilisasi untuk injeksi.
1 ampul air steril untuk injeksi 10 ml
1 spuit steril dan jarum suntik sekali pakai
1 jarum filter sekali pakai
1 jarum IV sekali pakai
Bahan kemasan *recombinant human coagulation factor for injection VIII*: botol kaca kelas I, sumbat karet butil, dan penutup plastik aluminium.

Q. Nomor Izin Edar

Dus, 1 vial dengan zat aktif 250 IU + 1 ampul dengan 10 ml pelarut
Reg. No. XXXXXXXXXXXXXXX

Dus, 1 vial dengan zat aktif 1000 IU + 1 ampul dengan 10 ml pelarut
Reg. No. XXXXXXXXXXXXXXX

HARUS DENGAN RESEP DOKTER

Berbahan Halal dan Dalam Upaya Memenuhi Proses Halal

R. Diimpor dan dikemas sekunder oleh:
PT Etana Biotechnologies Indonesia
Jakarta – Indonesia

S. Diproduksi oleh:
Serbuk liofilisasi untuk injeksi:
Sinocelltech, Ltd
No. 31, Kechuang 7th Street, Beijing Economic and Technological Development Area
Beijing – China

Pelarut:
Shijiazhuang No.4 Pharmaceutical Co., Ltd.
No. 518 East Huaian Road, Hi-Tech Industrial Development Zone, Shijiazhuang

Tanggal persetujuan pertama:
DD/MM/YYYY

Instruksi terperinci untuk rekonstitusi dan pemberian HEMOFE

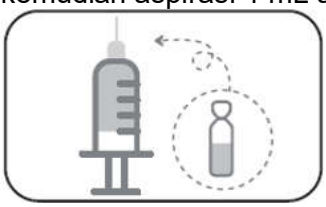
Anda akan membutuhkan *alcohol swab*, bantalan kasa, plester, dan tourniquet. Peralatan ini tidak termasuk dalam kemasan HEMOFE.

Rekonstitusi:

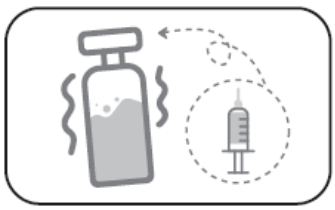
Jika lebih dari 1 vial HEMOFE diperlukan untuk injeksi, ikuti langkah-langkah persiapan dan rekonstitusi di bawah ini untuk rekonstitusi setiap vial serbuk liofilisasi. Cairan rekonstitusi perlu diambil dengan 1 jarum suntik steril berkapasitas besar. Gunakan jarum *filter* terpisah bertanda ② pada kemasan untuk mengambil obat rekonstitusi dari setiap vial dan jarum *filter* tidak boleh digunakan kembali.

(1) Selalu cuci tangan sebelum melakukan prosedur berikut.
(2) Keluarkan vial serbuk dari lemari pendingin dan biarkan mencapai suhu kamar.
(3) Lepaskan penutup atas plastik dari vial serbuk, desinfeksi sumbat karet dengan *alcohol swab*. **Catatan:** Jangan membuka atau menyentuh sumbat karet.

(4) Ambil 1 suntikan air steril untuk injeksi menggunakan *syringe* steril yang ditandai dengan ① pada kemasan, desinfeksi bagian luarnya dengan *alcohol swab*, dan kemudian aspirasi 4 mL air steril untuk injeksi dengan jarum suntik steril.

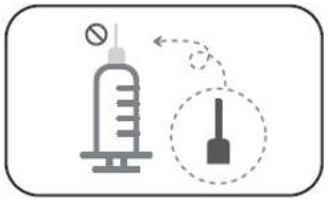


(5) Tusuk jarum suntik yang telah mengambil air steril untuk injeksi melalui sumbat karet vial serbuk dan perlahan-lahan suntikkan 4 mL air untuk injeksi ke dinding vial untuk menghindari timbulnya gelembung udara yang berlebihan.



Pemberian

(1) Periksa cairan Hemofe yang direkonstitusi sebelum pemberian dan harus berupa cairan bening yang tidak berwarna. Jangan gunakan jika ada masalah perubahan warna tertentu yang diamati.
(2) Desinfeksi kembali sumbat karet vial obat dengan alcohol swab.
(3) Buang jarum suntik dan pasang jarum *filter* yang bertanda ② pada kemasan.



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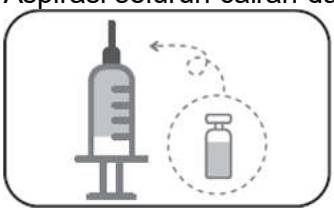
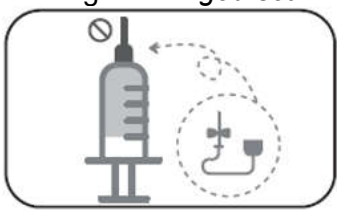
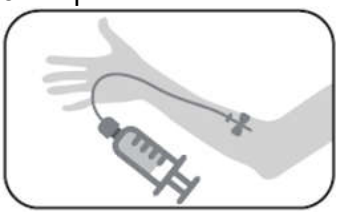
(4) Aspirasi seluruh cairan dalam vial ke dalam jarum suntik.



(5) Buang jarum *filter*, lepaskan luer adapter yang melekat pada *winged set* intravena, hubungkan *winged set* dengan *syringe*, dan keluarkan udara dari jarum intravena.



(6) Ikat *tourniquet* dan bersihkan kulit tempat injeksi dengan *alcohol swab*; lepaskan *tourniquet* setelah *venipuncture* dan berikan obat dengan injeksi intravena. Pemberian intravena harus diselesaikan biasanya dalam beberapa menit. Laju injeksi harus disesuaikan dengan tingkat kenyamanan dan toleransi pasien, dengan laju maksimum 5 mL per menit.



(7) Jangan memberikan Hemofe dalam tabung atau wadah yang sama seperti obat lain. Setelah menyuntikkan Hemofe, lepaskan dan buang jarum IV dengan benar. Semua cairan yang tidak digunakan, vial kosong, jarum bekas dan jarum suntik harus dibuang dalam wadah yang sesuai untuk mencegah melukai orang lain karena pembuangan yang tidak tepat.

HEMOFE 250 IU and 1000 IU Lyophilized Powder for Injection

This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Trade name: HEMOFE 250 IU and 1000 IU Lyophilized powder for injection

Generic name: Omfiloctocog alfa (Recombinant Human Coagulation Factor VIII)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substances: Omfiloctocog alfa (Recombinant human coagulation factor VIII)

Excipients: sodium chloride, arginine hydrochloride, sucrose, histidine, calcium chloride, and polysorbate 80

HEMOFE 250 IU lyophilized powder for injection
Each powder vial contains nominally 250 IU omfiloctocog alfa.
After reconstitution, 1 mL of solution contains approximately 62.5 IU omfiloctocog alfa.

HEMOFE 1000 IU lyophilized powder for injection
Each powder vial contains nominally 1000 IU omfiloctocog alfa.
After reconstitution, 1 mL of solution contains approximately 250 IU omfiloctocog alfa.

The potency (IU) is determined using the Chinese Pharmacopoeia one-stage clotting assay.
The specific activity of HEMOFE is approximately 6,000-14,000 IU/mg protein.

Omfiloctocog alfa (human coagulation factor VIII) is a purified protein that has 1,438 amino acids with an approximate molecular mass of 170 kDa. It is produced by recombinant DNA (rDNA) technology in Chinese hamster ovary (CHO) cells.

Omfiloctocog alfa is a B-domain truncated recombinant human coagulation factor VIII (the remained B-domain consists of 14 amino acids of the wild type B-domain) with glycosylation, sulfation and other modifications in the amino acid sequence.

Excipient with known effect:
154 mmol sodium chloride (9 mg) per mL of reconstituted solution.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Lyophilized powder for injection + solvent

HEMOFE is white to off-white loose body or a little powder, without melting signs; it should be colorless and transparent liquid after reconstitution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

HEMOFE is indicated for use in adults and children with hemophilia A (congenital deficiency of factor VIII) for on-demand treatment and prophylaxis of bleeding episodes.

Since there is no data available, HEMOFE is not indicated for prophylaxis of bleeding in perioperative setting.

HEMOFE is not indicated for the treatment of von Willebrand disease (vWD).

4.2 Posology and method of administration

Treatment should be initiated under the supervision of a physician experienced in the treatment of hemophilia.

Previously untreated patients
The safety and efficacy of HEMOFE in previously untreated patients have not yet been established.

Treatment monitoring
During the course of treatment, appropriate determination of factor VIII activity is advised to guide adjustments of the dosing regimen of HEMOFE, if needed. Due to different half-lives and incremental recoveries, individual patients may vary in their responses to factor VIII.

Doses based on bodyweight may require adjustments in underweight or overweight patients. In the case of major surgical interventions in particular, precise monitoring of the factor VIII substitution therapy by measurement of plasma factor VIII activity is indispensable.

When using an in vitro activated partial thromboplastin time (aPTT)-based one stage clotting assay for determining factor VIII activity in patients' blood samples, plasma factor VIII activity results can be significantly affected by the type of aPTT reagent and the reference standard used. Also, there can be significant discrepancies between assay results obtained by aPTT-based one stage clotting assay and the chromogenic assay according to European Pharmacopoeia. This is important particularly when changing the laboratory and/or reagents used in the assay.

The clinical effect of factor VIII is the most important element in evaluating the effectiveness of treatment. It may be necessary to adjust the individual dosing at the patient level in order to attain satisfactory clinical results. If the calculated dose fails to attain the expected factor VIII activity or if bleeding is not controlled after administration of the calculated dose, the presence of a circulating factor VIII-inhibitor in the patient should be suspected (see section 4.4).

Posology
The dose and duration of the replacement therapy depend on the severity of the factor VIII deficiency, the location and extent of the bleeding, as well as the patient's clinical condition. The number of units of factor VIII administered is expressed in International Units (IU), which are related to the current WHO concentrate standard for factor VIII products. Factor VIII activity in plasma is expressed either as a percentage (relative to normal human plasma) or preferably in International Units (relative to an International Standard for factor VIII in plasma). Plasma factor

VIII activity can be monitored using either a chromogenic substrate assay or a one stage clotting assay.

One International Unit (IU) of factor VIII activity is equivalent to that quantity of factor VIII in 1 mL of normal human plasma.

On demand treatment

The calculation of the required dose of factor VIII is based on the empirical finding that 1 International Unit (IU) factor VIII per kg body weight raises the plasma factor VIII activity by 2 IU/dL. The required dose is determined using the following formula:

Required units = body weight (kg) x desired factor VIII rise (%) (IU/dL) x 0.5 (IU/kg per IU/dL).

The amount to be administered and the frequency of administration should always be oriented to the clinical effectiveness in the individual case.

In the case of the following hemorrhagic events, the factor VIII activity should not fall below the given plasma activity level (in % of normal or IU/dL) in the corresponding period. **Table 1** below can be used to guide dosing in bleeding episodes:

Table 1 Guide for dosing in bleeding episodes

Degree of hemorrhage	FVIII level required (%)	Frequency of doses / Duration of therapy
Early hemarthrosis, muscle bleeding or oral bleeding	20-40	Repeat every 12-24 hours. At least 1 day, until the bleeding episode as indicated by pain is resolved or healing is achieved.
More extensive hemarthrosis, muscle bleeding or hematoma	30-60	Repeat injection every 12-24 hours for 3-4 days or more until pain and acute disability are resolved.
Life threatening hemorrhages	60-100	Repeat injection every 8-24 hours until threat is resolved.

Prophylaxis

All treatment decisions for identifying appropriate prophylactic treatment regimens should be guided by clinical judgment of the investigators based on individual patient characteristics and treatment response.

For long-term prophylaxis patients with severe hemophilia A, the usual recommended dose is 25-50 IU/kg every other day or 3 times a week (2-3 days between doses). Adjustments of doses and administration intervals may be considered based on achieved factor VIII activity and individual bleeding tendency. In some cases, especially in younger patients, shorter dosage intervals or higher doses may be necessary.

Older people

There is no experience in patients > 65 years.

Pediatric population

Pediatric patients (<6 years) have higher clearance and may require higher dosage and/or frequency.

Method of administration
Intravenous use.

HEMOFE should be administered by intravenous injection after reconstitution of the powder with 4 mL supplied solvent (sterilized water for injection). The rate of administration should be determined by the patient's comfort level up to a maximum of 5 mL/min depending on the total volume.

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Known allergic reaction to hamster protein.

4.4 Special warnings and precautions for use

Traceability
In order to improve traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Hypersensitivity
Hypersensitivity reactions are possible with HEMOFE. The product contains traces of hamster proteins, which in some patients may cause allergic reactions. If symptoms of hypersensitivity occur, patients should be advised to discontinue use of the medicinal product immediately and contact their physicians. Patients should be informed of the early signs of hypersensitivity reactions including hives, generalized urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis.

In case of anaphylaxis or shock, the current standard medical treatment for shock should be implemented.

Inhibitors
The formation of neutralizing antibodies (inhibitors) to factor VIII is a known complication in the management of individuals with hemophilia A. These inhibitors are usually IgG immunoglobulins directed against the factor VIII pro-coagulant activity, which are quantified in Bethesda Units (BU) per mL of plasma using the modified assay. The risk of developing inhibitors is correlated to the severity of the disease as well as the exposure to factor VIII, being highest within the first 50 exposure days but continuous throughout life although the risk is uncommon. Rarely, inhibitors may develop after the first 50 exposure days.

Cases of recurrent inhibitor (low titer) have been observed after switching from one factor VIII product to another in previously treated patients with more than 100 exposure days who have a previous history of inhibitor development. Therefore, it is recommended to monitor all patients carefully for inhibitor occurrence following any product switch.

The clinical relevance of inhibitor development depends on the titer of the inhibitor, with low titer posing a less risk of sufficient clinical response than high titer inhibitors. In general, all patients treated with coagulation factor VIII products should be carefully monitored for the development of inhibitors by appropriate clinical observations and laboratory tests. If the expected factor VIII

activity plasma levels are not attained, or if bleeding is not controlled with an appropriate dose, testing for factor VIII inhibitor presence should be performed. In patients with high levels of inhibitor, factor VIII therapy may not be effective and other therapeutic options should be considered. Management of such patients should be directed by physicians with experiences in the care of hemophilia and factor VIII inhibitors.

Cardiovascular events
In patients with existing cardiovascular risk factors, substitution therapy with Factor VIII may increase the cardiovascular risk.

Catheter-related complications
If a central venous access device (CVAD) is required, risk of CVAD-related complications including local infections, bacteremia and catheter site thrombosis should be considered. These complications have not been associated with the product itself.

Name and batch number of the medicinal product
It is strongly recommended that every time that HEMOFE is administered to a patient, the name and batch number of the product should be recorded in order to maintain a link between the patient and the batch number of the medicinal product.

Pediatric population
The listed warnings and precautions apply to both adults and children.

Excipient related considerations
After reconstitution this medicinal product contains 154 mmol sodium (9 mg) per mL of reconstituted solution.

4.5 Interaction with other medicinal products and other forms of interaction

No interactions of human coagulation factor VIII (rDNA) products with other medicinal products have been reported.

4.6 Fertility, pregnancy and lactation

Pregnancy
Animal reproduction studies have not been conducted with factor VIII. Based on the rare occurrence of hemophilia A in women, experiences regarding the use of factor VIII during pregnancy and breast-feeding are not available. Therefore, factor VIII should be used during pregnancy and lactation only if clearly indicated.

Fertility
No animal fertility studies have been conducted with HEMOFE and its effect on human fertility has not been established in controlled clinical trials. Since HEMOFE is a replacement protein of endogenous factor VIII, no adverse effects on fertility are expected.

4.7 Effects on ability to drive and use machines

HEMOFE has no influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

Hypersensitivity or allergic reactions (which may include angioedema, burning and stinging at the injection site, chills, flushing, generalized urticaria, headache, hives, hypotension, lethargy, nausea, restlessness, tachycardia, tightness of the chest, tingling, vomiting, and wheezing) have been observed rarely and may in some cases progress to severe anaphylaxis (including shock).

Very rarely development of antibodies to hamster protein and the related hypersensitivity reactions have been observed.

Development of neutralizing antibodies (inhibitors) may occur in patients with hemophilia A and treated with factor VIII, including with HEMOFE. If such inhibitors occur, the condition may manifest itself as an insufficient clinical response. In such cases, it is recommended that a specialized hemophilia center should be contacted.

Tabulated list of adverse reactions

Table 2 presented below is according to the MedDRA system organ classification (SOC and Preferred Term Level).

Frequencies have been evaluated according to the following convention: very common (≥1/10), common (≥1/100 to < 1/10), uncommon (≥1/1,000 to < 1/100), rare (≥1/10,000 to < 1/1,000), very rare (< 1/10,000); not known (cannot be estimated from the available data).

Within each frequency group, adverse reactions are presented in order of decreasing seriousness.

Table 2 Frequency of adverse drug reactions in clinical trials for PTPs*

System Organ Class	Adverse reaction	Frequency**
Gastrointestinal Disorders	Diarrhea	Common
Cardiac Disorders	Ventricular Extrasystoles	Uncommon
Investigations	Aspartate Aminotransferase Elevated	Uncommon
Investigations	Blood Pressure Increased	Uncommon
Nervous System Disorders	Somnolence	Uncommon
Blood and lymphatic system disorders	Factor VIII inhibition	Uncommon

* PTPs: Previously-treated patients.

** Frequency is based on studies of all factor VIII products and the studies included patients with severe hemophilia A.

Description of selected adverse reactions

During all clinical studies with HEMOFE in previously treated patients, a total of 8 adverse reactions were reported in 9 of 222 patients exposed to HEMOFE. The common adverse reactions were diarrhea.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions.

Pharmaceutical Industry Reporting Contacts
PT ETANA BIOTECHNOLOGIES INDONESIA
Kawasan Industri Pulogadung, Jl. Rawa Gelam V, Blok. L, Kav. 11-13, Jakarta
Email: pv@id.etanabiotech.com
Website: https://ebi-pharmacovigilance.azurewebsites.net/

MESO Center / National Pharmacovigilance Center
Direktorat Pengawasan Distribusi Produk Terapetik dan PKRT Badan POM RI
Jl. Percetakan Negara 23 Jakarta Pusat, 10560
No Telp: 021 – 4244 755 ext.111
Fax: 021 – 4288 3485
Email: pv-center@pom.go.id and Indonesia-meso-badanpom@hotmail.com

4.9 Overdose

No symptoms of overdose with recombinant coagulation factor VIII have been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antihemorrhagics, blood coagulation factor VIII, ATC code: B02BD02

Mechanism of action
HEMOFE (INN: omfiloctocog alfa), a glycoprotein, is a human coagulation factor VIII with a truncated B-domain. It has the same structure as human factor VIII when activated, and post-translational modifications are similar to those of the plasma-derived molecules. When injected into a hemophilia patient, factor VIII binds to endogenous von Willebrand Factor in the patient's circulation.

The factor VIII/von Willebrand factor complex consists of two molecules (factor VIII and von Willebrand factor) with different physiological functions. Activated factor VIII acts as a co-factor for activated factor IX, accelerating the conversion of factor X to activated factor X. Activated factor X converts prothrombin into thrombin. Thrombin then converts fibrinogen into fibrin and a clot can be formed. Hemophilia is a sex-linked hereditary disorder of blood coagulation due to decreased levels of factor VIII, which result in profuse bleeding into joints, muscles or internal organs, either spontaneously or as a result of accidental or surgical trauma. By replacement therapy the plasma levels of factor VIII are increased, thereby enabling a temporary correction of the factor deficiency and correction of bleeding tendencies.

Clinical efficacy during prophylaxis and treatment of bleeding episodes

Prophylaxis in adolescents/adults
The clinical efficacy of HEMOFE for prophylaxis in adolescents and adults (≥ 12 years) was investigated in a prospective, multi-center clinical studies in 73 previously treated patients (PTPs) with severe hemophilia A. Subjects received HEMOFE 25-50 IU/kg every other day or three times a week for 24 weeks of prophylaxis. Fifty-five (75.3%) subjects received prophylactic treatment 3

times per week, and 20 (27.4%) subjects received prophylactic treatment every other day. Five patients adjusted their dosage of HEMOFE and two of them also adjusted their prophylactic frequencies. The mean dose (range) for all prophylaxis regimens was 34.8 (25.1-46.8) IU/kg.

Fitting the bleeding events to the negative binomial model for calculation, the estimated mean (95% CI) of annualized bleeding rate (ABR) in adults and adolescents receiving HEMOFE was 2.82 (2.01, 3.96), whereas the spontaneous ABR was 1.29 (0.87, 1.92), traumatic ABR 1.33 (0.82, 2.16) and joint ABR 2.07 (1.40, 3.06). Of the 73 adults/adolescents on prophylaxis, 34 (43.8%) did not have any bleeds.

Of note, ABR is not comparable between different factor concentrates and different clinical studies.

Prophylaxis in children

The clinical efficacy of HEMOFE for prophylaxis in children (< 12 years) was investigated in a prospective, multicenter, open-label, non-controlled pivotal clinical trial. Seventy patients with FVIII exposure ≥50 EDs (<6 years old) and ≥150 EDs (6-12 years old) with severe (FVIII:C<1%) haemophilia A, received HEMOFE for 24 weeks of prophylaxis at 25-50 IU/kg, every other day or 3 times a week. Of 69 patients, 52 patients (75.4%) received prophylactic treatment three times a week, 32 patients (46.4%) received prophylactic treatment every other day, and 15 patients received dosing schedule adjustment once. The mean (SD) dose for prophylactic treatment is 34.2(5.2) IU/kg per injection.

Fitting the bleeding events to the negative binomial model for calculation, the mean (95% CI) of the total annualized bleeding rate (ABR) of all bleeding events in 68 subjects was 4.80 (3.61, 6.38), The mean (95% CI) of the total annualized bleeding rate (ABR) of bleeding events requiring treatment was 4.05 (2.96, 5.55).

Treatment of bleeding episodes during prophylaxis and during on-demand treatment

The efficacy of HEMOFE in the treatment of bleeding episodes was demonstrated in all age groups.

Based on the data from clinical study report (CSR) of clinical trial SCT800-A302, in 73 patients above 12 years of age, 94 breakthrough bleeding episodes were treated with HEMOFE during above prophylactic treatment study. During the period from start to the end of bleeding episodes, the hemostatic efficacy evaluated 8 hours after drug injections was “excellent” in 50 (53.2%) and “good” in 37 (39.4%) of the bleeding episodes, with a success rate of 92.6%. The average number of injections for each bleeding episode was 1.4, and 84 (89.4%) of bleeding episodes were resolved with 1-2 infusions.

Based on the data from CSR of clinical trial SCT800HA3, in an on-demand treatment study, 60 patient (≥12 years) with hemophilia A (FVIII:C ≤ 5%[FVIII:C＜1% in 54 patients], ≥50 EDs) were treated with HEMOFE, and the study lasted for 6 months. Among 1079 bleeding episodes recorded, the hemostatic efficacy evaluated 8 hours after all the bleeding episodes visits was “excellent” in 43.3% and “good” in 46.1%, with a success rate of 89.4%. The average number of injections for each bleeding episode was 1.5, and 92% of the bleeding episodes were resolved with 1-2 injections.

Based on the data from CSR of clinical trial SCT800-A303, in 68 patients below 12 years of age, 127 bleeding events required treatment of HEMOFE during the study. Of the 126 bleeding episodes

available for haemostatic efficacy assessment, the treatment success rate (excellent and good) was 92.1% (116 episodes). The average number of injections of this product from the start to the stop of bleeding was 1.9 and 100 (84.7%) bleeding events were resolved with 1-2 infusions.

5.2 Pharmacokinetic properties

Based on the data from CSR of clinical trial SCT800-A302, the PK profile of HEMOFE was evaluated in 18 PTPs (17 adults and 1 adolescents) with severe hemophilia A following the initial and repeated doses (after 24 weeks treatment) of 50 IU/kg. The plasma concentration was tested using both the one-stage clotting assay and the chromogenic assay. The PK profile obtained 6 months after the initial PK assessment was comparable with the PK profile obtained after the first dose. The PK parameters of SCT800 in the PK study are listed in **Table 3**.

Table 3 Single-dose Pharmacokinetics Parameters of HEMOFE 50 IU/kg in adolescents and adults using one-stage and chromogenic assay (Mean ± Standard Deviation).

Parameters N=No. of patients	One-stage Clotting Assay (N=18)		Chromogenic Assay (N=18)	
	Initial	24th Week Visit	Initial	24th Week Visit
AUC_{last} (IU*h/mL)	8.89±2.36	9.97±3.08	12.36±3.58	12.71±4.40
$AUC_{0\text{-}inf}$ (IU*h/mL)	9.40±2.74	10.72±3.76	13.35±4.37	13.83±5.47
$t_{1/2}$ (h)	10.26±3.27	10.95±4.34	11.52±3.61	11.43±3.96
IVR (IU/dL)/(IU/kg)	1.97±0.51	1.96±0.45	2.01±0.36	1.98±0.46
CL (mL/h/kg)	6.34±2.13	5.81±2.22	5.09±1.62	5.15±1.90
C_{max} (IU/mL)	1.08±0.28	1.08±0.24	1.25±0.23	1.23±0.28
V_{ss} (mL/kg)	79.40±16.81	77.84±18.27	68.91±9.54	73.28±17.46
$MRT_{(0\text{-}inf)}$ (h)	13.45±4.58	14.84±5.80	14.73±4.97	15.63±5.54

Based on the data from CSR of clinical trial SCT800-A303, the pharmacokinetics of HEMOFE were evaluated in 31 previously treated children (0 to <12 years of age) with severe haemophilia A following an intravenous injection of a single dose of 50 IU/kg. The plasma concentration was tested by the central laboratory using one-stage method. In comparison with children 6-12 years of age, children less than 6 years of age may have a higher clearance and shorter half-life and may need higher doses (**Table 4**).

Table 4 Single-dose pharmacokinetic parameters of HEMOFE 50 IU/kg in children using the one-stage assay (Mean ± Standard Deviation)

Parameter N=No. of patients	＜6 years old (N=16)	6-12 years old (N=15)	0-12 years old (N＝31)
AUC_{last} (IU*h/mL)	7.08 ±2.10	9.93 ± 3.40	8.51 ± 3.13
$AUC_{0\text{-}inf}$ (IU*h/mL)	7.52 ± 2.08	10.61 ± 3.69	9.06 ± 3.33

$t_{1/2}$(h)	6.73 ± 1.70	10.20 ± 2.92	8.41 ± 2.92
IVR (IU/dL)/(IU/kg)	2.04 ± 0.67	1.90 ±0.35	1.97 ± 0.53
CL (mL/h/kg)	7.78 ± 1.96	5.68 ± 1.71	6.73 ± 2.10
C_{max} (IU/mL)	1.12 ± 0.37	1.02 ± 0.21	1.07 ± 0.30
Vss (mL/kg)	70.74 ± 16.50	75.44 ± 14.85	73.09 ± 15.61
$MRT_{0\text{-}inf}$ (h)	9.37 ± 2.20	14.09 ± 3.77	11.73 ± 3.87

5.3 Preclinical safety data

Non-clinical data revealed no special concerns for humans based on the conventional safety assessments of safety pharmacology, repeated-dose toxicity, immunogenicity and immunotoxicity, local tolerability and haemolyticus studies.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lyophilized Powder for Injection:
Omfiloctocog alfa; sodium chloride; arginine hydrochloride; sucrose, histidine; calcium chloride; Polysorbate 80

Solvent:
Sterilized water for injection

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products or reconstituted with injection solutions other than the provided solvent. The reconstituted product should not be administered in the same tubing or container with other medicinal products.

6.3 Shelf life

Unopened vial:
Stored in refrigerator (2°C - 8°C), please use before the expiration date printed on the label or box.

Reconstituted solution:
From a microbiological point of view, the product should be used immediately. If not, in-use storage time and conditions prior to use are the responsibility of the users. Do not refrigerate after reconstitution. Any unused product stored at room temperature for more than 3 hours should be discarded.

6.4 Special precautions for storage

Stored in refrigerator (2°C - 8°C).

Do not freeze.

For storage at room temperature and storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Each pack of HEMOFE contains:
1 vial of recombinant human coagulation factor VIII lyophilized powder for injection
1 ampoule of sterilized water for injection 10 mL
1 sterile disposable syringe and needle
1 disposable filter needle
1 disposable IV needle

Recombinant human coagulation factor VIII for injection packaging materials: class I glass bottle, butyl rubber stopper, and aluminum plastic cover.

6.6 Special precautions for disposal and other handling

Detailed instructions for preparation and administration are contained in the Patient Information Leaflet provided with HEMOFE.

HEMOFE is to be administered intravenously after reconstitution of the powder with the supplied solvent (using 4 mL from the supplied 10 mL sterilized water for injection). After reconstitution the solution appears as a clear or slightly opalescent solution. The reconstituted medicinal product should be inspected visually for particulate matter and discoloration prior to administration. The solution should be clear and colorless. Do not use solutions that are cloudy or have deposits.

The medicinal product must be prepared for injection under aseptic conditions. If any component of the package is opened or damaged, do not use this component. The reconstituted product must be filtered prior to administration to remove potential particulate matter in the solution.

An infusion set (butterfly needle with tubing), sterile alcohol swabs, gauze pads and plasters will also be needed. These devices are not included in the HEMOFE package.

HEMOFE is for single use only.

Disposal:

After injection, safely dispose of all unused HEMOFE solution, the syringe with the injection set, the vial, and other waste materials. Do not throw it out with the ordinary household waste.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION NUMBERS

Box, 1 vial with 250 IU active ingredient + 1 ampoule with 10 ml solvent

Reg. No. XXXXXXXXXXXXXXX

Box, 1 vial with 1000 IU active ingredient + 1 ampoule with 10 ml solvent

Reg. No. XXXXXXXXXXXXXXX

HARUS DENGAN RESEP DOKTER

Berbahan Halal dan Dalam Upaya Memenuhi Proses Halal

8. REGISTERED & SECONDARY PACKED BY

PT Etana Biotechnologies Indonesia
Jakarta – Indonesia

9. MANUFACTURED BY

Lyophilized Powder for Injection:
Sinocelltech, Ltd.
No. 31, Kechuang 7th Street, Beijing Economic and Technological Development Area
Beijing – China

Solvent:

Shijiazhuang No.4 Pharmaceutical Co., Ltd.

No. 518 East Huaian Road, High-Tech Industrial Development Zone, Shijiazhuang

10. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

DD/MM/YYYY

11. DRUG CLASSIFICATION

Ethical Drug