

Koāte®-DVI

Faktor Antihemofilia (*Human*)

Baca leaflet ini dengan seksama sebelum Anda mulai menggunakan obat ini.

- Simpan leaflet ini. Anda mungkin perlu membacanya lagi.
- Jika Anda memiliki pertanyaan lebih lanjut, tanyakan kepada dokter atau apoteker Anda.
- Obat ini diresepkan untuk Anda. Jangan berikan kepada orang lain. Ini dapat membahayakan mereka, bahkan jika gejalanya sama dengan Anda.
- Jika salah satu efek samping menjadi serius, atau jika terdapat efek samping yang tidak tercantum dalam leaflet ini, silakan hubungi dokter atau apoteker Anda.

Dalam leaflet ini:

1. Apa itu Koāte-DVI dan indikasi penggunaannya
2. Sebelum Anda menggunakan Koāte-DVI
3. Cara menggunakan Koāte-DVI
4. Efek samping yang mungkin terjadi
5. Cara menyimpan Koāte-DVI
6. Informasi lebih lanjut

APA ITU KOĀTE-DVI DAN INDIKASI PENGGUNAANNYA

Koāte-DVI digunakan untuk pengobatan dan pencegahan perdarahan, atau untuk melakukan operasi darurat dan elektif, untuk pasien dengan hemofilia A (defisiensi faktor VIII bawaan).

Koāte-DVI adalah salah satu golongan obat yang disebut sebagai faktor pembekuan darah.

Koāte-DVI mengandung faktor koagulasi VIII (*human*) yang diperoleh dari plasma manusia.

Koāte-DVI menggantikan (sementara) faktor pembekuan darah yang hilang dengan tujuan mengendalikan atau mencegah episode perdarahan.

SEBELUM ANDA MENGGUNAKAN KOĀTE-DVI

Jangan menggunakan Koāte-DVI jika Anda alergi terhadap faktor pembekuan VIII (*human*) atau komposisi lainnya dari obat ini.

Jika Anda ingin informasi lebih rinci, tanyakan kepada dokter Anda.

Peringatan dan tindakan pencegahan

Bicarakan dengan dokter, apoteker atau perawat Anda sebelum menggunakan Koāte-DVI. Anda dapat mengalami reaksi anafilaktik (reaksi alergi berat) seperti ruam, rasa sesak di dada, pusing, mual, muntah, atau kesulitan bernapas, meskipun reaksi di atas jarang terjadi. Jika terdapat gejala tersebut, Anda harus segera menghentikan penggunaan produk ini dan hubungi dokter Anda.

Dokter Anda harus melakukan beberapa pemeriksaan untuk memastikan bahwa dosis Koāte-DVI yang Anda terima sudah cukup untuk mencapai dan mempertahankan kadar faktor koagulasi VIII dalam batas normal sehingga dapat menghentikan pendarahan.

Jika pendarahan Anda tidak terkontrol dengan Koāte-DVI, segera konsultasikan dengan dokter Anda. Ada kemungkinan Anda memiliki penghambat (inhibitor) faktor koagulasi VIII. Ini adalah antibodi yang menghalangi efek pembekuan darah dari faktor koagulasi VIII. Dokter Anda akan melakukan beberapa pemeriksaan untuk memastikan apakah inhibitor tersebut ada dalam darah Anda.

Jika Anda memerlukan Koāte-DVI dengan dosis besar dan/atau frekuensi yang sering, dan Anda memiliki golongan darah A, B, atau AB, ada kemungkinan Anda dapat mengalami penghancuran sel darah merah yang cepat (anemia hemolitik akut) yang dapat menyebabkan perdarahan. Dokter Anda akan memeriksa tanda-tanda anemia pada Anda, dan jika didapatkan, dokter akan meminta Anda berhenti menggunakan Koāte-DVI dan memulai terapi yang sesuai.

Koāte-DVI terbuat dari plasma manusia. Produk yang terbuat dari plasma manusia dapat mengandung agen infeksius, seperti virus, yang dapat menyebabkan penyakit. Risiko penularan agen infeksius telah diminimalisasi dengan melakukan penyaringan (*screening*) terhadap donor plasma untuk mengetahui adakah riwayat paparan terhadap virus tertentu, dengan mendeteksi keberadaan infeksi virus, dan dengan menonaktifkan dan/atau menghilangkan virus tertentu. Terlepas dari langkah-langkah tersebut, karena produk ini dibuat dari darah manusia, ia dapat membawa risiko penularan agen infeksius, misal, virus dan, secara teoritis, agen penyakit Creutzfeldt-Jakob (CJD). Ada juga kemungkinan bahwa agen infeksius yang belum teridentifikasi terdapat dalam produk tersebut.

Sangat disarankan untuk mencatat nama dan nomor *batch* produk setiap kali Anda menerima dosis Koāte-DVI agar dapat melanjutkan pencatatan semua *batch* yang telah digunakan.

Konsumsi Obat Lainnya

Beri tahu dokter atau apoteker Anda jika Anda sedang minum, baru saja minum atau hendak mengonsumsi obat lain.

Tidak ada interaksi antara Koāte-DVI dengan obat-obatan lain.

Jangan mencampur Koāte-DVI dengan obat lain yang Anda terima melalui suntikan. Gunakan hanya set infus yang disediakan karena Koāte-DVI dapat menempel pada set infus lainnya.

Hamil dan Menyusui

Berdasarkan kejadian hemofilia A yang jarang terjadi pada wanita, pengalaman penggunaan Koāte-DVI pada masa kehamilan dan menyusui tidak tersedia.

Penggunaan pada Anak-anak

Belum ada studi penggunaan Koāte-DVI pada anak-anak, namun Koāte-DVI telah digunakan secara luas pada anak-anak. Efek samping yang dilaporkan dari anak-anak tidak berbeda dari yang dilaporkan oleh orang dewasa.

CARA PENGGUNAAN KOĀTE-DVI

Jumlah Koāte-DVI yang harus Anda gunakan tergantung pada beberapa faktor, seperti berat badan, status klinis dan jenis serta tingkat keparahan perdarahan Anda. Dokter Anda akan menghitung dosis, frekuensi dan interval pemberian Koāte-DVI untuk mencapai kadar faktor koagulasi VIII yang sesuai pada darah Anda.

Bicarakan dengan dokter Anda tentang kapan Anda harus mengonsumsi Koāte-DVI.

Dokter Anda akan memberitahu lama perawatan Anda dengan Koāte-DVI.

Produk hanya dapat disuntikkan langsung ke pembuluh darah (secara intravena).

Gunakan Koāte-DVI dalam waktu 3 jam setelah dilarutkan (pencampuran dengan air steril untuk injeksi).

Anda akan diberikan pelatihan penuh sebelum menggunakan Koāte-DVI tanpa pengawasan rumah sakit. Silakan merujuk ke semua materi pelatihan Anda atau hubungi pusat hemofilia lokal untuk informasi lebih lanjut.

Larutkan produk seperti yang dijelaskan di akhir leaflet ini.

Anda tidak boleh mengadministrasikan Koāte-DVI sendiri: selalu didampingi oleh orang dewasa yang dapat bertanggung jawab.

Kecepatan pemberian tidak boleh lebih dari 10 mL/menit untuk menghindari efek samping yang tidak diinginkan.

Jangan berhenti menggunakan Koāte-DVI tanpa berkonsultasi dengan dokter Anda.

Jika Anda memiliki pertanyaan lebih lanjut tentang penggunaan obat ini, tanyakan kepada dokter, apoteker atau perawat Anda.

KEMUNGKINAN EFEK SAMPING

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

Efek samping yang paling umum pada uji klinis adalah rasa gugup, sakit kepala, nyeri perut, mual, parestesia (kesemutan di tangan, kaki) dan penglihatan yang kabur.

Pasien juga melaporkan adanya penghambat faktor koagulasi VIII; anemia hemolitik; hipersensitivitas (reaksi alergi) termasuk reaksi anafilaktik, ruam, dan urtikaria; perdarahan dari lokasi penyuntikan; dan kejang.

Pelaporan Efek Samping

Jika salah satu efek samping menjadi serius, atau jika terdapat efek samping yang tidak tercantum dalam leaflet ini, silakan beritahu dokter Anda.

CARA PENYIMPANAN KOÅTE-DVI

Jauhkan dari jangkauan dan pandangan anak-anak.

Simpan paket Koåte-DVI pada suhu 2° C hingga 8 ° C. Jangan dibekukan.

Koåte-DVI boleh disimpan dalam suhu kamar (tidak lebih dari 25°C) selama 6 bulan.

Jangan gunakan setelah tanggal kadaluwarsa.

Gunakan Koåte-DVI yang telah dilarutkan segera atau dalam waktu 3 jam setelah dilarutkan.

Setiap produk atau bahan limbah yang tidak digunakan harus dibuang sesuai dengan persyaratan lokal.

INFORMASI LAINNYA

Bentuk sediaan Koåte-DVI dan isi kemasan

Koåte-DVI tersedia dalam bentuk sediaan padat (endapan) steril berwarna putih hingga kuning pucat yang dikemas dalam vial kaca dengan *stopper*, *metal ring*, tutup plastik, dan *shrink band*.

Botol pelarut berisi air steril untuk injeksi. Air jernih dan tidak berwarna.

Jika dilarutkan dengan air steril yang disediakan, larutan Koåte-DVI akan tampak jernih hingga putih berkilau dan tidak berwarna hingga kuning pucat.

Setiap karton dilengkapi dengan vial sekali pakai yang mengandung faktor antihemofilia (*human*), 5 mL atau 10 mL air steril untuk injeksi, 1 jarum transfer steril *double-ended*, 1 jarum filter steril, dan 1 set administrasi steril.

Bahan

Bahan aktif: Faktor Antihemofilia (*Human*)

Bahan tambahan: natrium klorida, kalsium klorida, L-histidin, albumin manusia, air

Koāte-DVI juga mengandung faktor von Willebrand yang terbentuk secara alami, faktor pembekuan darah yang berbeda. Faktor VIII dan faktor von Willebrand terdapat pada plasma dalam bentuk ikatan. Keduanya ditemukan terikat bersama dalam Koāte-DVI.

HARUS DENGAN RESEP DOKTER

KEMASAN DAN NOMOR REGISTRASI

Reg. No.: Koāte-DVI 250IU: DK12590501744A1
Koāte-DVI 500IU: DK12590501744B1
Koāte-DVI 1000IU: DK12590501744B1

Diimpor oleh:

PT Combiphar
Bandung Barat, Indonesia

Diproduksi oleh:

Grifols Therapeutics LLC
North Carolina, USA

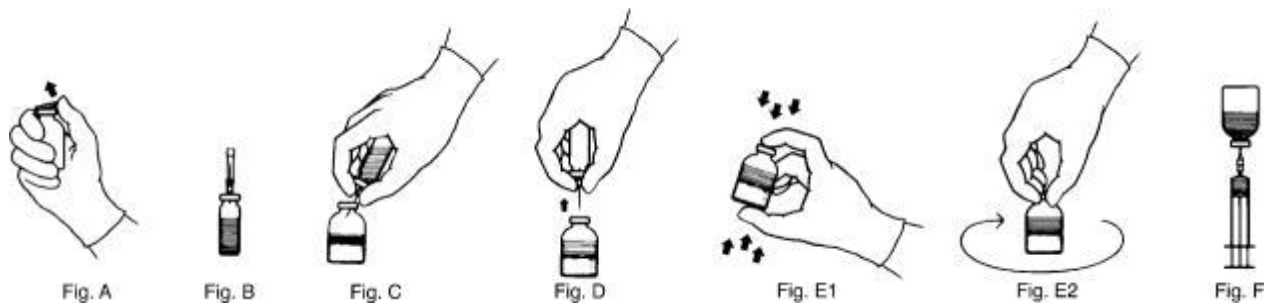
Penyediaan dan Penggunaan

Catatan: Teknik aseptik harus diikuti dengan cermat. Semua jarum dan tutup vial yang akan bersentuhan dengan produk yang akan diberikan melalui intravena tidak boleh bersentuhan dengan permukaan yang tidak steril. Jarum yang terkontaminsai harus dibuang dengan menempatkannya ke dalam wadah yang tahan tusukan, dan gunakan peralatan yang baru.

1. Setelah mengeluarkan semua peralatan dari kotak, hangatkan air steril (pengencer) pada suhu ruangan (25°C).
2. Lepaskan segel pengaman dari botol produk. Jika segel pengaman hilang atau menunjukkan tanda-tanda kerusakan, jangan gunakan produk tersebut dan segera hubungi **PT Combiphar [Telepon 0800-1-800088, WhatsApp 0818 0680 0088, email combicarecenter@combiphar.com]**.
3. Lepaskan penutup plastic dari setiap vial (Gambar a). Bersihkan penutup vial (sumbat abu-abu) dengan kapas beralkohol dan biarkan permukaannya kering. Setelah dibersihkan, hangan biarkan apapun menyentuh sumbat lateks (karet).
4. Lepaskan selubung plastic dari ujung pendek jarum transfer dengan hati-hati. Masukkan jarum yang terbuka ke dalam vial pengencer hingga ke pangkalnya (Gambar B).
5. Pegang dengan hati-hati selubung ujung jarum transfer yang lain dan putar untuk melepaskannya.
6. Balikkan vial pengencer dan masukkan jarum yang terpasang ke dalam vial konsentrat dengan sudut 45° (Gambar C). Ini akan mengarahkan aliran pengencer ke dinding vial konsentrat dan meminimalkan pembentukan busa. Vakum akan menarik pengencer ke dalam vial konsentrat. **
7. Lepaskan botol pengencer dan jarum transfer (Gambar D).

8. Setelah menambahkan pelarut, segera kocok dengan kuat selama 10 – 15 detik (Gambar E1), kemudian putar terus hingga larut sepenuhnya (Gambar E2). Akan terjadi sedikit pembuihan, tetapi usahakan untuk menghindari pembuihan yang berlebihan. Kemudian vial harus diperiksa secara visual untuk melihat adanya partikel dan perubahan warna sebelum diberikan..
9. Bersihkan kembali bagian atas vial Koate-DVI yang telah dilarutkan dengan kapas beralkohol dan biarkan permukaannya kering.
10. Pasang jarum filter (dari kemasan) ke jarum suntik steril, Ambil larutan Koate-DVI ke dalam jarum suntik melalui jarum filter (Gambar F).
11. Lepaskan jarum filter dari spuit dan ganti dengan jarum suntik atau jarum kupu-kupu yang sesuai untuk pemberian obat. Buang jarum filter ke dalam wadah yang tahan tusukan.
12. Jika pasien yang sama menggunakan lebih dari satu vial Koate-DVI, isi dari beberapa vial dapat disedot ke dalam jarum suntik yang sama melalui jarum filter yang disediakan.

** Jika vakum hilang dalam botol konsentrat selama rekonstitusi, gunakan jarum suntik steril untuk mengeluarkan air steril dari vial pengencer dan suntikkan ke dalam vial konsentrat, arahkan aliran cairan ke dinding vial.



Koāte[®]-DVI

Antihemophilic Factor (Human)

Double Viral Inactivation

Solvent/Detergent Treated and Heated in Final Container at 80°C

DESCRIPTION

Antihemophilic Factor (Human), Koāte[®]-DVI, is a sterile, stable, purified, dried concentrate of human Antihemophilic Factor (AHF, Factor VIII) which has been treated with tri-n-butyl phosphate (TNBP) and polysorbate 80 and heated in lyophilized form in the final container at 80°C for 72 hours. Koāte-DVI is intended for use in therapy of classical hemophilia (hemophilia A).

Koāte-DVI is purified from the cold insoluble fraction of pooled fresh-frozen plasma by modification and refinements of the methods first described by Hershgold, Pool, and Pappenhagen.⁽¹⁾ Koāte-DVI contains purified and concentrated Factor VIII. The Factor VIII is 300–1000 times purified over whole plasma. Part of the fractionation may be performed by another licensed manufacturer. When reconstituted as directed, Koāte-DVI contains approximately 50–150 times as much Factor VIII as an equal volume of fresh plasma. The specific activity, after addition of Albumin (Human), is in the range of 9–22 IU/mg protein.

Koāte-DVI must be administered by the intravenous route.

Koāte-DVI contains antihemophilic factor activity in international units (IU). One IU, as defined by the World Health Organization standard for blood coagulation Factor VIII, human, is approximately equal to the level of Factor VIII found in 1.0 mL of fresh pooled human plasma. The final product when reconstituted as directed contains not more than (NMT) 1500 µg/mL polyethylene glycol (PEG), NMT 0.05 M glycine, NMT 25 µg/mL polysorbate 80, NMT 5 µg/g tri-n-butyl phosphate (TNBP), NMT 3 mM calcium, NMT 1 µg/mL aluminum, NMT 0.06 M histidine, and NMT 10 mg/mL Albumin (Human).

CLINICAL PHARMACOLOGY

Hemophilia A is a hereditary bleeding disorder characterized by deficient coagulant activity of the specific plasma protein clotting factor, Factor VIII. In afflicted individuals, hemorrhages may occur spontaneously or after only minor trauma. Surgery on such individuals is not feasible without first correcting the clotting abnormality. The administration of Koāte-DVI provides an increase in plasma levels of Factor VIII and can temporarily correct the coagulation defect in these patients.

After infusion of Antihemophilic Factor (Human), there is usually an instantaneous rise in the coagulant level followed by an initial rapid decrease in activity, and then a subsequent much slower rate of decrease in activity.⁽²⁻⁴⁾ The early rapid phase may represent the time of equilibration with the extravascular compartment, and the second or slow phase of the

survival curve presumably is the result of degradation and reflects the true biologic half-life of the infused Antihemophilic Factor (Human).(3)

The removal and inactivation of spiked relevant and model enveloped and non-enveloped viruses during the manufacturing process for Koāte-DVI have been validated in laboratory studies at Grifols Therapeutics LLC. Studies performed with the model enveloped viruses indicated that the greatest reduction was achieved by TNBP/polysorbate 80 treatment and 80°C heat. For this reason, VSV (Vesicular Stomatitis Virus, model for RNA enveloped viruses) and HIV-1 (Human Immunodeficiency Virus Type 1) were studied only at these two steps of the manufacturing process. The efficacy of the dry heat treatment was studied using all of the viruses, including BVDV (Bovine Viral Diarrheal Virus, model for hepatitis C virus) and Reo (Reovirus Type 3, model for viruses resistant to physical and chemical agents, such as hepatitis A), and the effect of moisture content on the inactivation of HAV (Hepatitis A Virus), PPV (Porcine Parvovirus, model for parvovirus B19), and PRV (Pseudorabies Virus, model for large enveloped DNA viruses) was investigated.

Table 1. Summary of In Vitro Log₁₀ Viral Reduction Studies

	Enveloped Model Viruses				Non-enveloped Model Viruses		
	HIV-1	BVDV	PRV	VSV	Reo	HAV	PPV
Model for	HIV-1/2	HCV	Large enveloped DNA viruses	RNA enveloped viruses	HAV and viruses resistant to chemical and physical agents	HAV	B19
Global Reduction Factor	≥9.4	≥10.3	≥9.3	≥10.9	9.4	≥4.5	3.7

Similar studies have shown that a terminal 80°C heat incubation for 72 hours inactivates non-lipid enveloped viruses such as hepatitis A and canine parvovirus in vitro, as well as lipid enveloped viruses such as hepatitis C.(5-7)

Koāte-DVI is purified by a gel permeation chromatography step serving the dual purpose of reducing the amount of TNBP and polysorbate 80 as well as increasing the purity of the Factor VIII.

A two-stage clinical study using Koāte-DVI was performed in individuals with hemophilia A who had been previously treated with other plasma-derived Factor VIII concentrates. In Stage 1 of the pharmacokinetic study with 19 individuals, statistical comparisons demonstrated that Koāte-DVI is bioequivalent to the unheated product, Koāte®-HP. The incremental in vivo recovery ten minutes after infusion of Koāte-DVI was 1.90% IU/kg (Koāte-HP 1.82% IU/kg). Mean biologic half-life of Koāte-DVI was 16.12 hours (Koāte-HP 16.13 hours). In Stage II of the study, participants received Koāte-DVI treatments for six months on home therapy with a median of 52 days (range 23-94). No evidence of inhibitor formation was observed, either in the clinical study or in the preclinical investigations.(2)

INDICATIONS AND USAGE

Koāte-DVI is indicated for the treatment of classical hemophilia (hemophilia A) in which there is a demonstrated deficiency of activity of the plasma clotting factor, Factor VIII.

Koāte-DVI provides a means of temporarily replacing the missing clotting factor in order to control or prevent bleeding episodes, or in order to perform emergency and elective surgery on individuals with hemophilia.

Koāte-DVI contains naturally occurring von Willebrand factor, which is co-purified as part of the manufacturing process.

Koāte-DVI has not been investigated for efficacy in the treatment of von Willebrand disease, and hence is not approved for such usage.

CONTRAINDICATIONS

None known.

WARNINGS

Koāte-DVI is made from human plasma. Products made from human plasma may contain infectious agents, such as viruses, that can cause disease. The risk that such products will transmit an infectious agent has been reduced by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current virus infections, and by inactivating and/or removing certain viruses. Despite these measures, because this product is made from human blood, it may carry a risk of transmitting infectious agents, e.g., viruses and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent. There is also the possibility that unknown infectious agents may be present in such products. ALL infections thought by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to PT Combiphar [Phone 0800-1-800088, WhatsApp 0818 0680 0088, email combicarecenter@combiphar.com]. The physician should discuss the risks and benefits of this product with the patient, before prescribing or administering it to a patient.

Individuals who receive infusions of blood or plasma products may develop signs and/or symptoms of some viral infections, particularly hepatitis C. It is emphasized that hepatitis B vaccination is essential for patients with hemophilia and it is recommended that this be done at birth or diagnosis.(8,9) Hepatitis A vaccination is also recommended for hemophilic patients who are hepatitis A seronegative.

PRECAUTIONS

General

1. Koāte-DVI is intended for treatment of bleeding disorders arising from a deficiency in Factor VIII. This deficiency should be proven prior to administering Koāte-DVI.
2. Administer within 3 hours after reconstitution. Do not refrigerate after reconstitution.

3. **Administer only by the intravenous route.**
4. Filter needle should be used prior to administering.
5. Koāte-DVI contains levels of blood group isoagglutinins which are not clinically significant when controlling relatively minor bleeding episodes. When large or frequently repeated doses are required, patients of blood groups A, B, or AB should be monitored by means of hematocrit for signs of progressive anemia, as well as by direct Coombs' tests.
6. Product administration and handling of the infusion set and needles must be done with caution. Percutaneous puncture with a needle contaminated with blood can transmit infectious viruses including HIV (AIDS) and hepatitis. Obtain immediate medical attention if injury occurs.

Place needles in sharps container after single use. Discard all equipment including any reconstituted Koāte-DVI product in accordance with biohazard procedures.

Pregnancy Category C

Animal reproduction studies have not been conducted with Koāte-DVI. It is also not known whether Koāte-DVI can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Koāte-DVI should be given to a pregnant woman only if clearly needed.

Pediatric Use

Koāte-DVI has not been studied in pediatric patients. Koāte-HP, solvent/detergent treated Antihemophilic Factor (Human), has been used extensively in pediatric patients.

Spontaneous adverse event reports with Koāte-HP and Koāte-DVI for pediatric use were within the experience of those reports for adult use.

Information for Patients

Some viruses, such as parvovirus B19 or hepatitis A, are particularly difficult to remove or inactivate at this time. Parvovirus B19 most seriously affects pregnant women and immune-compromised individuals.

Symptoms of parvovirus B19 infection include fever, drowsiness, chills and runny nose followed about 2 weeks later by a rash and joint pain. Evidence of hepatitis A may include several days to weeks of poor appetite, tiredness, and low-grade fever followed by nausea, vomiting, and pain in the belly. Dark urine and a yellowed complexion are also common symptoms. Patients should be encouraged to consult their physician if such symptoms appear.

ADVERSE REACTIONS

Allergic-type reactions may result from the administration of Antihemophilic Factor (Human) preparations.[\(10,11\)](#)

Ten adverse reactions related to 7 infusions were observed during a total of 1053 infusions performed during the clinical study of Koāte-DVI, for a frequency of 0.7% infusions associated with adverse reactions. All reactions were mild and included paraesthesia, vision blurred, headache, nausea, abdominal pain, and feeling jittery.(2)

DOSAGE AND ADMINISTRATION

The reconstituted product must be administered intravenously by either direct syringe injection or drip infusion. The product must be administered within 3 hours after reconstitution.

General Approach to Treatment and Assessment of Treatment Efficacy

The dosages described below are presented as general guidance. It should be emphasized that the dosage of Koāte-DVI required for hemostasis must be individualized according to the needs of the patient, the severity of the deficiency, the severity of the hemorrhage, the presence of inhibitors, and the Factor VIII level desired. It is often critical to follow the course of therapy with Factor VIII level assays.

The clinical effect of Koāte-DVI is the most important element in evaluating the effectiveness of treatment. It may be necessary to administer more Koāte-DVI than would be estimated in order to attain satisfactory clinical results. If the calculated dose fails to attain the expected Factor VIII levels, or if bleeding is not controlled after administration of the calculated dosage, the presence of a circulating inhibitor in the patient should be suspected. Its presence should be substantiated and the inhibitor level quantitated by appropriate laboratory tests.

When an inhibitor is present, the dosage requirement for Antihemophilic Factor (Human) is extremely variable and the dosage can be determined only by the clinical response. Some patients with low titer inhibitors (10 Bethesda Units) can be successfully treated with Factor VIII without a resultant anamnestic rise in inhibitor titer.(12) Factor VIII levels and clinical response to treatment must be assessed to insure adequate response. Use of alternative treatment products, such as Factor IX Complex concentrates, Antihemophilic Factor (Porcine) or Anti-Inhibitor Coagulant Complex, may be necessary for patients with high titer inhibitors. Immune tolerance therapy using repeated doses of Factor VIII concentrate administered frequently on a predetermined schedule may result in eradication of the Factor VIII inhibitor.(13,14) Most successful regimens have employed high doses of Factor VIII administered at least once daily, but no single dosage regimen has been universally accepted as the most effective. Consultation with a hemophilia expert experienced with the management of immune tolerance regimens is also advisable.

Calculation of Dosage

The in vivo elevation in Factor VIII level (percent of normal) can be estimated by multiplying the dose of Antihemophilic Factor (Human) per kilogram of body weight (IU/kg) by 2%. This method of calculation is based on clinical findings by Abildgaard et al,(15) and is illustrated in the following examples:

Expected % Factor VIII increase (% of normal) = $\frac{\# \text{ units administered} \times 2\%/IU/kg}{\text{body weight (kg)}}$

Example for a 70 kg adult: $\frac{1400 \text{ IU} \times 2\%/IU/kg}{70 \text{ kg}} = 40\%$

or

Dosage required (IU) = $\frac{\text{body weight (kg)} \times \text{desired \% Factor VIII increase (\% of normal)}}{2\%/IU/kg}$

Example for a 15 kg child: $\frac{15 \text{ kg} \times 100\%}{2\%/IU/kg} = 750 \text{ IU required}$

The dosage necessary to achieve hemostasis depends upon the type and severity of the bleeding episode, according to the following general guidelines:

Mild Hemorrhage

Mild superficial or early hemorrhages may respond to a single dose of 10 IU per kg,(4) leading to an in vivo rise of approximately 20% in the Factor VIII level. Therapy need not be repeated unless there is evidence of further bleeding.

Moderate Hemorrhage

For more serious bleeding episodes (e.g., definite hemarthroses, known trauma), the Factor VIII level should be raised to 30%-50% by administering approximately 15 - 25 IU per kg. If further therapy is required, repeated doses of 10 - 15 IU per kg every 8-12 hours may be given.(16)

Severe Hemorrhage

In patients with life-threatening bleeding or possible hemorrhage involving vital structures (e.g., central nervous system, retropharyngeal and retroperitoneal spaces, iliopsoas sheath), the Factor VIII level should be raised to 80% - 100% of normal in order to achieve hemostasis. This may be achieved in most patients with an initial Antihemophilic Factor (Human) dose of 40-50 IU per kg and a maintenance dose of 20-25 IU per kg every 8-12 hours.(17,18) For major surgical procedures, Factor VIII levels should be checked throughout the perioperative course to ensure adequate replacement therapy.

Surgery

For major surgical procedures, the Factor VIII level should be raised to approximately 100% by giving a preoperative dose of 50 IU/kg. The Factor VIII level should be checked to assure that the expected level is achieved before the patient goes to surgery. In order to maintain

hemostatic levels, repeat infusions may be necessary every 6 to 12 hours initially, and for a total of 10 to 14 days until healing is complete. The intensity of Factor VIII replacement therapy required depends on the type of surgery and postoperative regimen employed. For minor surgical procedures, less intensive treatment schedules may provide adequate hemostasis.(17,18)

Prophylaxis

Factor VIII concentrates may also be administered on a regular schedule for prophylaxis of bleeding, as reported by Nilsson et al.(19)

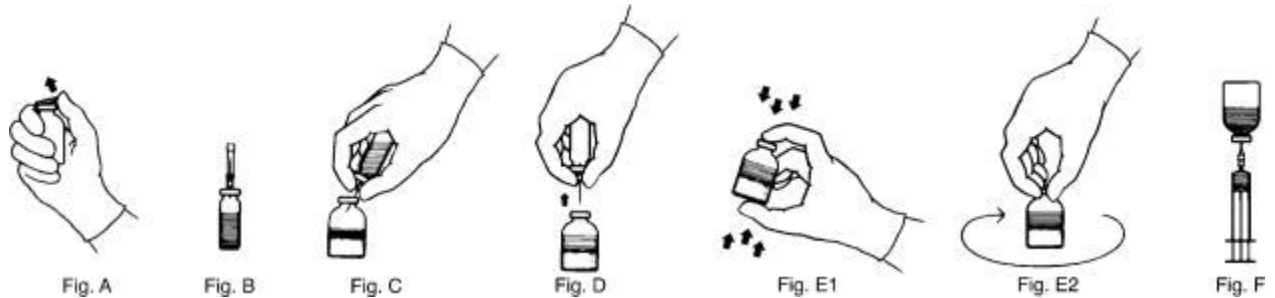
Reconstitution

Vacuum Transfer

Note: Aseptic technique should be carefully followed. All needles and vial tops that will come into contact with the product to be administered via the intravenous route should not come in contact with any non-sterile surface. Any contaminated needles should be discarded by placing in a puncture proof container, and new equipment should be used.

1. After removing all items from the box, warm the sterile water (diluent) to room temperature (25°C, 77°F).
2. Remove shrink band from product vial. **If the shrink band is absent or shows signs of tampering, do not use the product and notify PT Combiphar [Phone 0800-1-800088, WhatsApp 0818 0680 0088, email combicarecenter@combiphar.com] immediately.**
3. Remove the plastic flip tops from each vial (Fig. A). Cleanse vial tops (grey stoppers) with alcohol swab and allow surface to dry. After cleaning, do not allow anything to touch the latex (rubber) stopper.
4. Carefully remove the plastic sheath from the short end of the transfer needle. Insert the exposed needle into the diluent vial to the hub. (Fig. B)
5. Carefully grip the sheath of the other end of the transfer needle and twist to remove it.
6. Invert the diluent vial and insert the attached needle into the vial of concentrate at a 45° angle (Fig. C). This will direct the stream of diluent against the wall of the concentrate vial and minimize foaming. The vacuum will draw the diluent into the concentrate vial.**
7. Remove the diluent bottle and transfer needle (Fig. D).
8. Immediately after adding the diluent, agitate vigorously for 10-15 seconds, (Fig. E1) then swirl continuously until completely dissolved (Fig. E2). Some foaming will occur, but attempt to avoid excessive foaming. The vial should then be visually inspected for particulate matter and discoloration prior to administration.
9. Clean the top of the vial of reconstituted Koāte-DVI again with alcohol swab and let surface dry.
10. Attach the filter needle (from the package) to a sterile syringe. Withdraw the Koāte-DVI solution into the syringe through the filter needle (Fig. F).
11. Remove the filter needle from the syringe and replace with an appropriate injection or butterfly needle for administration. Discard filter needle into a puncture proof container.
12. If the same patient is using more than one vial of Koāte-DVI, the contents of multiple vials may be drawn into the same syringe through the filter needles provided.

** If vacuum is lost in the concentrate vial during reconstitution, use a sterile syringe and needle to remove the sterile water from the diluent vial and inject it into the concentrate vial, directing the stream of fluid against the wall of the vial.



Rate of Administration

The rate of administration should be adapted to the response of the individual patient, but administration of the entire dose in 5 to 10 minutes is generally well-tolerated.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

HOW SUPPLIED

Koāte-DVI is supplied in a kit containing one single use vial of Koāte-DVI lyophilized powder, one vial of Sterile Water for Injection, USP, one sterile double-ended transfer needle, one sterile filter needle, and one sterile administration set.

Approximate Factor VIII

Activity	Diluent
250 IU	5 mL
500 IU	5 mL
1000 IU	10 mL

STORAGE

Koāte-DVI should be stored under refrigeration (2-8°C; 36-46°F). Storage of lyophilized powder at room temperature (up to 25°C or 77°F) for 6 months, such as in home treatment situations, may be done without loss of Factor VIII activity. Freezing should be avoided as breakage of the diluent bottle might occur.

REFERENCES

1. Hershgold EJ, Pool JG, Pappenhagen AR. The potent antihemophilic globulin concentrate derived from a cold insoluble fraction of human plasma: characterization and further data on preparation and clinical trial. *J Lab Clin Med.* 1966;67(1):23–32.
2. Data on file.
3. Aronson DL. Factor VIII (antihemophilic globulin). *Semin Thromb Hemostas.* 1979;6(1):12-27.
4. Britton M, Harrison J, Abildgaard CF. Early treatment of hemophilic hemarthroses with minimal dose of new factor VIII concentrate. *J Pediatr.* 1974;85(2):245-7.
5. Winkelman L, Feldman PA, Evan DR. Severe heat treatment of lyophilised coagulation factors. *Curr Stud Hematol Blood Transfus.* 1989;56:55-69.
6. Skidmore SJ, Pasi KJ, Mawson SJ, et al. Serological evidence that dry heating of clotting factor concentrates prevents transmission of non-A, non-B hepatitis. *J. Med Virol.* 1990;30(1):50-2.
7. Hart HF, Hart WG, Crossley J, et al. Effect of terminal (dry) heat treatment on non-enveloped viruses in coagulation factor concentrates. *Vox Sang.* 1994;67(4):345-50.
8. National Hemophilia Foundation Medical and Scientific Advisory Council. MASAC recommendations concerning products licensed for the treatment of hemophilia and other bleeding disorders. Section F. (Document 205, November 2011), accessed 19 July 2012 at <http://www.hemophilia.org>.
9. CDC. Blood safety monitoring among persons with bleeding disorders - United States, May 1998-June 2002. *MMWR.* 2003;51:1152-4.
10. Eyster ME, Bowman HS, Haverstick JN. Adverse reactions to factor VIII infusions [letter]. *Ann Intern Med.* 1977;87(2):248.
11. Prager D, Djerassi I, Eyster ME, et al. Pennsylvania state-wide hemophilia program: summary of immediate reactions with the use of factor VIII and factor IX concentrate. *Blood.* 1979;53(5):1012-3.
12. Kasper CK. Complications of hemophilia A treatment: factor VIII inhibitors. *Ann NY Acad Sci.* 1991;614:97-105.
13. Mariani G, Hilgartner M, Thompson AR, et al. Immune tolerance to factor VIII: international registry data. *Adv Exp Med Biol.* 1995;386:201-8.
14. DiMichele D. Hemophilia 1996. New approach to an old disease. *Pediatr Clin North Am.* 1996 Jun;43(3):709-36.

15. Abildgaard CF, Simone JV, Corrigan JJ, et al. Treatment of hemophilia with glycine-precipitated factor VIII. N Engl J Med. 1966;275(9):471–5.
16. Abildgaard CF. Current concepts in the management of hemophilia. Semin Hematol. 1975;12(3):223-32.
17. Hilgartner MW. Factor replacement therapy. In: Hilgartner MW, Pochedly C, eds. Hemophilia in the child and adult. New York: Raven Press; 1989. p. 1-26.
18. Kasper CK, Dietrich SL. Comprehensive management of haemophilia. Clin Haematol. 1985;14(2):489-512.
19. Nilsson IM, Berntorp E, Löfqvist T, et al. Twenty-five years' experience of prophylactic treatment in severe haemophilia A and B. J Intern Med. 1992;232(1):25-32.

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PACKAGING AND REGISTRATION NUMBER

Koate DVI, Dus @ 250 IU + 1 vial pelarut @ 5 mL, Reg. No.: DKI2590501744A1
Koate DVI, Dus @ 500 IU + 1 vial pelarut @ 5 mL, Reg. No.: DKI2590501744B1
Koate DVI, Dus @ 1000 IU + 1 vial pelarut @ 10 mL, Reg. No.: DKI2590501744B1

GRIFOLS

Manufactured by:

Grifols Therapeutics LLC

Research Triangle Park, NC 27709 USA

Imported by:

PT Combiphar

Bandung Barat, Indonesia

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