

## REGISTRY OF CLOTTING FACTOR CONCENTRATES, 2006

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The Registry was created in 1997 by Meirione Costa e Silva of Brasilia and Dr. Kasper for the International Society on Thrombosis and Haemostasis. Its purpose is to help medical personnel identify available concentrates and stay abreast of pharmaceutical company changes. This year, Mark Brooker, Public Policy Officer of WFH, helped update it.

The registry provides an overview of available products and clarifies differences among them. It also helps doctors and pharmacists identify products that patients are offered during their foreign travels or those they may bring home with them, or have sent to them. Similarly, foreign patients traveling abroad may bring along their own concentrates, which may not be familiar to local health-care personnel.

Agencies contemplating bulk purchase of concentrates are advised to consult the WFH's 2003 publication "Guide for the Assessment of Clotting Factor Concentrates for the Treatment of Hemophilia" by Albert Farrugia.

Plasma obtained from donations of whole blood is called *recovered plasma*. Plasma obtained by apheresis is called *source plasma*. Donors of whole blood are not paid substantially in any of the countries listed in this registry. Donors of apheresis plasma are paid in most countries.

Several national fractionation centers produce concentrate from domestic recovered plasma for domestic use. A few fractionators (CSL in Australia, Grifols in Spain, Sanquin in The Netherlands) accept plasma from small

countries, fractionate it separately, and return it as concentrate to the donor country, a process called *contract or toll* fractionation. Several fractionators use source plasma from countries permitting paid apheresis. Such plasma may be blended with smaller amounts of unpaid recovered plasma.

In 2005, the American Red Cross exited the plasma concentrate business. Bayer Corporation transferred its plasma-product business to Talecris Biotherapeutics but continues to make its recombinant FVIII. In Europe, Sanquin now processes Finnish plasma into a FVIII product, Amofill®, and into batches of its factor IX concentrate, Nonafact®, for return to Finland.

Within tables, concentrates are grouped first according to method of fractionation, then according to method of viral inactivation or degree of purification from lowest to highest.

Fractionators cite the purification level of clotting factors as *specific activity*, or the amount of the desired clotting factor per milligram of total protein, minus any added albumin (SA s Alb). Specific activity may actually be measured or may be an approximation. Retention of plasma after donation and before processing to ascertain further information about a donor is called *inventory hold* or *quarantine*.

Tables 1A and 1B describe measures that help ensure the safe use of plasma. The array of serologic tests varies slightly from country to country. More sensitive nucleic acid tests that directly detect viruses are becoming commonplace.

Table 2 lists FVIII concentrates made by techniques generally associated with a lesser level of purification. Many contain von Willebrand factor (VWF), which stabilizes FVIII and is needed for treatment of Von Willebrand Disease (VWD). Table 3 lists FVIII concentrates made by techniques allowing higher level of purification, including recombinant FVIII concentrates.

Prothrombin complex concentrates, which are not highly purified, are described in Table 4. One product, Baxter's Proplex T®, is no longer produced but remaining stocks will be sold in 2006.

Table 5 lists concentrates primarily intended for use in patients with inhibitors. At the present time, all are activated concentrates (bypassing agents). The plasma-derived porcine FVIII concentrate, Hyate-C®, was discontinued in 2004. A recombinant porcine FVIII concentrate (from Ipsen) is in clinical trials and may be available in the future. Concentrates of factor IX alone are described in Table 6.

Concentrates for rare clotting factor deficiencies are listed in Table 7. They are not widely available, and there are some deficiencies for which no concentrate is made. Two concentrates of factor VII, that made by BPL in England and that made by LFB in France, are being discontinued. NovoSeven®, the recombinant activated factor VII concentrate, is increasingly used for patients with congenital deficiency of factor VII and now is licensed for that use in the USA. A prothrombin complex, Faktor IX HS Behring®, provides a high level of factor

X in addition to factor IX and is used, where available, for patients with factor X deficiency. Clinical trials have been performed on NovoNordisk's recombinant factor XIII concentrate but it is not yet on the market.

There is one concentrate of VWF virtually alone, LFB's Wilfactin®, Table 7. Another LFB product, Wilstart®, available only in France, combines 1000 IU of Wilfactin and 500 IU of Factane®, for use in acute bleeding in VWD or as the initial surgical dose. A new product, Octapharma's Wilate®, in Table 2, was developed for use in VWD as well as in hemophilia A. Several other products, in tables 2 and 3, also contain VWF and are used in VWD as well as in hemophilia.

For the first time, concentrates for deficiencies of anti-thrombotic factors are listed, in Table 8. Licensure has been requested for a recombinant antithrombin, Atrypn® (GTC Biotherapeutics in Massachusetts) made in the milk of transgenic goats.

The only plasminogen available is combined with streptokinase in the clotting product, Eminase® (Roberts Pharmaceutical Corporation, New Jersey.)

No shortages of factor VIII and factor IX concentrates were reported in the United States in 2005, nor were there any reports of breaches of safety. No HIV has been transmitted by any American concentrate since 1987. No hepatitis A, B or C has been transmitted by American concentrates since the Centers for Disease Control began its broad surveillance of persons with hemophilia in 1998.

TABLE 1A: SEROLOGIC TESTS ON INDIVIDUAL DONOR PLASMA

PLASMA SOURCE	Syphilis	HIV 1-2	p-24 antigen	HTLV-1	HTLV-2	HBcAb	HBsAb	HBsAg	HCV Ab	ALT <sup>1</sup>	B-19 parvovirus
US paid apheresis (Talecris, Grifols)	Yes <sup>2</sup>	Yes	No <sup>3</sup>	No	No	No	No	Yes	Yes	Yes	No
Other US paid apheresis <sup>4</sup>	Yes <sup>2</sup>	Yes	No <sup>3</sup>	No	No	No	No	Yes	Yes	Yes	No
United States, recovered, unpaid	Yes <sup>2</sup>	Yes	No <sup>3</sup>	Yes	Yes	Yes	No	Yes	Yes	Yes	No
Baxter BioScience: United States, Austria, Germany	Yes <sup>2</sup>	Yes	No	No	No	No	No	Yes	Yes	Yes	No
ZLB Behring: Austria, Germany, United States	Yes	Yes	No	No	No	No	No	Yes	Yes	Yes	No
Biotech: Austria, Belgium, Germany, United States	Yes	Yes	No	No	No	No	No	Yes	Yes	Yes	No
Intersero: Austria, Belgium, Germany	Yes	Yes	No	No	No	No	No	Yes	Yes	Yes	No
Germany unpaid	Yes	Yes	No	No	No	No	No	Yes	Yes	Yes	No
Octapharma: Sweden, Austria, Germany	Yes	Yes	No <sup>5</sup>	1 <sup>st</sup> donation	1 <sup>st</sup> donation	1 <sup>st</sup> donation	No	Yes	Yes	No	No
American Community Blood Centers, unpaid (Octapharma)	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	No	No
Finnish Red Cross BTS: Finland, unpaid	Yes	Yes	No	1 <sup>st</sup> donation & q 3 yrs	1 <sup>st</sup> donation & q 3 yrs	No	No	Yes	Yes	Yes	No
Sanquin: The Netherlands	Yes	Yes	No	Yes	Yes	No	No	Yes	Yes	No	No
LFB: France & Western Europe <sup>6,7</sup>	Yes	Yes <sup>7</sup>	No	Yes	Yes	Yes	No	Yes	Yes <sup>7</sup>	No	No
Grifols: Spain, Czech Republic, Slovakia	Yes	Yes	No	No	No	No	No	Yes	Yes	Yes	No
Kedrion: Italy	Yes	Yes	No	No	No	No	No	Yes	Yes	Yes	No
National Bioproducts Institute: South Africa	Yes	Yes	Yes	No	No	No	No	Yes	Yes	No	No
Australian Red Cross Blood Service <sup>8</sup>	Yes	Yes	No	Yes	Yes	No	No	Yes	Yes	No	No
New Zealand Blood Service <sup>8</sup>	Yes	Yes	No	1 <sup>st</sup> donation	1 <sup>st</sup> donation	No	No	Yes	Yes	No	No
Centre for Transfusion Medicine, Singapore <sup>8</sup>	Yes	Yes	No	No	No	No	No	Yes	Yes	No	No
National Blood Center, Malaysia <sup>8</sup>	Yes	Yes	No	No	No	No	No	Yes	Yes	No	No
Hong Kong Red Cross BTS <sup>8</sup>	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	No	No
Japan	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Korean Red Cross: South Korea <sup>9</sup>	Yes	Yes	Yes	No	No	No	No	Yes	Yes <sup>9</sup>	Yes	No
Shanghai RAAS Blood Products Co: China	Yes	Yes	No	No	No	No	No	Yes	Yes	Yes	No

1. ALT testing is not required for release of plasma in the USA. The requirement in Europe is country-specific.

2. Performed every 4 months in accordance with the US Code of Federal Regulations.

3. Not required if a US FDA licensed HIV-1 NAT test, approved as an alternative to HIV-1 p24 Ag testing, is used..

4. US paid apheresis source plasma is used by several European fractionators, as indicated; US unpaid plasma (recovered from whole blood donations) is used by fractionators in other countries. US recovered plasma originates from the American Red Cross and other licensed US blood banks.

5. Octapharma's p24 Ag test is performed on US plasma but not on European plasma (see NAT testing, Table 1B).

6. LFB uses plasma from unpaid donors from some western European countries that comply with French specifications.

7. Since 2001, NAT tests for HCV and HIV have been performed on individual donations at blood centers utilized by LFB.

8. CSL Bioplasma in Australia fractionates plasma on a contract (toll) basis for the Australian Red Cross Blood Transfusion Service, the New Zealand Blood Service, the Hong Kong Red Cross Blood Transfusion Service, the Center for Transfusion Medicine of Singapore and the National Blood Center of Malaysia, Kuala Lumpur.

9. NAT for HCV is performed on individual donations in Korea.

TABLE 1-B. PLASMA INVENTORY HOLD AND NAT TESTING OF MINI-POOLS

COMPANY OR FRACTIONATOR	INVENTORY HOLD	MINI-POOL SIZE	MINI-POOL NAT TESTS	MANUFACTURING POOL NAT TESTS	NAT ON FINAL PRODUCT
ZLB Behring: United States, Germany	60+ days	512	HAV, HBV, HCV, HIV-1, B-19 parvovirus	HAV, HBV, HCV, HIV, B-19 parvovirus	no
Baxter BioScience: United States, Austria	60+ days	512	HAV, HBV, HCV, HIV-1, B-19 parvovirus	HAV, HBV, HCV, HIV 1-2, B-19 parvovirus	
Talecris: United States	60+ days	96 or 480	HBV, HCV, HIV 1, B-19 parvovirus	HBV, HCV, HIV-1, B-19 parvovirus	No
Grifols: United States, Spain, Czech Republic, Slovakia	60+ days	512 or fewer	HAV, HBV, HCV, HIV, B-19 parvovirus	HBV, HCV, HIV	
BPL, UK: US plasma used	60 days	512	HAV, HBV, HCV, HIV 1-2, B-19 parvovirus	European requirement*	
SNBTS, UK: US & German plasma used	21+ days	24 and 96	HCV, HIV-1	HAV, HBV, HCV, HIV	
Biotech: Germany	60 days	960	HAV, HBC, HCV, HIV 1, B-19 parvovirus	HBV, HCV, HIV	
Intersero: Germany	60+ days	960	HAV, HBV, HCV, HIV-1, B-19 parvovirus	HBV, HCV, HIV	
German Red Cross BSO NSTOB	2 months	48	HAV, HBV, HCV, HIV-1, B-19 parvovirus	European requirement*	
Octapharma: Sweden, Austria, Germany, United States	2 months	(1)10,(2)480	(1)HBV, B-19 parvovirus; (2) HAV, HCV, HIV-1.	European requirement*	
Finnish Red Cross: Finland		96 – 480	HCV, B-19 parvovirus	HCV, HIV, B-19 parvovirus	
Sanquin: The Netherlands		(1) 48, (2) 480	(1) HCV, HIV (2) B-19 parvovirus	European requirement*	
LFB: France	3+ months	(1) 100; (2) 1000	(1) B-19 parvovirus; (2) HAV, HCV	HAV, HBV, HCV, HIV, B-19 parvovirus	
Kedrion: Italy	60+ days	480 or fewer	HBV, HCV, HIV, B-19 parvovirus (HAV if required)	European requirement*	
National Bioproducts Institute, South Africa		1** and 216	HCV, HIV	HCV, HIV	
CSL Bioplasma, Australia		480	HCV, HIV (except ARCBS and NZBS plasma)	HCV, HIV (ARCBS and NZBS)	
Australian Red Cross Blood Service Fractionated at CSL		1*** or 24***	HCV, HIV		
New Zealand Blood Service Fractionated at CSL		1*** or 16	HCV, HIV		
Hong Kong Red Cross BTS Fractionated at CSL		24 (ARCBS), 480 (CSL)	HCV, HIV (at both ARCBS and CSL)		
Centre for Transfusion Med, Singapore Fractionated at CSL		1** (Singapore) 480 (CSL)	HCV, HIV (CSL)		
National Blood Centre of Malaysia Fractionated at CSL		480 (CSL)	HCV, HIV (CSL)		
GreenCross: South Korea	45 days	< 450	HAV, HCV	HAV, HBV, HCV, HIV	HAV, HBV, HCV, HIV
Japanese Red Cross: Japan	6 months	20	HBV, HCV, HIV	HBV, HCV, HIV	HAV, HBV, HCV, HIV
Kaketsuken: Japan	6 months	(1) 50, (2) 500	(1) HBV, HCV, HIV-1, (2) HAV, B-19 parvovirus	HAV, HBV, HCV, HIV-1, B-19 parvovirus	HAV, HBV, HCV, HIV-1, B-19 parvovirus
Benesis, Japan	6 months	50	HBV, HCV, HIV-1	HBV, HCV, HIV-1	HAV, HBV, HCV, HIV-1, B-19 parvovirus
Shanghai RAAS Blood Products: China	60+ days	48	HBV, HCV, HIV-1	HBV, HCV, HIV-1	HBV, HCV, HIV-1

\*The European Pharmacopoeia requires HCV testing by NAT.

\*\* Since October, 2005, NAT tests for HCV, HBV and HIV are performed on individual donations.

\*\*\* "1" indicates single-bag testing.

**TABLE 2. FACTOR VIII CONCENTRATES MADE BY PRECIPITATION (PPT), GEL PERMEATION OR ION EXCHANGE CHROMATOGRAPHY**

BRAND	COMPANY	MANUFACTURE	PLASMA SOURCE	EXPORT/ DOMESTIC	FRACTIONATION	VIRAL INACTIVATION	SA s alb FVIII IU/mg	COMMENT
Factor 8 Y	BioProducts Lab.	Elstree, England	United States: paid; apheresis	Both	Heparin/glycine ppt	Dry heat, 80° C, 72 hr	2.5 - 4	Contains VWF
Haemosolva Factor VIII	National Bioproducts	Durban, South Africa	South Africa & United States: unpaid	Both	Heparin/ glycine ppt	TNBP/ polysorbate 80	8 - 12	No albumin added; contains VWF
HEMORAAAS SD plus H	Shanghai RAAS	Shanghai, China	China: paid and unpaid apheresis	Both	PEG/ glycine ppt	dry heat 100° C, 30 min S/D,	< 30	No albumin added, contains VWF
Haemate P (= Haemate HS)	ZLB Behring	Marburg, Germany	United States, Germany, Austria: paid & unpaid	Both	Multiple precipitation	Pasteurization, 60° C, 10 hr	38	Albumin added, contains VWF, ratio vWF/FVIII > 2.2
Humate P	ZLB Behring	Marburg, Germany	United States: paid; apheresis	To USA	Multiple precipitation	Pasteurization, 60° C, 10 hr	38	Same as above
Conco-eight-HT	Benesis	Osaka, Japan	Japan: unpaid	Domestic	Glycine precipitation, gel filtration	TNBP/ polysorbate 80 & dry heat, 60° C, 72 hr	50	Albumin added
Koate DVI	Talecris	Clayton, NC, USA	United States: paid; apheresis	Both	Multiple precipitation and size exclusion chromatography	TNBP/ polysorbate 80 & dry heat, 80° C, 72 hr	> 20	Albumin added, contains VWF
BIOSTATE	CSL Bioplasma	Melbourne, Australia	Australia, New Zealand, Malaysia, Singapore, Hong Kong: unpaid; United States: paid	Both	Heparin/ glycine ppt, gel filtration chromatography	TNBP/ polysorbate 80 & dry heat, 80° C, 72 hr	50	Albumin added, contains VWF; SA without albumin & VWF = 180
HEMORAAAS-IP, SD plus H	Shanghai RAAS	Shanghai, China	China: paid and unpaid apheresis	Both	PEG ppt & ion exchange chromatography	S/D; dry heat, 100° C, 30 min	< 100	No albumin added
HEMORAAAS-HP, SD plus H	Shanghai RAAS	Shanghai, China	China: paid and unpaid apheresis	Both	PEG ppt & ion exchange chromatography	S/D; dry heat, 100° C, 30 min	> 100	No albumin added
GreenEight	GreenCross	Seoul, Korea	Korea: unpaid; United States: paid; apheresis	Both	Ion exchange chromatography	TNBP/Triton X 100, Dry heat 100° C, 30 min	100+	No albumin added, contains VWF
Contact F	Kaketsuken	Kumamoto, Japan	Japan: unpaid	Domestic	Ion exchange chromatography	Dry heat, 65° C, 96 hr, 19 nm nanofiltration	50	Albumin added
Immunate	Baxter BioScience	Vienna, Austria	United States, Austria, Czech Republic, Germany, Sweden: mostly paid; apheresis	Both	Ion exchange chromatography	Solvent-detergent ; vapor- heat, 60° C, 10 hr at 190 mbar	Mean 70, SD 30	Albumin added, contains VWF
Liberate HT	SNBTS	Edinburgh, Scotland	United States & Germany: unpaid	Both	Ion exchange chromatography	TNBP/ polysorbate 80 & dry heat, 80° C, 72 hr	100	No albumin added, contains VWF
Emoclot D.I.	Kedrion	Italy	Europe and United States: paid & unpaid	Both	Ion exchange chromatography	TNBP/polysorbate 80 & dry heat, 100° C, 30 min	> 80	No albumin added, contains 0.4 IU VWF:RCo per IU FVIII
Haemocin SDH	Biotech	Dreieich, Germany	United States, Austria, Belgium, Germany: paid & unpaid	Both	Anion exchange chromatography	TNBP/polysorbate 80 & dry heat, 100° C, 30 min	100	No albumin added
Faktor VIII SDH Intersero	Intersero	Biotech, Dreieich, Germany	United States, Austria, Belgium, Germany: paid & unpaid	Domestic	Anion exchange chromatography	TNBP/polysorbate 80 & dry heat, 100° C, 30 min	100	No albumin added
Octanate	Octapharma	Vienna, Austria, Stockholm, Sweden & Lingsolheim, France	Sweden, Austria, Germany, United States	Both	Ion exchange chromatography	TNBP/polysorbate 80 & Terminal dry heat, 100° C, 30 min at controlled residual moisture	> 100	No albumin added, contains VWF
Wilate	Octapharma	Vienna, Austria	Sweden, Austria, Germany, United States	To Germany	Multiple precipitation, ion exchange and size exclusion chromatography	TNBP/Triton X 100, & terminal dry heat, 100° C, 120 min, at controlled residual moisture	> 100	No albumin added; contains VWF and FVIII in the physiological ratio
FACTANE	LFB	France	Western European unpaid	Both	Chromatography	TNBP/ polysorbate 80 & 35-15 nm nanofiltration	> 100	No albumin added, contains VWF
Beriate P	ZLB Behring	Marburg, Germany	United States, Austria, Germany: paid & unpaid	Both	Ion exchange chromatography	Pasteurization, 60° C, 10 hr	170	No albumin, stabilized in amino acids & sucrose
Optivate	Bio Products Laboratory	Elstree, England	United States paid; apheresis	Both	Cryoprecipitation, heparin and glycine precipitation, MPHS chromatography	Solvent-detergent and dry heat, 80° C, 72 hr	800	Contains VWF

**TABLE 3. FACTOR VIII CONCENTRATES: AFFINITY CHROMATOGRAPHY, OR RECOMBINANT**

BRAND	COMPANY	SITE OF MANU-FACTURE	PLASMA SOURCE	EXPORT/ DOMESTIC	FRACTIONATION	VIRAL INACTIVATION	SA SALB FVIII IU/ MG	COMMENTS
Alphanate	Grifols	Los Angeles, CA, USA	United States: paid apheresis	Both	Heparin ligand affinity chromatography	TNBP/polyorbate 80 & dry heat, 80° C, 72 hr	140	Albumin added, contains VWF; SA s alb & VWF = 1000-3000
Fanndi	Grifols	Barcelona, Spain	1. United States: paid apheresis 2. Spain: unpaid recovered & apheresis 3. Czech Republic: recovered & apheresis 4. Slovakia, recovered & apheresis	1. Both 2. Domestic only 3. to Czech Republic 4. to Slovakia	Same as above	Same as above	>100	Same as above
Monoclate P	ZLB Behring	Kankakee, IL, USA	United States: paid apheresis	Both	Monoclonal Ab affinity chromatography	Pasteurization at 60° C, 10 hr	> 3000	Albumin added, no VWF
Hemofil M AHF	Baxter BioScience	Los Angeles, CA, USA	United States: paid apheresis	Both	Monoclonal Ab affinity & ion exchange chromatography	TNBP/ Octoxynol 9	Approx. 2000	Albumin added, no functional VWF
Monarc-M	American Red Cross	Baxter, Los Angeles	United States: unpaid recovered	Both	Same as above	Same as above	Approx. 2000	As above
Replenate	Bio Products Laboratory	Elstree, England, UK	United States: paid apheresis	Domestic	Monoclonal Ab affinity & ion exchange chromatography	TNBP/ Triton X 100	> 2000	As above
Amofil	Sanquin OY	Sanquin, Amsterdam	Finland: unpaid recovered	To Finland	Same as above	Same as above	> 2000	As above
Octanativ-M	Octapharma	Stockholm, Sweden	Swedish unpaid recovered & apheresis	Both	Same as above	Same as above	>2000	As above
Aafact	Sanquin	Amsterdam, Netherlands	Netherlands: unpaid	Domestic	Same as above	Same as above	> 2000	As above
GreenMono	Greencross Corp	Seoul, Korea	Korea: unpaid	Domestic	Same as above	TNBP/ Triton X 100	> 2000	As above
Cross Eight M	Japanese Red Cross	Chitose City, Japan	Japan: unpaid	Domestic	Same as above	TNBP/ Triton X 100 & nanofiltration	> 2000	As above

**Recombinant factor VIII concentrates:**

Kogenate FS = KOGENATE Bayer (in EU)	Bayer	Berkeley, CA, USA	None, recombinant	Both	Recombinant: ion exchange & immunoaffinity chromatography	TNBP/ polysorbate 80	2600 - 6800	Full-length rFVIII; no VWF. Formulated with sucrose. Albumin not added during purification or formulation.
Helixate NexGen = Helixate FS	ZLB Behring	Made by Bayer, Berkeley, CA	None, recombinant	Both	(Identical to Kogenate FS)	TNBP/ polysorbate 80	2600 - 6800	Same as above
Recombinate rAHF	Baxter BioScience	Thousand Oaks, CA, USA	None, recombinant	Both	As above		> 4000	Full length rFVIII, no functional VWF.; Human serum albumin added as stabilizer
Advate rAHF PFM	Baxter Bioscience	Neuchatel, Switzerland	None, recombinant	Both	Recombinant	TNBP/ polysorbate 80, Triton X 100	4000 – 10,000	Full-length rFVIII, no functional VWF: no addition of human- or animal-derived plasma proteins or albumin in the cell culture, purification or final formulation.
Refacto	Wyeth	Stockholm, Sweden	None, recombinant	Both	Recombinant	TNBP/ Triton X 100	13,000	B-domain-deleted FVIII, no VWF. No albumin added in formulation.

TABLE 4: PROTHROMBIN COMPLEX CONCENTRATES ("PCC"; concentrates of prothrombin and factors VII, IX and X)

BRAND	COMPANY	SITE OF MANUFACTURE	PLASMA SOURCE	EXPORT/ DOMESTIC	FRACTIONATION	VIRAL INACTIVATION	SA: F. IX, IU/ mg	COMMENTS
Proplex – T	Baxter BioScience	Los Angeles, CA, USA	United States: paid apheresis	Both	Tricalcium phosphate absorption, PEG fractionation	Exposure to 20% ethanol; dry heat, 60° C, 144 hr	> 8	Heparin added; maximum 3.5 U factor VII per IU factor IX
Prothrorraas	Shanghai RAAS	Shanghai, China	China, paid/unpaid apheresis	Both	PEG precipitation, DEAE-sephadex	Solvent/ detergent, nanofiltration		
Beriplex P/N	ZLB Behring	Marburg, Germany	United States, Austria, Germany paid/unpaid	Both	DEAE-sephadex	Pasteurization at 60° C, 10 hr, & nanofiltration	3.5 – 5	Contains protein C 700-900 IU per 500 IU factor IX; anti-thrombin III, heparin & albumin added
Faktor IX HS Behring	ZLB Behring	Marburg, Germany	United States, Austria, Germany, paid/unpaid	Both	DEAE-sephadex and precipitations	Pasteurization at 60° C, 10 hr	15	Contains high amount of factor X; antithrombin III and heparin added, no albumin added
Haemosolvex Factor IX	National Bioproducts	Durban, South Africa	South Africa: unpaid	Both	DEAE-sephadex	TNBP/polysorbate 80	1.5	No albumin added; heparin added
Profilnine SD	Grifols	Los Angeles, CA, USA	United States: paid pheresis	Both	Double DEAE cellulose chromatography	Solvent/detergent	4	No albumin, heparin or antithrombin III added
Prothrombinex-HT	CSL Bioplasma	Melbourne, Australia	Australia, New Zealand, Hong Kong, Malaysia, unpaid	Both	DEAE cellulose absorption	Dry heat, 80° C, 72 hr	1 – 5	No albumin added
Prothromplex-T	Baxter BioScience	Vienna, Austria	United States, Austria, Czech Republic, Germany, Sweden: mostly paid apheresis	Both	Ion exchange adsorption	Vapor heat, 60° C for 10 hr at 190 mbar, then 80° C for 1 hr at 375 mbar		Anti-thrombin III & heparin added
Bebulin VH	Baxter BioScience	Vienna, Austria	United States: paid apheresis	Export to USA	Same as above	Same as above		Heparin added
HT DEFIX	SNBTS	Edinburgh, Scotland	United States & Germany: unpaid	Both	Ion exchange chromatography	Dry heat, 80° C, 72 hr	2	Anti-thrombin III added
Octaplex	Octapharma	Vienna, Austria & Lingslisheim, France	Sweden, Austria, Germany & United States	Both	Ion exchange chromatography	TNBP/ polysorbate 80 & nanofiltration	1 or more	Heparin added, no anti-thrombin or albumin added, low factor VIIa content
Facnyne	Greencross Corp	Seoul, Korea	Korea: unpaid	Domestic	Ion exchange chromatography	TNBP/ polysorbate 80	@ 6 – 7	No albumin added
Cofact	Sanquin	Amsterdam, Netherlands	Netherlands: unpaid	Domestic	DEAE ion exchange chromatography	TNBP/polysorbate 80 & 15 nm nanofiltration		Anti-thrombin III added
PPSB-human SD/Nano 300/600	German Red Cross NSTOB	Springe, Germany	Germany: unpaid	Domestic	DEAE-sephadex, ion exchange chromatography	TNBP/ polysorbate 80 & Two nanofiltration steps, 50 nm & 15-19 nm	1	Anti-thrombin III & heparin added; no albumin added
UMAN Complex D.I.	Kedrion	Italy	Europe & United States, unpaid & paid	Both	Anion exchange: DEAE-sephadex/ sepharose chromatography	TNBP/ polysorbate 80 & Dry heat, 100° C, 30 min	< 1.6	Anti-thrombin III & heparin added; no albumin added; factor II & factor X titration
KASKADIL	LFB	France	Western Europe, unpaid	Both	DEAE-sephadex absorption, anion exchange chromatography	TNBP/ polysorbate 80	0.6	

TABLE 5: CONCENTRATES PRIMARILY INTENDED FOR USE IN PATIENTS WITH INHIBITORS: Activated Concentrates (Bypassing agents)

FEIBA VH	Baxter Bioscience	Vienna, Austria	United States, Austria, Czech Republic, Germany, Sweden: mainly paid apheresis	Both	Surface-activated PCC, batch-controlled	Vapor heat, 60° C, 10 hr, 190mbar then 80° C, 1 hr, 375 mbar		No heparin added
NovoSeven = Niasase (in Canada)	Novo Nordisk	Copenhagen, Denmark	None	Both	Recombinant Factor VIIa	None		Also licensed for use in congenital deficiency of factor VII, in United States

**TABLE 6: HIGHLY PURIFIED FACTOR IX CONCENTRATES**

BRAND	COMPANY	SITE OF MANUFACTURE	PLASMA SOURCE	EXPORT/ DOMESTIC	FRACTIONATION	VIRAL INACTIVATION	S.A. s ALB, FIX IU/ MG	COMMENTS
Berinin-P = Berinin HS	ZLB Behring	Marburg, Germany	United States, Austria, Germany: paid & unpaid	Both	DEAE-sephadex, heparin affinity chromatography	Pasteurization at 60°, 10 hr	146	Anti-thrombin III & heparin added; no albumin added
Immune	Baxter BioScience	Vienna, Austria	United States, Austria, Czech Republic, Germany, Sweden: mostly paid apheresis	Both	Ion exchange & hydrophobic interaction chromatography	Polysorbate 80 & vapor heat, 60° C, 10 hrs, 190 mbar then 80° C, 1 hr, 375 mbar	Approx. 100	No albumin added
Hemo-B-RAAS	Shanghai RAAS	Shanghai, China	China: unpaid & paid apheresis	Both	Ion exchange & affinity chromatography	Solvent/ detergent, dry heat & nanofiltration	> 50	No albumin added
Octayne	Octapharma	Vienna, Austria & Lingolsheim, France	Sweden, Austria, Germany & United States	Export	Ion exchange & affinity chromatography	TNBP/ polysorbate 80	50 – 100	No albumin added
Octanine F	Octapharma	Vienna, Austria & Lingolsheim, France	Sweden, Austria, Germany & United States	Both	Ion exchange & affinity chromatography	TNBP/ polysorbate 80 & nanofiltration	> 120	No albumin added
Nanotiv	Octapharma	Stockholm, Sweden	Recovered & apheresis	Both	Ion exchange & heparin ligand chromatography	TNBP/ Triton X 100 & nanofiltration	150	No albumin added
HIP FIX	SNBTS	Edinburgh, Scotland	USA & Germany: Unpaid	Both	Ion exchange & heparin ligand chromatography	TNBP/ polysorbate 80; dry heat, 80° C, 72 hrs	180	Anti-thrombin III added, no albumin added
Mono FIX-VF	CSL Bioplasma	Melbourne, Australia	Australia, New Zealand, Singapore, Hong Kong: Unpaid	Both	Ion exchange & heparin affinity chromatography	TNBP/ polysorbate 80 & nanofiltration	70	Anti-thrombin III & heparin added, no albumin added
Christmass in-M	Benesis	Osaka, Japan	Japan: unpaid	Domestic	Ion exchange & immunoaffinity chromatography	TNBP/ polysorbate 80; dry heat, 60° C, 72 hr; 15 nm nanofiltration	Approx 170	Albumin added
Almafix	Kedrion	Italy	Europe & United States: paid & unpaid	Both	Anion exchange, DEAE sephadex/sepharose & heparin affinity chromatography	TNBP polysorbate 80; dry heat 100° C, 30 min; nanofiltration 35 + 15 nm (registration pending for nanofiltration)	> 100	Anti-thrombin III & heparin added, no albumin added
BETAFACT	LFB	France	Western Europe, unpaid	Both	DEAE-sephadex, anion exchange, affinity chromatography	TNBP/ polysorbate 80, 15 nm nanofiltration	> 110	No albumin added
Faktor IX SDN	Biotest	LFB, France	Western Europe, unpaid	Austria & Germany	As above	As above	> 110	No albumin added
Factor IX Grifols	Grifols	Barcelona, Spain	1. United States paid 2. Spain recovered and apheresis, unpaid	1. Both 2. Domestic	Precipitation & multiple chromatography	Solvent detergent, 15 nm nanofiltration	> 150	No albumin added
Alphanine	Grifols	Los Angeles, CA, USA	United States: paid apheresis	Both	Ion exchange and polysaccharide ligand chromatography	Solvent/detergent, nanofiltration	210	No albumin added
Mononine	ZLB Behring	Kankakee, IL, USA	United States: apheresis paid	Both	Immunoaffinity chromatography	Sodium thiocyanate & ultrafiltration	> 190	No albumin added
Nonafact	Sanquin	Amsterdam, The Netherlands	The Netherlands: unpaid	Both	Immunoaffinity & hydrophobic interaction chromatography	TNBP/ polysorbate 80; 15 nm nanofiltration	200 or more	No albumin added
Novact M	Kaketsuken	Kumamoto, Japan	Japan: unpaid	Domestic	Immunoaffinity chromatography	Dry heat, 65° C, 96 hr, 15 nm nanofiltration	Approx 200	Albumin added
Replene -VF	BioProducts Lab.	Elstree, England, UK	United States: paid apheresis	Both	Metal chelate chromatography	Solvent-detergent; 15 nm nanofiltration	200	No albumin added

**RECOMBINANT FACTOR IX CONCENTRATE**

BRAND	COMPANY	MADE AT	EXPORT/ DOMESTIC	FRACTIONATION	VIRAL INACTIVATION	S.A.: F. IX U/mg	COMMENTS
BeneFIX	Wyeth	Andover, MA; USA	Both	Recombinant	Nanofiltration	200 +	No human or animal proteins used in manufacture; no albumin added
BeneFIX	Baxter SA (Switzerland)	Wyeth, Andover, MA, USA	Europe	Recombinant	Nanofiltration	200+	No human or animal proteins used in manufacture; no albumin added

TABLE 7: OTHER CLOTTING FACTOR CONCENTRATES

BRAND	COMPANY	SITE OF MANUFACTURE	PLASMA SOURCE	EXPORT/ DOMESTIC	FRACTIONATION	VIRAL INACTIVATION	COMMENTS
Clottagen (fibrinogen)	LFB	France	Western Europe, unpaid	Both	Cryoprecipitate, adsorption on aluminum hydroxide gel, anion exchange chromatography	TNBP/ polysorbate 80	
Fibrinogen HT	Benesis	Osaka, Japan	Japan: unpaid	Domestic	Ethanol fractionation, glycine precipitation	TNBP/ polysorbate 80; dry heat, 60° C, 72 hr; 35 nm nanofiltration	No albumin added
Fibrinogen	SNBTS	Edinburgh, Scotland	United States & Germany, unpaid	Both	Multiple precipitation, ion exchange chromatography	TNBP/ polysorbate 80; Dry heat, 80° C, 72 hr	No albumin added
FIBRORAAS (fibrinogen)	Shanghai RAAS	Shanghai, China	China: paid & unpaid apheresis	Both	Multiple fractionation	TNBP/ polysorbate 80	
Haemocomplettan P = Haemocomplettan HS (fibrinogen)	ZLB Behring	Marburg, Germany	United States, Austria, Germany: paid & unpaid	Both	Multiple precipitation	Pasteurization at 60° C, 20 hr	Albumin added
Factor VII	Baxter BioScience	Vienna, Austria	United States, Austria, Czech Republic, Germany, Sweden: mostly paid apheresis	Both	Aluminum hydroxide absorption	Vapor heat, 60° C, 10 hr at 190 mbar then 80° C, 1 hr at 375 mbar	
Factor VII	Bio Products	Elstree, England, France	United States: paid apheresis France: unpaid recovered & apheresis	Both	Ion exchange chromatography	Dry heat, 80° C, 72 hr	S.A. 1.5 – 2 U/ mg protein
FACTEUR VII	LFB	France	France: unpaid recovered & apheresis	Both	DEAE adsorption, anion exchange chromatography	TNBP/ polysorbate 80	SA 1-2 U/ mg protein; no albumin added
NovoSeven (=Niasase) (activated factor VII)	NovoNordisk	Copenhagen, Denmark	None	Both	Recombinant	Not applicable	Approved for congenital factor VII deficiency in USA
Factor XI	Bio Products	Elstree, England, UK	United States: paid apheresis	Both	Affinity heparin sepharose chromatography	Dry heat, 80° C, 72 hr	Heparin, Anti-thrombin III added, S.A. 3- >5 U/ mg protein
HEMOLEVEN (Factor XI)	LFB	France	Western Europe, unpaid	Both	Dialysis, cation exchange chromatography	Solvent/ detergent, 15 nm nanofiltration	Heparin, Anti-thrombin III added, C-1 esterase inhibitor added
WILFACTIN (Von Willebrand Factor)	LFB	France	Western Europe, unpaid	Both	Aluminum hydroxide absorption, anion exchange & affinity chromatography	TNBP/polysorbate 80; 35 nm nanofiltration; dry heat 80° C, 72 hr	> 60 units ristocetin cofactor (VWF:RCo) per mg; low FVIII content; high molecular weight multimers of VWF present
Fibrogammin P = Fibrogammin HS (Factor XIII)	ZLB Behring	Marburg, Germany	United States, Austria, Germany: paid & unpaid	Both	Multiple precipitation	Pasteurization at 60° C, 10 hr	Albumin added

TABLE 8. CONCENTRATES OF ANTI-THROMBOTIC FACTORS : (A) Anti-thrombin concentrates

BRAND	COMPANY	SITE OF MANUFACTURE	PLASMA SOURCE	EXPORT/ DOMESTIC	FRACTIONATION	VIRAL INACTIVATION	COMMENTS
ACLOTINE	LFB	Lille, France	Western Europe, unpaid	Both	Anion exchange and affinity chromatography	Pasteurization, 60° C, 10 hrs	
Ambinex	Grifols	Barcelona, Spain	1. United States paid apheresis 2. Spain unpaid recovered and apheresis	1. Both 2. Domestic	Double heparin ligand chromatography	Pasteurization, 60° C, 10 hrs; 14 nm nanofiltration	Specific activity 7.9 ± 0.4 IU/mg
Anti-thrombin	GreenCros s	Seoul, Korea	Korea unpaid and United States paid apheresis	Both	Ion exchange and heparin affinity chromatography	Pasteurization, 60° C, 10 hrs	Specific activity more than 8.3 IU/mg
ATIII	BPL	Elstree, England	United States paid apheresis	Both	Cryosupernatant; heparin absorption, sepharose chromatography	Pasteurization 60° C, 10 hrs and dry heat, 80° C, 72 hrs	No heparin added
Kyberlin P	ZLB Behring	Marburg, Germany	United States, Austria, Germany; paid and unpaid	Both	Precipitations and affinity chromatography	Pasteurization, 60° C, 10 hrs	
Neuart	Benesis	Osaka, Japan	Japan, unpaid	Domestic	Ethanol fractionation	Pasteurization, 60° C, 10 hrs and 20 nm nanofiltration	Specific activity 9- 10 IU/mg
Thrombate-III	Talecris	Clayton, NC, USA			Ethanol fractionation	Pasteurization, 60° C, 10 hrs	
Thrombotrol-VF	CSL	Melbourne, Australia	Australia, New Zealand, unpaid	Both	Heparin, sepharose and gel filtration chromatography	Pasteurization, 60° C, 10 hrs and 15 nm nanofiltration	

**(B) Protein C concentrates**

Anact C (activated protein C)	Kaketsuken	Kumamoto, Japan	Japan, unpaid	Domestic	Affinity and ion exchange chromatography	Dry heat 65° C., 10 hrs, and 15 nm nanofiltration	
Ceprofin	Baxter	Vienna, Austria	United States & Europe	Both	Cryosupernatant; ion exchange and immunoaffinity chromatography	Detergent; vapor heat, 60° for 10 ht and 80° for 1 hr	Albumin added
PROTEXEL	LFB	Lille, France	Western Europe, unpaid	Both	Anion exchange chromatography	Solvent/Detergent (TNBP/polysorbate 80)	

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