Reconstitution: Use Aseptic Technique

1. Bring Autoplex® T, Anti-Inhibitor Coagulant Complex, Heat Treated, (dry concentrate), and Sterile Water for Injection, USP, (30 mL) (diluent) to room temperature.
2. Remove caps from concentrate and diluent bottles to expose central portions of rubber stoppers.
3. Cleanse stoppers with germicidal solution.
4. Remove protective covering from one end of the double-ended needle and insert exposed needle through **diluent** stopper.
5. Remove protective covering from the other end of the double-ended needle. Invert diluent bottle over the upright concentrate bottle, then **rapidly** insert free end of the needle through the concentrate bottle stopper at its center. Vacuum in the concentrate bottle will draw in diluent.
6. Disconnect the two bottles by removing needle from the diluent bottle, then remove needle from concentrate bottle stopper. Swirl or rotate the concentrate bottle until all material is dissolved. Do not shake vigorously.

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

Note: Do not refrigerate after reconstitution.

Rate of Administration

It is recommended that Autoplex® T, Anti-Inhibitor Coagulant Complex, Heat Treated, be infused initially at a rate of 2 mL/min. If infusion at this rate is well tolerated the administration rate may be gradually increased to 10 mL/min.

Administration: Use Aseptic Technique

When reconstitution of Autoplex® T, Anti-Inhibitor Coagulant Complex, Heat Treated, is complete, its infusion should commence as soon as practical; however, it must be completed within 1 hour.

The reconstituted solution should be at room temperature during infusion.

A. Intravenous Drip Infusion

When a Hyland administration set is used, follow directions for use printed on the administration set container. When an administration set from another source is used, follow directions accompanying that set where necessary. The use of a Hyland administration set is recommended as it contains a suitable filter.

B. Intravenous Syringe Injection

1. Attach filter needle to syringe and draw back plunger to admit air into the syringe.
2. Insert needle into the reconstituted Autoplex® T, Anti-Inhibitor Coagulant Complex, Heat Treated.
3. Inject air into bottle and then withdraw the reconstituted material into the syringe.
4. Remove and discard the filter needle from the syringe; attach a suitable needle and inject intravenously as instructed under **Rate of Administration.**
5. If patient is to receive more than one bottle of concentrate, the contents of two bottles may be drawn into the same syringe by drawing up each bottle through a separate unused filter needle. This practice lessens the loss of concentrate. Please note: filter needles are intended to filter the contents of a single bottle of Autoplex® T, Anti-Inhibitor Coagulant Complex, Heat Treated, only.

How Supplied

Autoplex® T, Anti-Inhibitor Coagulant Complex, Heat Treated, is packaged with 30 mL Sterile Water for Injection, USP; a double-ended needle; a filter needle; and a package insert.

Storage

Autoplex® T, Anti-Inhibitor Coagulant Complex, Heat Treated, should be stored under ordinary refrigeration (2 - 8˚C, 36 - 46˚F). Avoid freezing to prevent damage to the diluent bottle.

References

1. Gazengel C, Larrieu MJ: Lack of seroconversion for LAV/HTLV-III in patients exclusively given unheated activated prothrombin complex prepared with ethanol step. **Lancet 2**:1189, 1985
2. Kurczynski EM, Penner JA: Activated prothrombin concentrate for patients with factor VIII inhibitors. **New Eng J Med 291**:164-167, 1974
3. Penner JA, Kelly PE: Management of patients with factor VIII or IX inhibitors. **Semin Thromb Hemostas 1**:386-399, 1975
4. Buchanan GR, Kevy SV: Use of prothrombin complex concentrates in hemophiliacs with inhibitors: Clinical and laboratory studies. **Pediatrics 62**:767-774, 1978
5. Mannucci PM, Federici F, Vigano S, *et al*: Multiple dental extractions with a new prothrombin complex concentrate in two patients with factor VIII inhibitors. **Thromb Res 15**:359-364, 1979
6. Shapiro SS: Antibodies to blood coagulation factors. **Clinics in Haematology 8**:207-214, 1979
7. Roberts HR: Hemophiliacs with inhibitors: Therapeutic options. **New Eng J. Med 305**:757-758, 1981

Bibliography

Abildgaard CF, Penner JA, Watson-Williams EJ: Anti-Inhibitor Coagulant Complex (Autoplex) for treatment of factor VIII inhibitors in hemophilia. **Blood 56**:978, 1980

Fekete LF, Holst SL, Peetoom F, *et al*: "Auto" Factor IX Concentrate: A new therapeutic approach to treatment of hemophilia A patients with inhibitors. **Proceedings, 14th International Congress of Haematology**. Sao Paulo, Brazil, 1972

Horwith G, Revie DR. Efficacy of viral clearance methods used in the manufacture of activated concentrates: focus on AUTOPLEX® T. **Haemophilia 5 (Supple 3)**: 19, 1999

Kantrowitz JL *et al*. Early experience with the use of Anti-Inhibitor Coagulant Complex to treat bleeding in hemophiliacs with inhibitors to factor VIII. **Clin Ther 9** (4): 405, 1987

Kelly P, Penner JA: Antihemophilic factor inhibitors: Management with prothrombin complex concentrates. **JAMA 236**:2061, 1976

Lundblad RL *et al*. Measurement of active coagulation factors in Autoplex® T with colorimetric active site-specific assay technology. **Thrombosis and Haemostatsis 80 (5)**: 3, 1998

Seligsohn U, Kasper CK, Østerud B, *et al*: Activated factor VII. Presence in factor IX concentrates and persistence in the circulation after infusion. **Blood 53**:828, 1979

White, GC, Seventeen years' experience with Autoplex®/Autoplex® T: evaluation of inpatients with severe haemophilia A and factor VIII inhibitors at major haemophilia centre. **HAEMOPHILIA: Vol. 6**, No. 5, 508-512, 2000.

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FPO

Anti-Inhibitor Coagulant Complex Heat Treated Autoplex® T

Caution: This product is to be used only in patients with inhibitors to Factor VIII.

Warning: This is a potent drug with potential hazards. For maximal safety and efficacy, carefully read and follow directions below.

Description

Autoplex® T*, Anti-Inhibitor Coagulant Complex, Heat Treated, is a sterile product prepared from pooled human plasma with subsequent alcohol fractionation to Cohn Fraction IV_1. It contains, in concentrated form, variable amounts of activated and precursor vitamin K-dependent clotting factors. Factors of the kinin generating system are also present. The product is standardized by its ability to correct the clotting time of Factor VIII deficient plasma or Factor VIII deficient plasma which contains inhibitors to Factor VIII.

When reconstituted, this product contains a maximum of 2 units per mL of heparin and a residual amount of polyethylene glycol (2 mg per mL, maximum). It also contains 0.02 M sodium citrate and the sodium content is 177 ± 15 milliequivalents per liter.

Laboratory testing of several lots of Autoplex® T, Anti-Inhibitor Coagulant Complex, Heat Treated, has shown the presence of Factor VIII coagulant antigen (VIII:CAg). Although anamnestic response to this antigen following administration of the product was not observed during the clinical trials, the possibility of such a response does exist.

Each lot of Autoplex® T, Anti-Inhibitor Coagulant Complex, Heat Treated, is assayed and labeled for units of Hyland Factor VIII correctional activity. Factor VIII correctional activity may not be exclusively related to the efficacious component(s). (See **Clinical Pharmacology**.)

During the manufacturing process, this product was heated for 6 days at 60˚C. This heating step is designed to reduce the risk of transmission of hepatitis and other viral diseases. However, no procedure has been shown to be totally effective in removing hepatitis infectivity from Anti-Inhibitor Coagulant Complex.

Autoplex® T, Anti-Inhibitor Coagulant Complex, Heat Treated, **must** be administered intravenously.

Clinical Pharmacology

The Factor VIII correctional activity of Autoplex® T, Anti-Inhibitor Coagulant Complex, Heat Treated, is thought to be, in part, related to the Factor Xa content of the product. It is additionally hypothesized that the elevated Factor VII-VIIa content of this product is also a contributing factor in the *in vivo* reestablishment of normal hemostasis by way of Factor X activation in conjunction with tissue factor, phospholipid and ionic calcium.

*This product and/or its manufacture covered by U.S. Patent Nos. 4,286,056, 4,287,180, 4,357,321, 4,382,083, 4,459,288, and 4,495,278. The "T" indicates that the product is heat treated.

Control of thrombin formation is regulated by (1) the presence of antithrombin III and other serine protease inhibitors which neutralize Factors IXa and Xa, (2) the short biological half-lives of Factors VII and VIIa and (3) the presence of the circulating Factor VIII inhibitor which additionally controls overactivation of the intrinsic coagulation system.

A retrospective study conducted with patients receiving unheated Autoplex®, Anti-Inhibitor Coagulant Complex, supports the effectiveness of the purification process in reducing viral burden in the product. In the study, none of the patients who received that product exclusively seroconverted for HIV antibodies, while 56% of those patients who received other treatment modalities seroconverted during the three year study.[1]

Autoplex® T is manufactured by the modified Cohn-Oncley cold ethanol fractionation process which includes a series of cold-ethanol precipitation, centrifugation and/or filtration of human plasma. Autoplex® T solution is then lyophilized and heat treated at 60˚C ± 1˚C for 144 to 153 hours. These processes accomplish both purification and virus inactivation.

In vitro studies demonstrate that the manufacturing process for Autoplex® T, Anti-Inhibitor Coagulant Complex, Heat Treated, provides for significant viral reduction. These studies, summarized in Table 1, demonstrate viral clearance during the Autoplex® T manufacturing process using Sindbis Virus (SIN) and Bovine Viral Diarrhea virus (BVD) as lipid-enveloped models for RNA viruses such as hepatitis C virus; human immunodeficiency virus, type 1 (HIV-1), a relevant blood borne pathogen; and a herpes virus, pseudorabies virus (PRV), as a model for lipid enveloped DNA viruses. Additionally, studies using three non-enveloped viruses were performed: encephalomyocarditis virus, a model for non-lipid enveloped viruses such as hepatitis A virus; hepatitis A virus, a relevant RNA virus; and porcine parvovirus (PPV), a model for non-lipid enveloped DNA viruses including human B19 parvovirus. The cumulative reduction factors obtained from a combination of these steps indicate that the Autoplex® T manufacturing process is capable of eliminating/inactivating a wide range of relevant and model viruses exhibiting diverse physicochemical properties.

Table 1
***In Vitro* Virus Clearance During the Autoplex® T Manufacturing Process**

Process Step Evaluated	Lipid-Enveloped Viruses				Non-Lipid Enveloped Viruses		
	SIN	BVD	PRV	HIV-1	EMC	HAV	PPV
Processing of Cryo-Poor Plasma to Fraction I+II+III Centrifugate	2.6	1.2	4.6	5.8‡	2.1	1.9	1.4
Processing of Fraction I+II+III Centrifugate to Fraction IV_1 Precipitate	N/A	0.5*	0.5*	8.2	N/A	0.7*	0.2*
Fraction IV_1 Supernatant Precipitated with Calcium Phosphate	1.4	N/A	N/A	N/A	1.5	N/A	N/A
aPCC Precipitated with 5% PEG	1.4	N/A	N/A	N/A	1.5	N/A	N/A
Lyophilization and Heat Treatment Cycle	5.0	4.3	3.4	6.1	7.1	2.3	N/A
Cumulative Log Reduction factors Log_{10}	**10.4**	**5.5**	**8.0**	**14.3**	**12.2**	**4.2**	**1.4**

* Since reduction factor of ≤ 1.0 is within the variability limit of the assay, these values are not included in the cumulative reduction factor calculation.
‡ This value is not included in cumulative because 8.2 claimed in the next step has the same virus inactivation mechanism.
N/A Steps not evaluated.

Indications and Usage

Autoplex® T, Anti-Inhibitor Coagulant Complex, Heat Treated, is indicated for use in patients with Factor VIII inhibitors who are bleeding or are to undergo surgery.[2-5] The intravenous administration of this preparation is intended to control bleeding episodes in such patients.

Approximately 10% of individuals with hemophilia A (classical hemophilia) have laboratory-measurable inhibitors to Factor VIII.[6] For these patients, the treatment of choice depends upon the following factors: the severity of the bleeding episode, the existing level of inhibitor and whether the patient responds to infusion of Factor VIII with increasing antibody titers (anamnestic rise of Factor VIII antibody).

The following table is presented as a guide in determining the preferred therapy with respect to the use of Anti-Inhibitor Coagulant Complex or Antihemophilic Factor (Human) in patients with Factor VIII inhibitors. Inhibitor level categories are given in the shaded areas of the table and the corresponding recommended product or products are given in the unshaded areas. Other regimens have been proposed.[7]

HISTORICAL MAXIMUM LEVEL OF FACTOR VIII INHIBITOR \ PRESENT LEVEL OF FACTOR VIII INHIBITOR	< 2 B.U.[a]	2-10 B.U.	> 10 B.U.
<2 B.U.	AHF[b]	AICC[c] or AHF	AICC
2-10 B.U.	AICC or AHF	AICC or AHF	AICC
>10 B.U.	AICC	AICC	AICC

[a] B.U. designates Bethesda Units.
[b] AHF designates Antihemophilic Factor (Human).
[c] AICC designates Anti-Inhibitor Coagulant Complex.

Patients whose present Factor VIII inhibitor levels are greater than 10 Bethesda Units, as well as patients whose inhibitor levels are historically known to rise to greater than 10 Bethesda Units following treatment with Antihemophilic Factor (Human), should be treated with Anti-Inhibitor Coagulant Complex.

Patients whose present Factor VIII inhibitor levels are between 2 and 10 Bethesda Units and whose inhibitor levels are historically known to remain in this range following treatment with Antihemophilic Factor (Human) may be treated with either Antihemophilic Factor (Human) or Anti-Inhibitor Coagulant Complex, depending on the patient's clinical history and the severity of the bleeding episode.

Patients with Factor VIII inhibitor levels of less than 2 Bethesda Units whose inhibitor levels are historically known to remain at 2 Bethesda Units or less following treatment with Antihemophilic Factor (Human) may be treated with appropriate doses of Antihemophilic Factor (Human).

For patients who have low levels of Factor VIII inhibitor and whose history does not include adequate laboratory indications of an anamnestic response to Antihemophilic Factor (Human), the treatment of choice should be based on clinical judgement. In such patients who are having non-critical or minor

bleeding episodes, the use of Autoplex® T, Anti-Inhibitor Coagulant Complex, Heat Treated, will maintain the inhibitor at a low level and allow the use of other coagulant therapeutic agents in subsequent major emergencies.

Contraindications

The use of Autoplex® T, Anti-Inhibitor Coagulant Complex, Heat Treated, is contraindicated in patients with signs of fibrinolysis and in patients with disseminated intravascular coagulation (DIC).

Warnings

Autoplex® T, Anti-Inhibitor Coagulant Complex, Heat Treated, 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 (See Clinical Pharmacology). Despite these measures, such products can still potentially transmit disease. 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. 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 the U.S. distributor, Nabi®, at 1-800-327-7106. The physician should discuss the risks and benefits of this product with the patient. Physicians should also report adverse reactions or any disease condition which may occur concomitantly with the administration of this product to the U.S. distributor, Nabi®.

If the infusion of the concentrate occurs more than 1 hour following reconstitution, there may be increased prekallikrein activator (PKA) with consequent hypotension.

Precautions

General

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, or immune-compromised individuals.

Symptoms of parvovirus B19 infection include fever, drowsiness, chills, and runny nose followed about two 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.

Certain components used in the packaging of this product contain natural rubber latex.

Identification of the clotting deficiency as that caused by the presence of Factor VIII inhibitors is essential before the administration of Autoplex® T, Anti-Inhibitor Coagulant Complex, Heat Treated, is initiated.

Signs and/or symptoms of hypotension may occur with this product. In these cases, stopping the infusion allows the symptoms to disappear. With all but the most reactive individuals, the infusion may be resumed at a slower rate.

If clinical signs of intravascular coagulation occur, the infusion should be stopped promptly and the patient monitored for DIC by the appropriate laboratory tests. Symptoms of DIC include changes in blood pressure and

pulse rate, respiratory distress, chest pain and cough. Laboratory indications of DIC include prolonged thrombin time, prothrombin time and partial thromboplastin time tests. Other indications of DIC are decreased fibrinogen concentration, decreased platelet count and/or the presence of fibrinogen/fibrin degradation products.

Special caution should be taken in the use of this concentrate in newborns, where a high morbidity and mortality may be associated with hepatitis, and in individuals with pre-existing liver disease.

Laboratory Tests

In some cases, laboratory tests such as the activated partial thromboplastin time test may not correlate with clinical response, in that the appearance of hemostatic improvement may occur without a reduction of partial thromboplastin time. However, the prothrombin time would be expected to be shortened.

In children, fibrinogen levels should be determined prior to the initial infusion and monitored during the course of the treatment.

Drug Interactions

Since only limited data are available on the administration of highly activated prothrombin complex products together with antifibrinolytic agents such as epsilon-aminocaproic acid (EACA) or tranexamic acid,[5] the concomitant use of Autoplex® T, Anti-Inhibitor Coagulant Complex, Heat Treated, with such agents is not recommended.

Pregnancy

Pregnancy Category C. Animal reproduction studies have not been conducted with Autoplex® T, Anti-Inhibitor Coagulant Complex, Heat Treated. It is also not known whether Autoplex® T, Anti-Inhibitor Coagulant Complex, Heat Treated, can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Autoplex® T, Anti-Inhibitor Coagulant Complex, Heat Treated, should be given to a pregnant woman only if clearly needed.

Adverse Reactions

As with other plasma preparations, reactions manifested by fever, chills or indications of protein sensitivity may be observed with the administration of Autoplex® T, Anti-Inhibitor Coagulant Complex, Heat Treated. Signs and/or symptoms of high prekallikrein activity, such as changes in blood pressure or pulse rate may also be observed. It is advisable that appropriate medications be available for the treatment of acute allergic reactions or acute vasoactive reactions, should they occur.

A rate of infusion that is too rapid may cause headache, flushing, and changes in pulse rate and blood pressure. In such instances, stopping the infusion allows the symptoms to disappear promptly. With all but the most reactive individuals, infusion may be resumed at a slower rate.

Dosage and Administration

Each bottle of Autoplex® T, Anti-Inhibitor Coagulant Complex, Heat Treated, is labeled with the number of Hyland Factor VIII Correctional Units that it contains. One Hyland Factor VIII Correctional Unit is that quantity of activated prothrombin complex which, upon addition to an equal volume of Factor VIII deficient or inhibitor plasma, will correct the clotting time (ellagic acid-activated partial thromboplastin time) to 35 seconds (normal).

The recommended dosage range is 25 to 100 Hyland Factor VIII Correctional Units per kg of body weight, depending upon the severity of hemorrhage. If no hemostatic improvement is observed approximately 6 hours following the initial administration, the dosage should be repeated.

Subsequent dosage and administration intervals should be adjusted according to the patient's clinical response. (See **Laboratory Tests**.)