

The preceding dosage formula for Factor VII deficiency is presented as a reference and a guideline. Exact dosage determinations should be made based on the medical judgment of the physician regarding circumstances, condition of patient, degree of deficiency, and the desired level of Factor VII to be achieved. If an inhibitor to Factor VII is present, sufficient additional dosage to overcome the inhibitor would be needed.<sup>22,23</sup>

#### Reconstitution: Use Aseptic Technique

1. Bring **PROPLEX T**, Factor IX Complex, Heat Treated (dry concentrate) and Sterile Water for Injection, USP, (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 double-ended needle and insert exposed needle through **diluent** stopper.
5. Remove protective covering from other end of 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. The vacuum in the concentrate bottle will draw in the diluent.
6. Disconnect the two bottles by removing needle from diluent bottle stopper, then remove needle from concentrate bottle. Swirl or rotate concentrate bottle until all material is dissolved. Be sure that the material is completely dissolved, otherwise active material will be removed by the filter.

Note: Do not refrigerate after reconstitution.

#### Rate of Administration

**PROPLEX T**, Factor IX Complex, Heat Treated should be infused slowly, at a rate of approximately two to three mL per minute. If headache, flushing, changes in pulse rate or blood pressure appear, the infusion rate should be decreased. In such instances it is advisable, initially, to stop the infusion until the symptoms disappear, then resume the infusion at a slower rate.

#### Administration: Use Aseptic Technique

When reconstitution of **PROPLEX T**, Factor IX Complex, Heat Treated is complete, its infusion should commence within three hours. However, it is recommended that the infusion begin as promptly as is practical.

The reconstituted material should be at room temperature during infusion.

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

#### A. Intravenous Drip Infusion

Follow directions for use printed on the administration set container. Make certain that the administration set contains an adequate 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 **PROPLEX T**, Factor IX 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 at a rate **not exceeding 3 mL per minute**.
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 **PROPLEX T**, Factor IX Complex, Heat Treated only.

#### How Supplied

**PROPLEX T**, Factor IX Complex, Heat Treated is furnished with a suitable volume of Sterile Water for Injection, USP; a double-ended needle; a filter needle; and package insert.

#### Storage

**PROPLEX T**, Factor IX Complex, Heat Treated should be stored under ordinary refrigeration (2° to 8°C, 36° to 46°F). Avoid freezing to prevent damage to the diluent bottle.

#### References

1. White GC, Lundblad RL, Kingdon HS: Prothrombin complex concentrates: Preparation, properties and clinical uses. **Curr Top Hematol** 2:203-244, 1979
2. Marder VJ, Shulman NR: Clinical aspects of congenital Factor VII deficiency. **Am J Med** 37:182-192, 1964

3. Mollison PL: The transfusion of platelets, leucocytes and plasma components (Ch 3) in **Blood Transfusion in Clinical Medicine, Sixth Ed.** Oxford, Blackwell Scientific Publications, 1979, pp 103-113
4. Zauber NP, Levin J: Factor IX levels in patients with hemophilia B (Christmas disease) following transfusion with concentrates of Factor IX or fresh frozen plasma (FFP). **Medicine** 56:213-224, 1977
5. Colombo M, Carnelli V, Gazengel C, *et al*: Transmission of non-A, non-B hepatitis by heat-treated Factor VIII concentrate. **Lancet** 2:1-4, 1985
6. Update: Acquired immune deficiency syndrome (AIDS) in persons with hemophilia. **Morbidity and Mortality Weekly Report** 33:589-591, October 26, 1984
7. Spire B, Barre-Sinoussi F, Montagnier L, *et al*: Inactivation of lymphadenopathy associated virus by chemical disinfectants. **Lancet** 2:899-901, 1984
8. Piszkiwicz D, Kingdon H, Apfelzweig R, *et al*: Inactivation of HTLV-III/LAV during plasma fractionation. **Lancet** 2:1188-1189, 1985
9. 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
10. Petricciani J, McDougal JS, Evatt BL: Case for concluding that heat-treated, licensed anti-haemophilic factor is free from HTLV-III. **Lancet** 2:890-891, 1985
11. Rouzioux C, Chamaret S, Montagnier L, *et al*: Absence of antibodies to AIDS virus in haemophiliacs treated with heat-treated Factor VIII concentrate. **Lancet** 1:271-272, 1985
12. Lusher JM, Shapiro SS, Palascak JE, *et al*: Efficacy of prothrombin-complex concentrates in hemophiliacs with antibodies to Factor VIII. A multicenter therapeutic trial. **New Eng J Med** 303:421-425, 1980
13. Ragni MV, Lewis JH, Spero JA, *et al*: Factor VII deficiency. **Am J Hematology** 10:79-88, 1981
14. Aronson DL: Factor IX complex. **Semin Thromb Hemostas** VI:28-43, 1979
15. Fuerth JH, Mahrer P: Myocardial infarction after Factor IX therapy. **JAMA** 214:1455-1456, 1981
16. Abildgaard CF: Hazards of prothrombin-complex concentrates in treatment of hemophilia. **New Eng J Med** 304:670, 1981
17. Hutchison JL, Freedman SO, Richards BA, *et al*: Plasma volume expansion and reactions after infusion of autologous and nonautologous plasma in man. **J Lab Clin Med** 56:734-746, 1960
18. Mollison PL: Some unfavourable effects of transfusion (Ch 15) in **Blood Transfusion in Clinical Medicine, Sixth Edition.** Oxford, Blackwell Scientific Publications, 1979, p 626
19. Levine PH: Hemophilia and allied conditions, in **Current Therapy, 1979.** Conn HF (ed), Philadelphia, W.B. Saunders Co., 1979, pp 268-275
20. Nilsson IM: Clinical experience with a Swedish Factor IX concentrate, in **Haemophilia.** Ala F, Denson KWE (eds), Amsterdam, Excerpta Medica, 1973, pp 249-253
21. Owen CA Jr, Bowie EJW: Infusion therapy in hemophilia A and B, in **Handbook of Hemophilia.** Brinkhous KM, Hemker HC (eds), Amsterdam, Excerpta Medica, 1975, pp 449-473
22. Hoag MS, Aggeler PM, Fowell AH: Disappearance rate of concentrated proconvertin extracts in congenital and acquired hypoproconvertinemia. **J Clin Invest** 39:554-563, 1960
23. Bedizel M, Albers R: Hereditary Factor VII deficiency in newborns. **Clinical Pediatrics** 22:774-775, 1983

To enroll in the confidential, industry-wide Patient Notification System, call 1-888-UPDATE U (1-888-873-2838).

Baxter, Proplex, Autoplex, and Hemofil are trademarks of Baxter International, Inc., and are registered in the U.S. Patent and Trademark office.

**Baxter Healthcare Corporation**  
Westlake Village, CA 91362 USA  
U.S. License No. 140  
Printed in U.S.A.

Revised November 2002

FPO  
12015

8061

**Baxter**

## PROPLEX T Factor IX Complex Heat Treated

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

#### Description

**PROPLEX T**, Factor IX Complex, Heat Treated is a sterile product prepared from pooled normal human plasma. It contains, in concentrated form, clotting Factors II (prothrombin), VII, IX, and X. Other proteins are also present in minimal amounts. The product also contains a small amount of heparin, 1.5 units or less per mL of reconstituted material, as a stabilizing agent. This amount does not affect the clinical usefulness of the complex in moderate dosage.

**PROPLEX T**, Factor IX Complex, Heat Treated **must** be administered intravenously.

During the manufacturing process, this product was heat treated at 60 ± 1.0°C for 144-153 hours. This heating step was designed to reduce the risk of transmission of hepatitis and other viral infections. However, no procedure has been shown to be totally effective in removing viral infectivity from **PROPLEX T**, Factor IX Complex, Heat Treated.

#### Clinical Pharmacology

**PROPLEX T**, Factor IX Complex, Heat Treated is a combination of vitamin K-dependent clotting factors found in normal plasma. The administration of **PROPLEX T**, Factor IX Complex, Heat Treated provides an increase in plasma levels of Factor VII and Factor IX and can temporarily correct the coagulation defect of patients with deficiencies in these factors. Plasma levels of Factors II and X will also be increased.

The half-life of Factor VII in non-treated Factor IX Complex, administered to Factor VII deficient patients, has been found to range from 3 to 6 hours.<sup>1,2</sup>

The half-life of Factor IX in non-treated Factor IX Complex, administered to Factor IX deficient patients, has been found to range from 24 to 32 hours.<sup>3,4</sup>

**PROPLEX T**, Factor IX Complex, Heat Treated is manufactured by the modified Cohn-Onclay cold ethanol fractionation process which includes a series of cold-ethanol precipitation, centrifugation and/or filtration of human plasma. **PROPLEX T**, Factor IX Complex, Heat Treated solution is then lyophilized and heat treated at 60 ± 1.0°C for 144-153 hours. This process accomplishes both purification of **PROPLEX T**, Factor IX Complex, Heat Treated and reduction of viruses.

The **PROPLEX T**, Factor IX Complex, Heat Treated manufacturing process provides a significant viral reduction in *in vitro* studies.<sup>10</sup> These viral reduction studies, summarized in Table 1, demonstrate viral clearance during the **PROPLEX T**, Factor IX Complex, Heat Treated manufacturing process using bovine diarrhoea virus (BVD) as a model for lipid enveloped RNA viruses such as hepatitis C virus (HVC); 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. Studies were also performed with two non-lipid enveloped viruses: hepatitis A (HAV) virus, a relevant non-lipid enveloped RNA virus; and porcine parvovirus (PPV), as a model for non-lipid enveloped DNA viruses. These studies indicate that specific steps in the manufacture of **PROPLEX T**, Factor IX Complex, Heat Treated are capable of eliminating/inactivating a wide range of relevant and model viruses exhibiting diverse physicochemical properties.

\*Manufactured under U.S. Patent No. 4,495,278. The "™" indicates that the product is heat treated.  
©Copyright 1986, 2002 Baxter Healthcare Corporation.  
All rights reserved.

Table 1

**In Vitro Virus Clearance During the Fractionation Process of PROPLEX T**

Process Step Evaluated	Viral Reduction Factor (log <sub>10</sub> )				
	Lipid-enveloped			Non-lipid enveloped	
	PRV	BVD	HIV-1	HAV	PPV
<b>Cohn-Oncley Cold Ethanol Fractionation Process</b>	<b>4.6</b>	<b>1.2</b>	<b>8.2</b>	<b>1.9</b>	<b>1.4</b>

The effectiveness of the heating step in reducing viral infectivity was assessed by *in vitro* viral inactivation studies using, as markers, viruses not commonly found in plasma and the results are listed in Table 2 for **PROPLEX T, Factor IX Complex, Heat Treated**. The model viruses used were sindbis virus (SIN), a lipid enveloped RNA virus; vesicular stomatitis virus (VSV), an enveloped RNA virus and pseudo rabies virus (PRV), a lipid enveloped DNA virus. When known quantities of these viruses were added to the product, the heat treatment employed inactivated the following quantities of virus (Table 2):

Table 2

**In Vitro Virus Clearance During the Lyophilization and Heat Treatment of PROPLEX T**

Process Step Evaluated	Viral Reduction Factor (log <sub>10</sub> )		
	Lipid-enveloped		
	SIN	PRV	VSV
<b>Lyophilization and Heat Treatment Cycle</b>	<b>10.5</b>	<b>1.4</b>	<b>5.6</b>

In addition, it has been shown that cytomegalo virus does not survive the manufacturing process. As these data indicate, all viruses are not equally affected by the heat treatment. Work by Colombo, *et al* with first-exposure hemophiliacs who received heat treated Antihemophilic Factor (Human) showed that while some reduction of hepatitis infectivity may have been achieved by heat treatment, a substantial portion of the patients who had not previously received blood products developed signs and/or symptoms of hepatitis.<sup>5</sup> (See **Warnings**).

It has been reported that HIV is heat labile and that it is inactivated by treatment with 19-20% alcohol.<sup>6,7,8</sup> Lengthy exposure to 20% ethanol occurs in the Cohn cold ethanol fractionation procedure from which this product is derived. In a retrospective study conducted with patients receiving AUTOPLEX, Anti-Inhibitor Coagulant Complex which is also derived from the Cohn process, none of the patients who received AUTOPLEX, Anti-Inhibitor Coagulant Complex exclusively seroconverted for HIV antibodies, while 56% of those patients who received other treatment modalities seroconverted during the three year study.<sup>9</sup> Heat treatment has also been shown to be an effective means of inactivating HIV.<sup>10</sup> In a study comparing heat treated **HEMOFIL T, Antihemophilic Factor (Human)**, to untreated Antihemophilic Factor (Human) products, none of the patients receiving the heat treated product developed antibodies to HIV, while 17% of the patients receiving untreated products did seroconvert by the end of the study.<sup>11</sup>

**Indications and Usage**

**PROPLEX T, Factor IX Complex, Heat Treated** is indicated for:

- Factor IX deficiency (Hemophilia B, Christmas disease). The intravenous administration of **PROPLEX T, Factor IX Complex, Heat Treated** is intended to prevent or control bleeding episodes in patients with this deficiency. Factor IX Complex should not be used in patients with mild Factor IX deficiency for whom fresh frozen plasma is effective.
- Bleeding episodes in patients with inhibitors to Factor VIII. Lusher, *et al*, have described the use of **PROPLEX T, Factor IX Complex, Heat Treated** in hemarthroses occurring in hemophiliacs with inhibitors to Factor VIII.<sup>12</sup>
- Factor VII deficiency. The Factor VII content present in **PROPLEX T, Factor IX Complex, Heat Treated** has been shown to be effective in prevention or control of bleeding episodes in patients with Factor VII deficiency.<sup>13</sup>

**Contraindications**

The use of Factor IX Complex is potentially hazardous in patients with signs of fibrinolysis and in patients with disseminated intravascular coagulation (DIC).

**Warnings**

**PROPLEX T, Factor IX 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. There is also the possibility that unknown infectious agents may be present in such products. Because this product is made from human blood, it may carry a risk of transmitting infectious agents, e.g., viruses, and theoretically, the Creutzfeldt-Jacob 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 Baxter Healthcare Corporation at 1-800-423-2862. The physician should discuss the risks and benefits of this product with the patient.

**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 deficiency as one of either Factor IX, Factor VII or Factor VIII with inhibitors is essential before administration of the PROPLEX T, Factor IX Complex, Heat Treated is initiated.**

With the exception of its use in treating hemarthroses occurring in Factor VIII-inhibitor patients, no benefits may be expected from this product in treating deficiencies other than those of Factor IX or Factor VII.

**Caution:** It is important that the dosage regimen chosen is carefully evaluated with respect to the entire spectrum of factors present in this product. Levels of Factors II, IX and X should be monitored during therapy to prevent unnecessarily high levels of these factors, which may increase the risk of intravascular coagulation. **PROPLEX T, Factor IX Complex, Heat Treated** is prepared by calcium phosphate absorption of cold ethanol precipitated material and therefore, contains higher ratios of Factor VII and Factor X to Factor IX than products prepared by cationic exchange.<sup>14</sup>

The use of high doses of prothrombin complex concentrates has been reported to be associated with instances of myocardial infarction, disseminated intravascular coagulation, venous thrombosis and pulmonary embolism.<sup>1, 12, 15, 16</sup>

If signs of intravascular coagulation, thrombosis, or emboli occur, which include changes in blood pressure and pulse rate, respiratory distress, chest pain and cough, the infusion should be stopped promptly. In general, the risk of enhancing DIC may be reduced by raising the patient's Factor VII or Factor IX level to not more than about 50% of normal. If the need exists to raise the patient's Factor IX or Factor VII level higher than 50% of normal, the physician should monitor infusion of material to detect signs and symptoms of DIC.

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

**Laboratory Tests**

Since the dosage of **PROPLEX T, Factor IX Complex, Heat Treated** is calculated on the basis of its potency, frequent laboratory tests to monitor the effectiveness of treatment usually are unnecessary. This is particularly true for single dose treatment of an uncomplicated hemarthrosis. However, if a major bleeding episode is being treated in the hospital, or if adequate hemostatic levels of Factor VII or Factor IX are needed to permit performance of surgery, Factor VII or Factor IX assays should be performed at least once a day, prior to infusion, to ensure that the daily dose of **PROPLEX T, Factor IX Complex, Heat Treated** is sufficient to maintain adequate levels of the desired clotting factor.

**Pregnancy**

Pregnancy (Category C). Animal reproduction studies have not been conducted with **PROPLEX T, Factor IX Complex, Heat Treated**. It is also not known whether

**PROPLEX T, Factor IX Complex, Heat Treated** can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. **PROPLEX T, Factor IX Complex, Heat Treated** should be given to a pregnant woman only if clearly needed.

**Adverse Reactions**

As with other plasma preparations, reactions manifested by chills and fever may occasionally be seen, particularly when large doses of **PROPLEX T, Factor IX Complex, Heat Treated** are administered.<sup>17,18</sup>

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, the infusion may be resumed at a slower rate. (See **Rate of Administration**.)

The risk of thrombosis is present with the administration of **PROPLEX T, Factor IX Complex, Heat Treated**.

**Dosage and Administration**

Each bottle of **PROPLEX T, Factor IX Complex, Heat Treated** is labeled with both the Factor IX and Factor VII content. The Factor IX content is expressed in International Units per bottle and is traceable to the World Health Organization International Standard through a secondary concentrate standard. The Factor VII content is expressed in units per bottle and is traceable to pooled normal plasma through a secondary standard.

The amount of **PROPLEX T, Factor IX Complex, Heat Treated** required to restore normal hemostasis varies with the circumstances and with the patient. Dosage depends on the degree of deficiency and the desired hemostatic level of the deficient factor. As a guide to calculation of dosage, experience indicates that the following formulas may be used:<sup>4,19</sup>

**Factor IX Deficiency**

Units required to raise blood level percentages:

1.0 unit/kg x body weight (in kg) x desired increase (% of normal)

If a 70 kg (154 lb) patient with a Factor IX level of 0% needs to be elevated to 25%, give 1.0 unit/kg x 70 kg x 25 = 1750 units

In preparation for and following surgery, levels above 25%, maintained for at least a week after surgery, are suggested. Laboratory control to assure such levels is recommended. To maintain levels above 25% for a reasonable time, each dose should be calculated to raise the level to 40% to 60% of normal.

(See **Precautions**.)

The preceding dosage formula for Factor IX deficiency is presented as a reference and a guideline. Exact dosage determinations should be made based on the medical judgment of the physician regarding circumstances, condition of patient, degree of deficiency, and the desired level of Factor IX to be achieved. If an inhibitor to Factor IX is present, sufficient additional dosage to overcome the inhibitor would be needed.

For maintenance of an elevated level of the deficient factor, dosage may be repeated as often as needed. Clinical studies suggest that relatively high levels may be maintained by daily or twice-daily doses, while the lower effective levels may require injections only once every two or three days. A single dose may be sufficient to stop a minor bleeding episode.<sup>20,21</sup>

**Factor VIII Inhibitor**

In using Factor IX Complex in the treatment of hemarthroses occurring in hemophiliacs with inhibitors to Factor VIII, dosage levels approximating 75 Factor IX units per kg of body weight have been employed successfully.<sup>12</sup>

**AUTOPLEX T, Anti-Inhibitor Coagulant Complex**, is recommended when hemarthroses occurring in hemophiliacs with inhibitors to Factor VIII cannot be resolved by administration of Factor IX complex, and in other types of bleeding episodes in Factor VIII-inhibitor patients.

**Factor VII Deficiency**

Units required to raise blood level percentages:

0.5 unit/kg x body weight (in kg) x desired increase (% of normal)

Repeat dose every 4 to 6 hours as needed.

If a 70 kg (154 lb) patient with a Factor VII level of 0% needs to be elevated to 25%, give 0.5 unit/kg x 70 kg x 25 = 875 units.

In preparation for and following surgery, levels above 25%, maintained for at least a week after surgery, are suggested. Laboratory control to assure such levels is recommended. To maintain levels above 25% for a reasonable time, each dose should be calculated to raise the level to 40 to 60% of normal. (See **Precautions**.)