A. Intravenous Drip Infusion

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

B. Intravenous Syringe Injection

1. After reconstituting the concentrate as described under "Reconstitution", insert the **filter** needle (on syringe) through the bottle stopper.
2. Inject air and withdraw the reconstituted material into the syringe.
3. 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.**
4. If patient is to receive additional bottles of concentrate, the same syringe may be refilled through **filter** needles; this practice lessens the loss of concentrate.

HOW SUPPLIED

Factor IX Complex (Human), PROPLEX, is furnished with a suitable volume of Sterile Water for Injection, USP, a double-ended needle, and a filter needle.

The number of International Units of Factor IX activity, as determined for each lot, is stated on the label of each bottle.

STORAGE

Factor IX Complex (Human), PROPLEX, should be stored under ordinary refrigeration (2 to 8°C, 36 to 46°F). Freezing should be avoided as breakage of the diluent bottle might occur.

Factor IX Complex (Human), PROPLEX, may be stored at room temperature for time periods up to four weeks.

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Printed in U.S.A. 30-35-00-021E Revised October 1984

HYLAND®

SAMPLE

FACTOR IX COMPLEX (HUMAN) PROPLEX®

WARNING: THIS IS A POTENT DRUG WITH POTENTIAL HAZARDS. FOR MAXIMAL SAFETY AND EFFICACY, CAREFULLY READ AND FOLLOW DIRECTIONS BELOW.

DESCRIPTION

Factor IX Complex (Human), PROPLEX*, is prepared from pooled normal human plasma. It contains, in concentrated form, clotting Factors II (prothrombin), VII (proconvertin), IX (PTC, antihemophilic factor B), and X (Stuart-Prower factor); other proteins are also present. 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.

Each lot of Factor IX Complex (Human), PROPLEX, is assayed and labeled for Factor IX activity expressed in International Units of Factor IX.

Factor IX Complex (Human) is to be administered only by the intravenous route.

CLINICAL PHARMACOLOGY

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

The half-life of Factor IX Complex (Human), PROPLEX, administered to Factor IX-deficient patients has been found to range from 10 to 14 hours.

INDICATIONS AND USAGE

Factor IX Complex (Human), PROPLEX, is indicated for:

1. Factor IX deficiency (hemophilia B, Christmas disease). The intravenous administration of Factor IX Complex (Human), PROPLEX, is intended to prevent or control bleeding episodes in patients with this deficiency. Factor IX Complex (Human) should not be used in patients with mild Factor IX deficiency for whom fresh frozen plasma is effective.
2. Bleeding episodes in patients with inhibitors to Factor VIII. Lusher, *et al*,[1] have described the use of Factor IX Complex (Human) in hemarthroses occurring in hemophiliacs with inhibitors to Factor VIII.

CONTRAINDICATIONS

None known.

*Manufactured under U.S. Patents Nos. 3,415,804 and 3,560,475.

WARNINGS

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

This product is prepared from large pools of human plasma. Such plasma may contain the causative agent of viral hepatitis. Although each unit of source plasma used in the preparation of this product has been found to be nonreactive for hepatitis B surface antigen (HBsAg) by licensed third generation reagents, the concentrate has not been subjected to any treatment known to diminish the risk of transmission of hepatitis. The product should, therefore, be administered only when its expected effect outweighs the hepatitis risk associated with its use.

PRECAUTIONS

General

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 not attempting to raise the patient's Factor IX level to more than about 50% of normal. If the need exists to raise the patient's Factor IX level higher than 50% of normal, the physician should monitor infusion of material to detect signs and symptoms of DIC.

The use of high doses of prothrombin complex concentrates has been reported to be associated with instances of myocardial infarction and disseminated intravascular coagulation.[1-4]

Identification of the deficiency as one of Factor IX is essential before administration of Factor IX Complex (Human), PROPLEX, is initiated.

With the exception of its use in treating hemarthroses occurring in Factor VIII-inhibitor patients, no benefit may be expected from this product in treating other deficiencies.

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 Factor IX Complex (Human), PROPLEX, with respect to Factor IX 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 IX are needed to permit performance of surgery, Factor IX assays should be performed at least once a day, prior to infusion, to ensure that the daily dose of Factor IX Complex (Human) is sufficient to maintain Factor IX levels above 25% of normal.

Pregnancy

Pregnancy Category C. Animal reproduction studies have not been conducted with Factor IX Complex (Human). It is also not known whether Factor IX Complex (Human) can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Factor IX Complex (Human) 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,[5,6] particularly when large doses of Factor IX Complex (Human), PROPLEX, are administered.

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. (See "Rate of Administration".)

The risk of thrombosis is present with the administration of Factor IX Complex (Human).

DOSAGE AND ADMINISTRATION

Each bottle of Factor IX Complex (Human), PROPLEX, is labeled with the number of Factor IX International Units it contains. The stated potency is based upon the use of a standard traceable to a World Health Organization International Standard. One Factor IX unit is defined as the activity present in 1 ml of normal pooled human plasma less than 1 hour old (100% level).

The amount of Factor IX Complex (Human), PROPLEX, 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, recent experience[7,8] indicates that the following formula may be used:

- Units required to raise blood level percentages:

  1.0 unit/kg × body weight (in kg) × 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 × 70 kg × 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 inhibitors to Factor IX appear to be 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.[9,10]

In using Factor IX Complex (Human) 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 were employed.[1]

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

Reconstitution

1. Bring Factor IX Complex (Human), PROPLEX, (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.

When reconstituting with a double-ended needle:

4. Remove protective covering from one end of double-ended needle, using care not to touch the exposed end. Insert exposed needle through **diluent** stopper.
5. Remove protective covering from other end of double-ended needle, using aseptic technic as above. 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 concentrate bottle will draw in diluent.
6. Disconnect the two bottles by removing needle from concentrate bottle stopper. Agitate or rotate bottle until all material is dissolved. **Be sure that the material is completely dissolved; otherwise active material will be removed by the filter.**

When reconstituting with a syringe:

4. Without touching exposed needle, attach **filter** needle to syringe (use plastic syringe), withdraw entire contents of the diluent (water) bottle into syringe, then inject diluent into bottle of dry concentrate.
5. Withdraw needle from the concentrate bottle stopper, leaving needle on syringe, and protect needle from contamination. Agitate 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

Factor IX Complex (Human) 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

When reconstitution of Factor IX Complex (Human), PROPLEX, is complete, its infusion should commence within three hours. However, it is recommended that the infusion **begin as promptly** as is practicable.

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.