For the use of a Registered Medical Practitioner or a Hospital only.

Human Prothrombin Complex I.P., 250 IU

Pro-throm

प्रो-थ्रोम

For Intravenous Use Only

DESCRIPTION

Pro-throm™ is a sterile freeze dried powder for injection of Human Prothrombin Complex 250 IU. It is prepared from large pools of human plasma obtained from healthy donors.The reconstituted solution of 10 ml of Human Prothrombin Complex 250 IU is intended for intravenous use only.

COMPOSITION

Pro-throm™ is presented as powder containing Human Prothrombin complex. Each vial of the product contains the following IU of the human coagulation factors as below:

Each vial contains:	
Human Coagulation Factor II	175 - 412 IU
Human Coagulation Factor VII	40 - 260 IU
Human Coagulation Factor IX	250 IU
Human Coagulation Factor X	150 - 530 IU
Protein C	230 - 450 IU
Protein S	220 - 440 IU
Heparin	15 - 30 IU
Total protein	Not more than 52 g/L

Specific activity of Factor IX is ≥ 0.6 IU/mg protein.

The activities of all coagulation factors as well as Protein C and S (antigen) have been tested according to the current valid international WHO-Standards.

PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: antihaemorrhagics, blood coagulation Factors II, VII, IX and X incombination.

The coagulation Factors II, VII, IX and X, which are synthesized in the liver with the help of vitamin K, are commonly called the prothrombin complex. In addition to the coagulation factors Pro-throm™ contains the vitamin K dependent coagulation inhibitors Protein C and Protein S.

Factor VII is the zymogen of the active serine protease Factor VIIa by which the extrinsic pathway of blood coagulation is initiated. The tissue thromboplastin Factor -Factor VIIa complex activates coagulation factors IX and X, where by factor Ixa and Xa are formed. With further activation of the coagulation cascade, prothrombin (Factor II) is activated and transformed to thrombin. By the action of thrombin, fibrinogen is converted to fibrin, which results in clot formation. The normal generation of thrombin is also of vital importance for platelet function as a part of the primary haemostasis.

Isolated severe deficiency of Factor VII leads to reduced thrombin formation and a bleeding tendency due to impaired fibrin formation and impaired primary haemostasis. Isolated deficiency of Factor IX is one of the classical haemophilias (haemophilia B). Isolated deficiency of Factor II or Factor X is very rare but in severe form they cause a bleeding tendency similar to that seen in classical haemophilia.

The further ingredients,the coagulation inhibitors Protein C and Protein S, are also synthesized in the liver. The biological activity of Protein C is enforced by the cofactor Protein S.

Activated Protein C inhibits the coagulation by inactivating the coagulation Factors Va and VIIIa. Protein S as cofactor of Protein C supports the inactivation of the coagulation. Protein C deficiency is associated with an increased risk of thrombosis.

Acquired deficiency of the vitamin K -dependent coagulation factors occurs during treatment with vitamin K antagonists. If the deficiency becomes severe, a severe bleeding tendency results, characterised by retroperitoneal or cerebral bleeds rather than muscle and joint haemorrhage. Severe hepatic insufficiency also results in markedly reduced levels of the vitaminK-dependent coagulation factors and a clinical relevant bleeding tendency. However this is often complex due to a simultaneously ongoing low-grade intravascular coagulation,low platelet levels, deficiency of coagulation inhibitors and disturbed fibrinolysis.

The administration of human prothrombin complex provides an increase in plasma levels of the vitamin K-dependent coagulation factors, and can temporarily correct the coagulation defect of patients with deficiency of one or several of these factors.

POSOLOGY AND METHOD OF ADMINISTRATION

Posology

Only general dosage guidelines aregiven below. Treatment should be initiated under the supervision of a physician experienced inthe treatment of coagulation disorders. The dosage and duration of the substitution therapy depend on the indication for treatment, severity of the disorder, on the location and extent of bleeding and on the patient's clinical condition.

The amount and the frequency of administration should be calculated on an individual patient basis. Dosage intervals must be adapted to the different circulating half-lives of the respective coagulation factors in the prothrombin complex. Individual dosage requirements can only be identified on the basis of regular determinations of the individual plasma levels of the coagulation factors of interest, or on global tests of the prothrombin complex levels (INR, Quick's test), and a continuous monitoring of the clinical condition of the patient.

In case of major surgical interventions, precise monitoring of the substitution therapy by means of coagulation assays is essential (specific coagulation factor assays and/or global tests for prothrombin complex levels).

-Bleeding and perioperative prophylaxis of bleedings during vitamin K antagonist treatment.

The dose will depend on the INR before treatment and the targeted INR. The pre-treatment INR should be measured as closeas possible to the time of dosing in order to calculate the appropriate dose of Pro-throm™ In the following table approximate doses (ml/kg body weight of the reconstituted product and IU Factor IX/kg b.w.) required for normalization of INR (e.g. ≤ 1.3) at different initial INR levels are given.

Pre-treatment INR	2.0–3.9	4.0–6.0	>6.0
Approximate dose ml/kg body weight	1	1.4	2
Approximate dose IU (Factor IX)/ kg body weight	25	35	50

Dose is based onbody weight up to but not exceeding 100 kg. For patients weighing more than 100 kg, the maximum single dose (IU of Factor IX) should therefore not exceed 2500 IU for an INR of 2.0–3.9, 3500 IU for an INR of 4.0–6.0 and 5000 IU for an INR of > 6.0.

The correction of the vitamin K antagonist-induced impairment of haemostasis is commonly reached approximately 30 minutes after the injection. The simultaneous administration of vitamin K should be considered in patients receiving Pro-throm™ for urgent reversal of vitamin K antagonists since vitamin K usually takes effect within 4-6 hours. Repeated dosing with Pro-throm™ forpatients requiring urgent reversal of vitamin K antagonist treatment is not supported by clinical data and therefore not recommended.

These recommendations are based on data from clinical studies with a limited number of subjects. Recovery and the duration ofeffect may vary, therefore monitoring of INR during treatment is mandatory.

- **Bleedings and perioperative prophylaxis in congenital deficiency of any of the vitamin K dependent coagulation factors when specific coagulation factor products are not available.**

The calculation of the required dosage of prothrombin complex concentrate is based on data from clinical studies:

• 1 IU of Factor IX per kg body weight can be expected to raise the plasma Factor IX activity by 1.3% (0.013 IU/ml) of normal
• 1 IU of Factor VII per kg body weight raises the plasma Factor VII activity by 1.7% (0.017 IU/ml) of normal
• 1 IU of Factor II per kg body weight raises the plasma Factor II activity by 1.9% (0.019 IU/ml) of normal
• 1 IU of Factor X per kg body weight raises the plasma Factor X activity by 1.9% (0.019 IU/ml) of normal.

The dose of a specific factor administered is expressed in International Units (IU), which are related to the current WHO standard for each factor. The activity in the plasma of a specific coagulation factor is expressed either as a percentage (relativeto normal plasma) or in International Units (relative to the international standard for the specific coagulation factor).

One International Unit (IU) of a coagulation factor activity is equivalent to the quantity in one ml of the normal human plasma.

For example, the calculation of the required dosage of Factor X is based on the finding that 1 International Unit (IU) of Factor X per kg body weight raises the plasma Factor X activity by 0.019 IU/ml.

The required dosage is determined using the following formula:

Required units = body weight [kg] x desired Factor X rise [IU/ml] x 53

where, 53 (ml/kg) is the reciprocal of the estimated recovery.

Note that the calculation is based upon data from patients receiving vitamin K antagonists. A calculation based upon data from healthy subjects would provide a lower estimate of the required dose.

If the individual recovery is known, that value should be used for calculation.

Product specific information is available from clinical studies in healthy volunteers (N=15), inreversal of vitamin K antagonist treatment for acute major bleeding or perioperative prophylaxis of bleeding (N=98,N=43).

Pediatric population

The safety and efficacy in children and adolescents has not yet been established in controlled clinical studies.

Older population

The posology and method of administration in older people (> 65 years) is equivalent to the general recommendations.

Indications:

- Treatment and perioperative prophylaxis of bleedings in acquired deficiency of the prothrombin complex coagulation factors, such as deficiency caused by treatment with vitamin K antagonists, or in case of over dose of vitamin K antagonists, when rapid correction of the deficiency is required.
- Treatment and perioperative prophylaxis of bleedings in congenital deficiency of any of the vitamin K dependent coagulation factors when purified specific coagulation factor products are not available.

Method of administration

The reconstituted solution should be administered intravenously.

GENERAL INSTRUCTIONS

The solution should be clear or slightly opalescent. After reconstitution, product should be inspected visually for particulate matter and discoloration prior to administration.

Do not use solutions that are cloudy or have deposits. Do not use if gel or precipitate is observed when reconstituted.

For reconstitution and withdrawal procedures, aseptic technique must be maintained.

Reconstitute with 10 ml sterile WFI. The product reconstitutes quickly. After reconstitution the solution is to be used immediately. However, if it is not administered immediately, the reconstituted solution can be stored for upto 8 hours below 25°C, provided sterility of the stored product is maintained. Use Syringe filter for administration.

Care should be taken that no blood enters the syringe filled with product, as there is a risk that the blood could coagulate in the syringe and fibrin clots could therefore be administered to the patient.

In case more than one vial of Pro-throm™ is required, it is possible to pool several vials of Pro-throm™ for a single infusion via a commercially available infusion device.

Patients weighing < 70 kg are instructed to be dosed with maximum infusion speed of 0.12 ml/kg/min (less than 8 ml/min)

The Pro-throm™ solution must not be diluted.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

The advice of a specialist experienced in the management of coagulation disorders should be sought.

In patients with acquired deficiency of the vitamin K-dependent coagulation factors (e.g.as induced by treatment of vitamin K antagonists), Pro-throm™ should only be used when rapid correction of the prothrombin complex levels is necessary, such as major bleedings or emergency surgery. In othercases, reduction of the dose of the vitamin K antagonist and/or administration of vitamin K is usually sufficient.

Patients receiving a vitamin K antagonist may have an underlyinghyper coaguable state and infusion of human prothrombin complex may exacerbate this.

In congenital deficiency of any of the vitamin K- dependent factors, specific coagulation factor products should be used when available.

If allergic or anaphylactic-type reactions occur, the administration of Pro-throm™ has to be stopped immediately (e.g.discontinue injection) and an appropriate treatment has to be initiated. Therapeutic measures depend on the kind and severity of the undesirable effect. The current medical standards for shock treatment are to be observed.

There is a risk of thrombosis or disseminated intravascular coagulation when patients, with either congenital or acquired deficiency, are treated with human prothrombin complex particularly with repeated dosing. The risk may be higher intreatment of isolated Factor VII deficiency, since the other vitamin K -dependent coagulation factors, with longer half-lives, may accumulate to levels considerably higher than normal. Patients given human prothrombin complex should be observed closely for signs or symptoms of disseminated intravascular coagulation or thrombosis.

Because of the risk of thromboembolic complications, close monitoring should be exercised when administering Pro-throm™ to patients with a history of coronary heart disease or myocardial infarction, to patients with liver disease, to patients per-or post operatively, to neonates or to patients at risk of thrombo embolic phenomena or disseminated intravascular coagulation or simultaneous inhibitor deficiency. In each of these situations, the potential benefit of treatment with Pro-throm™ should be weighed against the potential risk of such complications.

In patients with disseminated intravascular coagulation, it may, under certain circumstances, be necessary to substitute the coagulation factors of the prothrombin complex. This substitution may, however, only be carried out after termination of the consumptive state (e.g. by treatment of the underlying cause, persistent normalization of the antithrombin III level).

Reversing vitamin K antagonists exposes patients to the thrombo embolic risk of the underlying disease. Resumption of anticoagulation should becarefully considered as soon as possible.

Undesirable reactions may include the development of heparin-induced thrombocytopenia, type II (HIT, type II). Characteristic signs of HIT are a platelet count drop > 50 per cent and/or the occurrence of new or unexplained thromboembolic complications during heparin therapy. On set is typically from 4 to 14 days after initiation of heparin therapy but may occur within 10 hours in patients recently exposed to heparin (within the previous 100 days).

Nephrotic syndrome has been reported in single cases following attempted immune tolerance induction in haemophilia B patients with Factor IX inhibitors and a history of allergic reaction.

No data are available regarding the use of Pro-throm™ in case of perinatal bleeding due to vitamin K deficiency in neonates.

Pro-throm™ contains up to 460 mg sodium per 100 ml (approximately 200 mmol/L). It needs to be taken into consideration for patients on a controlled sodium diet.

CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients of this medicine.

In the case of disseminated intravascular coagulation, prothrombin complex-preparations may only be applied after termination of the consumptive state.

Known history of heparin-induced thrombocytopenia.

Virus safety

Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/ removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents can not be totally excluded. This also applies to unknown or emerging viruses and other pathogens. The manufacturing procedure incorporates two dedicated orthogonal viral clearance steps ensuring viral safety of the product. This includes solvent detergent treatment and dried heat treatment.

The measures taken are considered effective for enveloped viruses such as human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV),and for the non-enveloped hepatitis A and parvovirus B19 viruses. Only on being declared non reactive for HBsAg, HCV, HIV antibodies and negative for HIV, HCV, HBV by NAT the plasma is used for processing.

The drug product is also tested for viral markers like HBV, HIV & HCV. Multiple chromatography steps have been incorporated for assurance of product safety. The process parameters, characterizations and final product quality are designed such, that they meet the regulatory requirements.

Appropriate vaccination (hepatitis A and B) should be considered for patients in regular/repeated receipt of human plasma-derived prothrombin complex products.

It is strongly recommended that every time that Pro-throm™ is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product.

Interaction with other medicinal products and other forms of interaction

Human prothrombin complex products neutralize the effect of vitamin K antagonist treatment, but no interactions with other medicinal products are known.

When performing clotting tests which are sensitive to heparin in patients receiving high doses of human prothrombin complex, the heparin as a constituent of the administered product must be taken in to account.

FERTILITY, PREGNANCY AND LACTATION

Pregnancy and Breastfeeding

The safety of human prothrombin complex for use in human pregnancy and during lactation has not been established. Animal studies are not suitable to assess the safety with respect to pregnancy, embryonal / foetal development, parturition or post natal development.

Therefore, human prothrombin complex should be used during pregnancy and lactation only if clearly indicated.

Fertility

No fertility data are available.

POSSIBLE SIDE EFFECTS

Allergic or anaphylactic- type reactions have been uncommonly observed, including severe anaphylactic reactions.

Replacement therapy may lead to the formation of circulating antibodies inhibiting one or more of the human prothrombin complex factors. If such inhibitors occur, the condition will manifest itself as a poor clinical response. In such cases, it isrecommended to contact a specialized haemophilia center for guidance. Anaphylactic reactions have been observed in patients with antibodies to Factors contained in the drug.

Increase in body temperature has been commonly observed.

There is a risk of thromboembolic episodes following the administration of human prothrombin complex.

PACKING UNIT

Injection is supplied as sterile freeze dried powder form in a single dose vial.

SHELFLIFE

24 months from the manufacturing date.

Do not use after expiry date mentioned on label.

STORAGE CONDITION

Store between 2°C and 8°C. Do not freeze.

Store in airtight container and protect from light.

Report suspected adverse reaction at: Hemofluidsafety@intaspharma.com

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Manufactured and Marketed by:

INTAS

INTAS PHARMACEUTICALS LTD.

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Front Side

Back Side