

SUMMARY OF PRODUCT CHARACTERISTICS

PROTHROMPLEX Total

Prothrombin Complex Human Steam Treated

SPC 0307 in effect since April 2007
based on the Company Core Data Sheet in effect since January 2007

1. NAME OF THE MEDICINAL PRODUCT

Prothromplex Total 600 IU

Powder and solvent for solution for intravenous injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient: human prothrombin complex factors

Prothromplex Total 600 IU is a powder for solution for intravenous application. Each vial nominally contains the following IU of the human coagulation factors.

	Per vial IU	After reconstitution with 20 ml Sterilised Water for Injections IU/ml
Human coagulation factor II	600	30
Human coagulation factor VII	500	25
Human coagulation factor IX	600	30
Human coagulation factor X	600	30

Each vial contains at least 400 IU protein C.

Furthermore it contains heparin sodium (max. 0.5 IU/IU factor IX) and antithrombin III (0.75 – 1.5 IU/ml).

The total protein content per vial is 300 – 750 mg. The specific activity of the product is at least 0.6 IU/mg, expressed as the factor IX activity.

The activity (IU) of factor IX is determined by the one-step coagulation test described in the European Pharmacopoeia, and measured against the International Standard for Factor IX Concentrates of the World Health Organisation (WHO).

The activity (IU) of factor II, factor VII and factor X is determined by the chromogenic assay described in the European Pharmacopoeia, and measured against the International Standards for factor II, factor VII and factor X concentrates of the WHO.

The activity (IU) of protein C is determined by chromogenic assay and measured against the International Standard for protein C concentrates of the WHO.

For a full list of Excipients – see point 6.1

3. PHARMACEUTICAL FORM

Powder and solvent for solution for intravenous injection.

White or slightly coloured powder or friable solid. After reconstitution the solution has a pH of between 6.5 and 7.5 and an osmolality of not lower than 240 mosmol/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Treatment of bleeding and perioperative prophylaxis of bleeding in acquired deficiency of prothrombin complex coagulation factors, such as a deficiency caused by treatment with vitamin K antagonists or by overdosage with vitamin K antagonists, when rapid correction of the deficiency is required.
- Treatment of bleeding and perioperative prophylaxis in congenital deficiency of any of the vitamin K-dependent coagulation factors, when purified specific coagulation factor product is not available.

4.2 Posology and method of administration

Posology

Only general dosage guidelines are given below. Treatment should be initiated under the supervision of a physician experienced in the treatment of coagulation disorders. The dosage and duration of the substitution therapy depend on the 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-life of the different coagulation factors in the prothrombin complex (see point 5.2).

Individual dosage requirements can only be identified on the basis of regular monitoring of the individual plasma levels of the respective coagulation factors or 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 (e.g. Quick value, prothrombin time INR,) and continuous monitoring of the patient's clinical condition.

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

Bleeding and perioperative prophylaxis of bleeding during vitamin K antagonist treatment:

In severe bleeding or before operations with a high risk of bleeding, normal values (Quick value 100%, INR 1.0) are to be aimed for. The following rule of thumb applies: 1 IU/kg body weight raises the Quick value by about 1%.

Bleeding and perioperative prophylaxis of bleeding in congenital deficiency of any vitamin K-dependent coagulation factor, when the specific factor concentrate is not available:

The calculated required dosage for treatment is based on the empirical finding that approximately 1 IU of factor VII or factor IX per kg body weight raises the plasma factor VII activity by 0.019 IU or factor IX activity by 0,09 IU/ml. 1 IU of factor II or X per kg body weight raises the plasma factor II or X activity by 0.02 IU/ml and 0.017 IU/ml, respectively.

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 plasma of a specific

coagulation factor is expressed either as a percentage (relative to 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 normal human plasma.

For example the calculation of the required dosage of factor X is based on the empirical finding that 1 International Unit (IU) of factor X per kg body weight raises the plasma factor X activity by 0.017 IU/ml. The required dosage is determined using the following formula:

Required units = body weight (kg) x desired factor X rise (IU/ml) x 60
where 60 (ml/kg) is the reciprocal of the estimated recovery.

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

Method of administration

Dissolve the product as described in at 6.6. The product should be administered intravenously. The recommended infusion rate should not exceed 2 ml per minute.

4.3 Contraindications

- Hypersensitivity to the active ingredient or to any of the components/excipients
- Known allergy to heparin or history of heparin-induced thrombocytopenia.

4.4 Special warnings and precautions for use

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

In patients with acquired deficiency of coagulation factors of the prothrombin complex (e.g. as induced by treatment of vitamin K antagonists) *Prothromplex Total* should only be used when rapid correction of the prothrombin complex level is necessary, such as major bleeding or emergency surgery. In other cases, 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 underlying hypercoagulable state and infusion of human prothrombin complex may exacerbate this.

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

If allergic or anaphylactic type reactions occur, the injection/infusion must be stopped immediately. In case of shock, standard medical treatment for shock has to be implemented.

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 cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens.

The measures taken are considered effective for enveloped viruses such as HIV, HBV, HCV, for the non-enveloped viruses HAV and parvovirus B19.

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

It is required that every time that *Prothromplex Total* is administered to a patient the name and batch number of the product (*Prothromplex Total*) are recorded.

There is a risk of thrombosis and disseminated intravascular coagulation when patients with congenital or acquired coagulation disorders are treated with human prothrombin complex concentrates, particularly with repeated dosing. The risk may be higher in the treatment of isolated FVII 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 concentrates should be observed closely for signs and symptoms of intravascular coagulation or thrombosis. Because of the risk of thromboembolic complications, close monitoring should be exercised when administering human prothrombin complex concentrates to patients with a history of coronary heart disease, to patients with liver disease, to pre or postoperative patients, to neonates, or to patients at risk of thromboembolic events or disseminated intravascular coagulation. In each of these situations the potential benefit of treatment should be weighed against the risk of these complications.

4.5 Interactions with other medicinal products

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

Interference with biological testing

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 into account.

4.6 Pregnancy and lactation

The safety of human prothrombin complex concentrates 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 postnatal development. Therefore, human prothrombin complex should be used during pregnancy and lactation only if clearly indicated.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

The following undesirable effects are based on post-marketing experience with drugs of the same class:

As in every therapy with plasma derivatives, hypersensitivity reactions (e.g. fever, urticaria, nausea, vomiting, dyspnoea, drop in blood pressure, and possibly anaphylactic shock) may occur.

In the course of treatment with blood or plasma derivatives, the development of circulating inhibitors with subsequent inactivation of the coagulation factors may occur in rare cases. The appearance of such inhibitors manifests as insufficient clinical response.

There is a risk of thromboembolic episodes following the administration of human prothrombin complex (see section 4.4).

For safety with regard to transmissible agents, see 4.4.

The adverse events listed in the table below, which are sorted by System Organ Class (SOC) have been reported with *Prothromplex Total*.

MedDRA system organ class database	Preferred Term in the MedDRA Database
Immune system disorders	Anaphylactic shock, anaphylactic reaction
Cardiac disorders	Heart failure
Vascular disorders	Flush Thrombophlebitis
Skin and subcutaneous tissue disorders	Erythematous rash, itching
Respiratory, thoracic and mediastinal disorders	Pulmonary embolism
Renal and urinary disorders	Nephrotic syndrome
General disorders and administration site conditions	Fever
Gastrointestinal Disorders	Vomiting Nausea

4.9 Overdose

The use of high doses of human plasma prothrombin complex products has been associated with instances of myocardial infarction, disseminated intravascular coagulation, venous thrombosis and pulmonary embolism. Therefore in case of overdose the risk of development of thromboembolic complications or disseminated intravascular coagulation is enhanced.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antihæmorrhagics, coagulation factors IX, II, VII and X in combination, ATC-Code: B02BD01.

The coagulation factors II, VII, IX and X, which are synthesised in the liver and required vitamin K, are commonly called the Prothrombin Complex.

Factor VII is the zymogen of the active serine protease factor VIIa by which the intrinsic pathway of coagulation is initiated. The tissue factor-factor VIIa complex activates the coagulation factors X and IX, whereby factors IXa and Xa are formed. With further activation of the coagulation cascade, prothrombin (factor II) is activated and converted to thrombin. By the action of thrombin fibrinogen is converted to fibrin, which results in clot formation. The normal generation of thrombin is also essential for platelet function as 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 factor IX deficiency is one of the classical haemophilias (haemophilia B). Isolated deficiency of factor II or factor X is very rare, but in severe forms cause a bleeding tendency similar to that seen in classical haemophilia.

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

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

5.2 Pharmacokinetic properties

Coagulation factor	Half life
Factor II	40 – 60 hours
Factor VII	3 – 5 hours
Factor IX	16 – 30 hours
Factor X	30 – 60 hours

5.3 Preclinical safety data

The factors of the human prothrombin complex (in a concentrate) are normal components of human plasma and behave in the same way as endogenous coagulation factors.

As higher doses lead to volume overload, toxicity testing has no significance after a single administration.

Toxicity studies after repeated administration in animal tests are unfeasible as heterologous proteins develop and interfere with subsequent tests.

As human coagulation factors are not seen as carcinogenic or mutagenic, experimental studies, particularly in heterologous species, were not deemed necessary.

6. PHARMACEUTICAL DETAILS

6.1 List of excipients

Powder:

Sodium chloride
Sodium citrate
Heparin sodium
Antithrombin III

Solvent:

Sterilised water for injections

6.2 Incompatibilities

Prothromplex Total must not be mixed with other medicinal products or solvents, other than the enclosed sterilised water for injections.

Only the provided injection/infusion sets should be used..

6.3 Shelf life

3 years.

Within the stated shelf life, the product can be stored at room temperature (max. 25°C) for one period of up to 6 months. The beginning of storage at room temperature should be recorded on the package. After storage at room temperature, *Prothromplex Total* must be used or discarded immediately, not returned to the refrigerator.

The chemical and physical stability of the reconstituted solution has been documented for 3 hours at 20°C to 25°C.

However, from a microbiological viewpoint, *Prothromplex Total* should be used immediately after reconstitution. The reconstituted solution must not be returned to the refrigerator.

6.4 Special precautions for storage

Store in a refrigerator at 2°C to 8°C. Do not freeze.

Protect from light. Store the medicinal product in the outer carton.

Keep out of the reach and sight of children.

6.5 Nature and contents of container

The powder is supplied in rubber stoppered single dose glass Type II vials. The solvent is supplied in rubber stoppered single dose glass Type II/Type I vials.

Content of package:

- 1 vial with *Prothromplex Total* 600 IU – powder for solution for intravenous injection
- 1 vial with 20 ml Sterilized Water for Injections
- 1 transfer needle
- 1 filter needle
- 1 hypodermic needle
- 1 aeration needle
- 1 butterfly needle (infusion set)

Pack size: 1 x 600 IU

6.6 Instructions for handling

Only the enclosed administration set is to be used for reconstitution.

Prothromplex Total 600 IU must be reconstituted immediately before administration.

The preparation does not contain any preservatives. colourless to slightly yellowish and clear to slightly opalescent and essentially free from visible particles.

Reconstituted product should be inspected visually for particulate matter and discoloration prior to administration. Do not use solutions that are cloudy or have deposits.

Reconstitution of the powder for solution for injection:

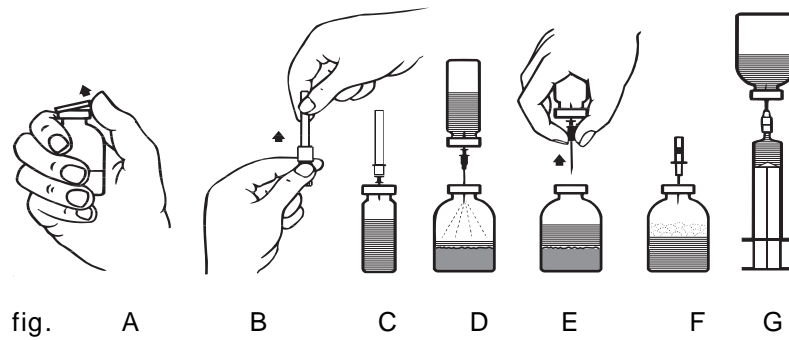
1. Warm the unopened vial containing the solvent (Sterile Water for Injections) to room temperature (maximum 37°C).
2. Remove protective caps from the concentrate vial and from the solvent vial (Fig. A) and cleanse the rubber stoppers of both.
3. Remove protective covering from one end of the enclosed transfer needle by twisting, remove and insert the needle through the rubber stopper of the solvent vial (Fig. B and C).
4. Remove protective covering from the other end of the transfer needle taking care not to touch the exposed end.
5. Invert the solvent vial over the concentrate vial, and insert the end of the transfer needle through the rubber stopper of the powder vial (Fig. D). The solvent will be sucked in by the vacuum in the powder vial.
6. Disconnect the two vials by removing the transfer needle from the powder vial (Fig. E). Gently agitate the concentrate vial to accelerate dissolution.
7. Upon complete dissolution of the powder, insert the enclosed aeration needle (Fig. F) and any foam will collapse. Remove the aeration needle.

Injection / Infusion:

Use aseptic technique. !

1. Remove protective covering from one end of the enclosed filter needle by twisting and fit the needle onto the sterile disposable syringe. Draw the solution into the syringe (Fig. G).
2. Disconnect the filter needle from the syringe and slowly (maximum infusion/injection rate: 2 ml per minute) administer the solution intravenously with the enclosed infusion set (or the enclosed disposable needle).

If *Prothromplex Total* is administered as infusion, only the provided infusion set should be used.



After administration, discard all unsealed needles, together with the syringe and/or the infusion set in the product box.

Any unused, dissolved product or waste material should be disposed of in accordance with national requirements.

7. MARKETING AUTHORISATION HOLDER

8. MARKETING AUTHORISATION NUMBERS

9. DATE OF FIRST AUTHORIZATION / RENEWAL OF THE AUTHORIZATION

10. DATE OF REVISION OF THE TEXT

March 2007

Baxter is a trademarks of Baxter International Inc.