

Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

Prothromplex TOTAL 600 IU powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance: human prothrombin complex

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

	per vial IU	after reconstitution in 20 ml sterilized water for injections IU/ml
Human coagulation factor II	480 - 900	24 - 45
Human coagulation factor VII	500	25
Human coagulation factor IX	600	30
Human coagulation factor X	600	30

The total protein content per vial is 300 - 750 mg. The specific activity of the product is at least 0.6 IU/mg, in relation to the factor IX activity.

One vial contains at least 400 IU Protein C co-purified with the blood coagulation factors.

The activity (IU) of factor IX was determined by the one-step coagulation test described in the European Pharmacopoeia, which is calibrated 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 was determined by the chromogenic assay described in the European Pharmacopoeia, which is calibrated against the International Standards for Factor II, Factor VII and Factor X Concentrates of the World Health Organisation (WHO).

The activity (IU) of protein C was determined by the chromogenic assay described in the European Pharmacopoeia, which is calibrated against the International Standard for Protein C Concentrates of the World Health Organisation (WHO).

Excipients with known effect: Prothromplex TOTAL 600 IU contains the calculated value of 80 mg sodium per vial. Furthermore each vial contains heparin sodium (max. 0.5 IU/IU factor IX).

For the full list of the excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

Powder: White to light yellow, freeze dried powdery or compact dry substance.

Solvent: Sterilized water for injections.

After reconstitution, the pH value of the solution is 6.5 to 7.5 and the osmolality does not lie below 240 mosm/kg. The solution is clear or slightly opalescent.

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 in case of overdose with vitamin K antagonists, when rapid correction of the deficiency is required.

Treatment and perioperative prophylaxis of hemorrhages in congenital deficiency of vitamin K-dependent coagulation factors, when purified specific coagulation factor concentrate is not available.

Prothromplex TOTAL 600 IU is indicated in adults. There are insufficient paediatric data to recommend the administration of Prothromplex TOTAL 600 IU in children.

4.2 Posology and method of administration

Posology

Except for the therapy of bleeding and perioperative prophylaxis of bleeding during vitamin K antagonist treatment, 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 coagulation disorder, on the location and extent of the bleeding and on the patient's clinical condition.

Dosage and frequency of administration should be calculated on an individual patient basis. Dosage intervals must be adjusted to the different circulating half-lives of the various coagulation factors in the prothrombin complex (see section 5.2).

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 the global test of the prothrombin complex level (e.g. Quick's time value, INR, prothrombin time) 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 assays is essential (specific coagulation factor assays and/or global tests for prothrombin complex levels).

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

In severe hemorrhages or before operations with a high risk of bleeding, normal values (Quick's time value 100%, INR 1.0) are to be aimed for.

The following rule of thumb applies: 1 IU factor IX/kg body weight raises the Quick's time value by about 1%.

If Prothromplex TOTAL 600 IU administration is based on the INR measurement the dose will depend on the INR before treatment and the targeted INR.

The dosing in the table below should be followed according to the recommendation made in the publication Makris et al 2001¹.

¹ 1. Makris M, Watson HG: The Management of Coumarin-Induced Over-Anticoagulation Br.J.Haematol. 2001; 114: 271-280

dosing of Prothromplex TOTAL 600 IU according to initial INR measurement	
INR	dose IU/kg (IUs refer to Factor IX)
2.0-3.9	25
4.0-6.0	35
>6.0	50

The correction of the vitamin K antagonist induced impairment of hemostasis persists for approximately 6 - 8 hours. However, the effects of vitamin K, if administered simultaneously, are usually achieved within 4 - 6 hours. Thus, repeated treatment with human prothrombin complex is not usually required when vitamin K has been administered.

As these recommendations are empirical and recovery and the duration of effect may vary, monitoring of INR during treatment is mandatory.

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

The calculated required dosage for treatment is based on the empirical finding that approximately 1 IU of factor IX per kg body weight raises the plasma factor IX activity by about 0.015 IU/ml; and 1 IU of factor VII per kg body weight raises the plasma factor VII activity by about 0.024 IU/ml. One IU of factor II or X per kg body weight raises the plasma factor II or X activity by 0.021 IU/ml.²

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 i (relative to normal human plasma) or in International Units (relative to the international standard for specific factor concentrates). 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.

Maximum single dose:

In order to correct the INR it is not necessary to exceed the dose of 50 IU/kg. If the severity of bleeding requires a higher dose the risk /benefit has to be evaluated by the treating physician.

Paediatric population

The safety and efficacy of the use of Prothromplex TOTAL 600 IU in paediatric patients have not been established in Baxter clinical trials.

Method of administration

Intravenous use

Prothromplex TOTAL 600 IU should be administered via the intravenous route slowly. It is recommended not to administer more than 2 ml per minute (60 IU/min).

² Ostermann H, Haertel S, Knaub S, Kalina U, Jung K, Pabinger I. Pharmacokinetics of Beriplex P/N prothrombin complex concentrate in healthy volunteers. *Thromb Haemost.* 2007;98(4):790-797.

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- 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 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 with vitamin K antagonists) Prothromplex TOTAL 600 IU should only be used when rapid correction of the prothrombin complex levels is necessary, such as major bleeding or emergency surgery. In other cases, reduction of the dose of 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 vitamin K-dependent factors, specific coagulation factor product should be used when available.

Allergic-type hypersensitivity reactions including anaphylactic reactions and anaphylactic shock have been reported with Prothromplex TOTAL 600 IU.

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

Thromboembolism, DIC, Fibrinolysis

There is a risk of thrombosis and disseminated intravascular coagulation (DIC) when patients, with either congenital or acquired deficiency are treated with human prothrombin complex concentrates, including Prothromplex TOTAL 600 IU, particularly with repeated dosing.

Arterial and venous thromboembolic events including myocardial infarction, cerebrovascular accident (e.g. stroke), pulmonary embolism as well as DIC have been reported with Prothromplex TOTAL 600 IU.

The risk may be higher in treatment of isolated F 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 concentrates should be observed closely for signs and symptoms of intravascular coagulation or thrombosis. Because of the risk of thromboembolic complications, particularly close monitoring should be exercised when administering prothrombin complex concentrates to

- patients with a history of coronary heart disease,
- patients with liver disease,
- pre or post-operative patients,
- neonates, or
- other 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.

Virus safety

Standard measures to prevent infections which can be transmitted by medicinal products made from human blood or plasma include donor selection, testing of individual donations and plasma pools for specific infection markers and the execution of effective manufacturing steps to inactivate/remove viruses. Nevertheless, when medicinal products prepared from human blood or plasma are administered, infectious diseases due to transmission of infective agents cannot be totally excluded. This also applies to unknown or emerging viruses or other pathogens.

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

The measures taken may be of limited value against non-enveloped viruses such as parvovirus B19. Parvovirus B19 infection may be serious for pregnant women (fetal infection) and for individuals with immunodeficiency or increased erythropoiesis (e.g. haemolytic anaemia).

When a medicinal product prepared from human blood or plasma is administered regularly/repeatedly, appropriate vaccinations (hepatitis A and B) must be considered.

In the patient's interests, it is strongly recommended that every time Prothromplex TOTAL 600 IU is administered to a patient, the name and batch number of the product are documented with the enclosed self-adhesive label in order to maintain a link between the patient and the batch of the product.

Sodium

Prothromplex TOTAL 600 IU contains the calculated value of 80 mg sodium per vial or 0.13 mg sodium per international unit Prothromplex TOTAL 600 IU (e.g a dose of 50 IU/kg body weight contains 6.5 mg sodium/kg body weight; a dose of 35 IU/kg body weight contains 4.6 mg sodium/kg body weight and a dose of 25 IU/kg body weight contains 3.3 mg sodium/kg body weight). This is to be taken into consideration in patients on a controlled sodium diet.

Heparin

Heparin may cause allergic reactions and reduced blood cell counts which may affect the blood clotting system. Patients with a history of heparin-induced allergic reactions should avoid the use of heparin-containing medicines.

Paediatric population:

There are insufficient data to recommend the administration of Prothromplex TOTAL 600 IU in children.

4.5 Interaction with other medicinal products and other forms of interaction

Human prothrombin complex products neutralize the effect of vitamin K antagonist treatment. No interaction studies have been performed.

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 Fertility, pregnancy and lactation

The effects of Prothromplex TOTAL 600 IU on fertility have not been established in controlled clinical trials.

The safety of human prothrombin complex for use in human pregnancy and during lactation has not been established.

There are no adequate data from the use of Prothromplex TOTAL 600 IU in pregnant or lactating women.

Animal studies are not suitable to assess the safety with respect to pregnancy, embryonal/foetal development, parturition or postnatal development. Therefore Prothromplex TOTAL 600 IU should be used during pregnancy and lactation only if clearly indicated.

See section 4.4 for information on the risk of Parvovirus B19 infection in pregnant women.

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

Summary of the safety profile

Immune system disorders:

Replacement therapy with human prothrombin complex concentrates, including therapy with Prothromplex TOTAL 600 IU, may result in 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.

Vascular disorder:

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 section 4.4.

Tabulated list of adverse reactions

The acute myocardial infarction, venous thrombosis and pyrexia presented in the tabulated list of adverse reactions below have been reported in one clinical study with Prothromplex TOTAL 600 IU in oral anticoagulant reversal in patients (n=61) with acquired prothrombin complex coagulation factors (II, VII, IX, X) deficiency. The other adverse reactions included in the table have been reported from post-marketing experience only.

In the table below all adverse reactions are listed by MedDRA System Organ Class (SOC) (Version 15.1), then by Preferred Term.

Frequency categories are defined as:

very common	($\geq 1/10$)
common	($\geq 1/100$ to $< 1/10$)
uncommon	($\geq 1/1,000$ to $< 1/100$)
rare	($\geq 1/10,000$ to $< 1/1,000$)
very rare	($< 1/10,000$)
not known	(cannot be estimated from the available data)

Adverse reactions from post-marketing experience are included in this table and the frequency category was assigned by statistics based on the assumption that each adverse reaction could have occurred in the clinical trial with 61 patients.

System organ class	Undesirable effect	Frequency
<i>Blood and lymphatic system disorders</i>	Disseminated intravascular coagulation Inhibitors to one or more of the prothrombin complex factors (Factors II, VII, IX, X)*	Common
<i>Immune system Disorders</i>	Anaphylactic shock Anaphylactic reaction Hypersensitivity	Common
<i>Nervous system disorders</i>	Cerebrovascular accident Headache	Common
<i>Cardiac disorders</i>	Heart failure Acute myocardial infarction Tachycardia	Common
<i>Vascular disorders</i>	Arterial thrombosis Venous thrombosis Hypotension Flushing	Common
<i>Respiratory thoracic and mediastinal disorders</i>	Pulmonary embolism Dyspnea Wheezing	Common
<i>Gastrointestinal disorders</i>	Vomiting Nausea	Common
<i>Skin and subcutaneous tissue disorders</i>	Urticaria Rash erythematous Pruritus	Common
<i>Renal and urinary disorders</i>	Nephrotic syndrome	Common
<i>General and administration site conditions</i>	Pyrexia	Common

* Development in patients with congenital deficient factors.

Class reactions

Skin and subcutaneous tissue disorders: Angiodema, Paresthesia

General disorders and administrative site conditions : Infusion site reaction

Nervous system disorders: Lethargy

Psychiatric disorders: Restlessness

Paediatric population

For information on paediatric population see statement in section 4.2.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V [to be completed nationally].

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 the development of thromboembolic complications or disseminated intravascular coagulation is enhanced.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antihemorrhagics, coagulation factors IX, II, VII and X in combination

ATC Code: B02BD01

The coagulation factors II, VII, IX and X, are synthesized in the liver with the help of vitamin K, are commonly called the Prothrombin Complex.

Factor VII is the zymogen of the active serine protease factor VIIa by which the extrinsic pathway of blood coagulation is initiated. The tissue factor/factor VIIa complex activates 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 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 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 hemostasis. Isolated deficiency of factor IX is one of the classical hemophilias (hemophilia B). Isolated deficiency of factors II or X is very rare, but in severe forms they cause a bleeding tendency similar to that seen in classical hemophilia.

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

The administration of human prothrombin complex concentrates 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.

Paediatric population

There are insufficient data to recommend the administration of Prothromplex TOTAL 600 IU in children.

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 like endogenous coagulation factors.

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

Toxicity studies after repeated administration in animal tests are unfeasible since interference through the development of antibodies to heterologous proteins occurs.

Since human coagulation factors are not seen as cancerogenic or mutagenic, experimental studies, especially in heterologous species, were not deemed necessary.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder: Sodium chloride
Sodium citrate dihydrate
Heparin sodium 0.2 - 0.5 IU/IU FIX
Antithrombin III 15 - 30 IU per vial (0.75 - 1.5 IU/ml)

Solvent: sterilized water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6. For reconstitution only the enclosed reconstitution set should be used and for injection/infusion only the provided injection/infusion set, should be used because treatment failure can occur as a consequence of coagulation factor adsorption to the internal surface of some injection/infusion equipment.

As with all coagulation factor preparations, the efficacy and tolerance of the medicinal product may be impaired by mixing with other medicinal products. It is advisable to rinse a common venous access with isotonic saline solution before and after the administration of Prothromplex TOTAL 600 IU.

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 six months. The beginning and end of storage at room temperature should be recorded on the package. After storage at room temperature, Prothromplex TOTAL 600 IU must not be returned to the refrigerator (2°C to 8°C) but must be used within six months or be disposed of.

The chemical and physical in-use stability has been demonstrated for three hours at 20 - 25°C.

From a microbiological point of view, Prothromplex TOTAL 600 IU should be used immediately after reconstitution since the preparation does not contain any preservatives. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user. The ready-to-use solution must not be returned to the refrigerator.

6.4 Special precautions for storage

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

Store in the original package in order to protect from light.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

The powder is supplied in vials made of surface treated, colorless glass (hydrolytic class II), the solvent in vials made of surface treated, colorless glass (hydrolytic class I). Both the product vials and the solvent vials are closed by stoppers made of butyl rubber.

Content of package

- 1 vial with Prothromplex TOTAL 600 IU powder for solution for injection
- 1 vial with 20 ml sterilized water for injections

According to country specific labelling the following combinations of devices are packed with the product:

1 aeration needle, 1 filter needle, 1 transfer needle

[1 disposable syringe, 1 triple set (aeration needle, butterfly needle and disposable needle), 1 filter needle, 1 transfer needle]

[1 triple set (aeration needle, butterfly needle and disposable needle), 1 filter needle, 1 transfer needle]

[1 transfer needle, 1 filter needle, 1 aeration needle, 1 butterfly needle, 1 disposable needle]

[1 transfer needle, 1 filter needle, 1 disposable syringe, 1 aeration needle, 1 twin set (butterfly needle, disposable needle)]

Pack size

1 x 600 IU

6.6 Special precautions for disposal and other handling

Only the enclosed reconstitution set is to be used for reconstitution. Prothromplex TOTAL 600 IU is only to be reconstituted immediately before administration. The solution is clear or slightly opalescent. Cloudy solutions or those with deposits are to be disposed of.

Reconstitution of the powder for solution for injection:

Use aseptic technique!

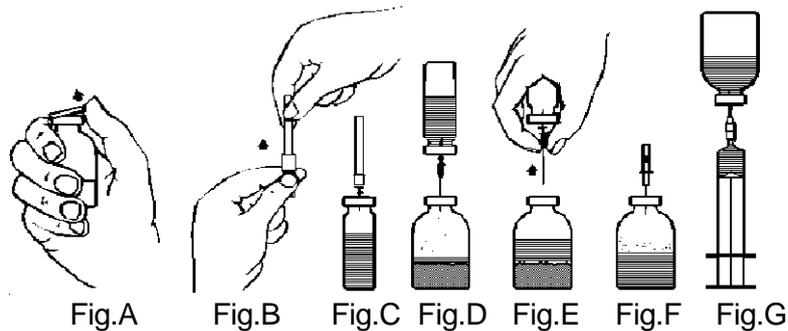
1. Warm the unopened vial containing the solvent (sterilized water for injections) to room or body temperature (maximum 37°C).
2. Remove protective caps from the powder vial and the solvent vial (fig. A) and clean the rubber stoppers of both vials.
3. Remove protective covering from one end of the enclosed 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 powder 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 together with the solvent vial from the powder vial (Fig. E). Gently agitate the powder 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!

Before administration, the reconstituted solution should always be checked visually for floating particles or discoloration.

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



After administration, discard all needles unsealed, together with the syringe and/or the infusion set in the product box, to avoid putting other persons at risk.

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

7. MARKETING AUTHORIZATION HOLDER

<to be completed nationally>

8. MARKETING AUTHORIZATION NUMBER(S)

<to be completed nationally>

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Date of first authorization: 15 June 2010

Date of latest renewal: 12 December 2012

10. DATE OF REVISION OF THE TEXT

08/2015