Package leaflet: Information for the patient

Prothromplex TOTAL 600 IU

Powder and solvent for solution for injection

Active substance: Human Prothrombin Complex

Read all of this leaflet carefully before administration of this medicine, because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Prothromplex TOTAL is and what it is used for

Prothromplex TOTAL is a preparation made from human plasma (the liquid part of blood). It contains the blood clotting factors II, VII, IX and X (prothrombin complex coagulation factors), as well as protein C.

These clotting factors are vitamin K dependent and, like vitamin K, they play an important role in blood clotting. In the event of a deficiency of one of these factors, blood does not clot as rapidly as usual, which leads to an increased bleeding tendency.

Prothromplex TOTAL is used for:
- the treatment of bleeding
- the prevention of bleeding immediately before or after surgery
- the conditions acquired deficiency and congenital deficiency of coagulation factors

Acquired deficiency:
You may develop a deficiency of the vitamin K-dependent coagulation factors (acquired deficiency), for example, from treatment with or an overdose of medicinal products that reduce the effect of vitamin K (so-called vitamin K antagonists).

Congenital deficiency:
If you were born with a deficiency (congenital deficiency), this medicine may be given to you immediately before or after surgery if the appropriate individual factor concentrate is not available.

2. What you need to know before you use Prothromplex TOTAL

Do not use Prothromplex TOTAL

- if you are allergic to clotting factors or any of the other ingredients of this medicine (listed in section 6).
- if you have or are suspected to have had a heparin-triggered drop in blood platelets, the cells that are important for blood clotting (heparin-induced thrombocytopenia).

Warnings and precautions

Traceability

It is strongly recommended that every time you receive a dose of Prothromplex TOTAL the name and batch number of the product are recorded in order to maintain a record of the batches used.

Talk to your doctor before using Prothromplex TOTAL:

- as there is the rare possibility that you may develop a severe sudden allergic reaction (anaphylactic reaction) to Prothromplex TOTAL because such allergic-type reactions have been reported with Prothromplex TOTAL. More detailed information on early symptoms of such an allergic reaction you can find in section 4 “Possible Side Effects”.

- if you have *acquired deficiency* of vitamin K-dependent coagulation factors. This acquired deficiency may be caused by treatment with medicinal products which neutralize blood coagulation through the inhibition of vitamin K. In this case, Prothromplex TOTAL must be administered only when a rapid correction of the concentration of the coagulation factors of the prothrombin complex is required, for example in severe bleeding or emergency surgery. In all other cases, a reduction of the dose of the vitamin K antagonists or an administration of vitamin K is sufficient.

- if you receive *medicinal products to inhibit blood coagulation* (vitamin K antagonists). You may have an increased disposition to coagulation which may be increased through the infusion of human prothrombin complex concentrate.

- if you have *congenital deficiency* of a vitamin K-dependent coagulation factor, a specific individual factor concentrate will be administered to you by your doctor if it is available.

- if you are treated with a prothrombin complex concentrate, especially in case that you have received it repeatedly, because blood clots (thrombosis) may occur and be washed into the blood stream (embolisms).

- because of the potential for the occurrence of blood clots, if you belong to one of the following patient groups:
  - patients with a disease of the coronary vessels or a heart infarction
  - patients with liver disease
  - pre-or post-operative patients
  - newborns
  - patients with a risk of thromboembolic complications or disseminated intravascular coagulation (DIC)

In all these situations, the doctor will carefully weigh the benefits of treatment with Prothromplex TOTAL against the potential risk of these complications.

Virus safety
When medicines are made from human blood or plasma, certain measures are put in place to prevent infections being passed on to patients. These include

- careful selection of blood and plasma donors to make sure those at risk of carrying infections are excluded,
- testing of each donation and pools of plasma for signs of virus/ infections,
- inclusion of steps in the processing of the blood and plasma that can inactivate or remove viruses.

Despite these measures, when medicines prepared from human blood or plasma are administered, the possibility of passing on infection cannot be totally excluded. This also applies to unknown or emerging viruses or other types of infections.

The measures taken are considered effective for enveloped viruses such as human immunodeficiency virus (HIV), hepatitis B virus and hepatitis C virus, and for the non-enveloped hepatitis A 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 (infection of the unborn child) and
- for individuals whose immune system is depressed or who have some types of anaemia (e.g. sickle cell disease or haemolytic anaemia)

Your doctor may recommend that you consider vaccination against hepatitis A and B if you regularly or repeatedly receive human plasma-derived prothrombin complex concentrates.

Children and adolescents

The safety and efficacy of the use of Prothromplex TOTAL in patients under 18 years have not been established in clinical trials.

Other medicines and Prothromplex TOTAL

Tell your doctor or pharmacist if you are taking/using, have recently taken/used or might take/use any other medicines.

Please inform your attending doctor if you receive medicinal products to inhibit blood coagulation (vitamin K antagonists). You may have an increased disposition to coagulation which may be increased through the infusion of human prothrombin complex concentrate.

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.

Pregnancy, breast-feeding and fertility

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before using this medicine.

Prothromplex TOTAL is to be used during the pregnancy and breast-feeding period only if clearly indicated.

There is no information on the effects of Prothromplex TOTAL on fertility.

Driving and using machines

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

Prothromplex TOTAL contains sodium and heparin

This medicine contains the calculated value of 81.7 mg sodium in each vial or 0.14 mg sodium (main component of cooking/table salt) per International Unit. This is equivalent to 4.1% of the recommended maximum daily dietary intake of sodium for an adult.

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.

3. How to use Prothromplex TOTAL

Your therapy should be initiated, administered and monitored by a doctor who is experienced in the treatment of coagulation disorders.

The required amount of Prothromplex TOTAL as well as the duration of the treatment depends on various factors such as body weight, the degree of severity of your disease, localization and extent of the bleeding or the necessity to prevent bleeding in surgical procedures.

The doctor will determine the dosage which is suitable for you and will monitor the coagulation and your clinical condition regularly (see section “The following information is intended for healthcare professionals only”).

Method of administration

Intravenous use.

Prothromplex TOTAL administration is supervised by a doctor.

After reconstitution with the enclosed sterilized water for injections, Prothromplex TOTAL is administered slowly into a vein (intravenously). The speed of administration depends on your well-being and should not exceed 2 ml per minute (60 IU/min).

Use in children and adolescents

There are insufficient data to recommend the administration of Prothromplex TOTAL in patients under 18 years.

If you use more Prothromplex TOTAL than you should

In the event of overdose, there is a risk of the development of thromboembolic complications or consumption coagulopathy.

When high doses of human prothrombin complex concentrates were administered, heart attack, increased consumption of blood platelets and coagulation factors with pronounced clot formation in the blood vessels (DIC, disseminated intravascular coagulation, consumption coagulopathy), venous thrombosis and pulmonary embolism have been observed.

If you forget to take Prothromplex TOTAL

Not applicable.

If you stop taking Prothromplex TOTAL

Not applicable.

If you have any further questions on the use of this medicine, ask your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

As in all therapies with plasma derivatives, there is the possibility that you may develop a sudden allergic reaction (anaphylactic reaction). In individual cases, a severe hypersensitivity reaction including shock may develop.
Therefore, please pay attention to potential early symptoms of an allergic reaction such as:

- erythema (reddening of the skin)
- skin rash
- appearance of hives on the skin (nettle rash / urticaria)
- itching anywhere on the body
- swelling of lips and tongue
- breathing difficulties / dyspnoea
- tightness of the chest
- general indisposition
- dizziness
- drop in blood pressure

If you notice one or several of the listed symptoms, discontinue the infusion at once. Call your doctor immediately. Severe symptoms require immediate emergency treatment.

When using prothrombin complex concentrates (including Prothromplex TOTAL), patients may develop resistance (inhibitors) to one or several of the coagulation factors with subsequent inactivation of the blood coagulation factors. The occurrence of such inhibitors may manifest as an insufficient response to the treatment.

During the treatment with prothrombin complex concentrates, blood clots (thromboses) may develop and be washed into the blood stream (embolisms). This may lead to complications such as heart infarction, an increased consumption of blood platelets and blood coagulation factors with pronounced blood clot formation in the blood vessels (consumption coagulopathy), obstruction of the veins by blood clots (venous thrombosis) and obstruction of a lung blood vessel by a blood clot (pulmonary infarction).

<u>The following side effects may affect up to 1 in 10 people while using Prothromplex TOTAL:</u>

- blood clot formation throughout the body (disseminated intravascular coagulation), resistance (inhibitors) to one or more of the prothrombin complex factors (Factors II, VII, IX, X)

- severe sudden allergic reaction (anaphylactic shock), anaphylactic reaction, hypersensitivity stroke, headache
- heart attack (acute myocardial infarction), palpitation of the heart (tachycardia)
- arterial thrombosis, venous thrombosis, drop of blood pressure (hypotension) reddening of the skin (flushing)
- occlusion of a lung vessel through a blood clot (pulmonary embolism), breathing difficulties, breathlessness (dyspnoea), wheezing
- vomiting, feeling of sickness (nausea)
- nettle rash on the entire body (urticaria) skin rash (rash erythematous), itching (pruritus)
- a certain kidney disorder with symptoms such as swelling of the eyelids, face and lower legs with weight gain as well as loss of protein via the urine (nephrotic syndrome)
- fever (pyrexia)

The following side effects have been observed with other prothrombin complex concentrates:

- swelling of face, tongue and lips (angioedema) skin sensation such as burning, prickling, itching or tingling (paraesthesia)
- infusion site reaction
- lethargy
- restlessness

Reporting of side effects

If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Prothromplex TOTAL

Store in a refrigerator (2 °C to 8 °C). Do not freeze.
Store in the original package in order to protect from light.

Keep this medicine out of the sight and reach of children.

Do not use the medicine after the expiry date which is stated on the label and outer carton after "EXP." The expiry date refers to the last day of that month.

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 must not be returned to the refrigerator (2°C to 8°C) but must be used within six months or be disposed of.

The ready-to-use solution should be used immediately.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Prothromplex TOTAL contains

Powder:

The substance is Human Prothrombin Complex consisting of Human Coagulation Factors II, VII, IX and X and Protein C.

	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

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

The other ingredients are: sodium chloride, sodium citrate dihydrate, heparin sodium (0.2 - 0.5 IU/IU factor IX) and antithrombin III 15 - 30 IU per vial (0.75 - 1.5 IU/ml).

Solvent:

Sterilized water for injections.

What Prothromplex TOTAL looks like and contents of the pack

Powder and solvent for solution for injection.

Prothromplex TOTAL is a white to light yellow, freeze dried powdery or compact dry substance.

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.

Powder and solvent are supplied in single-dose vials made of glass (hydrolytic class I and class II, respectively). The vials are closed with stoppers made of butyl rubber.

Contents of the pack

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

Pack size

1 x 600 IU

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder

Baxalta Innovations GmbH
Industriestrasse 67
A-1221 Vienna
Austria

Manufacturer

Baxter AG
Industriestrasse 67
A 1221 Vienna, Austria

Takeda Manufacturing Austria AG
Industriestrasse 67
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This medicinal product is authorised in the Member States of the EEA under the following names:

Austria:	Prothromplex TOTAL 600 I.E. Pulver und Lösungsmittel zur Herstellung einer Injektionslösung
Belgium, Luxembourg	Prothromplex 600 UI, poudre et solvant pour solution injectable
Bulgaria	Prothromplex Total NF 600 IU
Czech Republic, Poland	Prothromplex Total NF
Denmark, Norway, Portugal	Prothromplex
Estonia, Greece	Prothromplex TOTAL
Germany	Prothromplex NF 600
Hungary:	Prothromplex TOTAL 600 NE
Ireland, Malta, United Kingdom	Prothromplex TOTAL 600 IU
Italy	PROPLEX
Lithuania	Prothromplex 600 TV milteliai ir tirpiklis injekciniam tirpalui
Latvia	Prothromplex TOTAL 600 SV pulveris un šķīdinātājs injekciju šķīduma pagatavošanai
Netherlands	Prothromplex 600 IE poeder en oplosmiddel voor oplossing voor injection
Romania	Prothromplex TOTAL 600 UI pulbere şi solvent pentru soluţie injectabilă
Slovakia	Prothromplex NF 600 IU
Slovenia	PROPLEX 600 i.e. prašek in vehikel za raztopino za injiciranje
Spain	Prothromplex Total 600 UI

This leaflet was last revised in October 2020.

The following information is intended for healthcare professionals only:

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 must 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.
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 haemorrhages 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 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 2001 [1].

dosing of Prothromplex TOTAL 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 haemostasis 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.**

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

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 per kg body weight of Factor VII 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 (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 in paediatric patients have not been established in Baxter clinical trials.

Interactions with other medicinal products and other forms of interaction

If high doses of Prothromplex TOTAL are applied, the heparin contained in the preparation is to be taken into consideration when carrying out heparin-sensitive coagulation analyses.

Incompatibilities

This medicinal product must not be mixed with other medicinal products except the enclosed solvent.

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.

Special precautions for disposal and other handling

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

[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.

Only reconstitute Prothromplex TOTAL immediately before administration. Then the solution is to be utilized straight away. (The solution does not contain any preservatives.)

The solution is clear or slightly opalescent. Before administration, always check the reconstituted solution visually for suspended particles or discolorations. Cloudy solutions or solutions with precipitate 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

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

Use aseptic technique.

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).

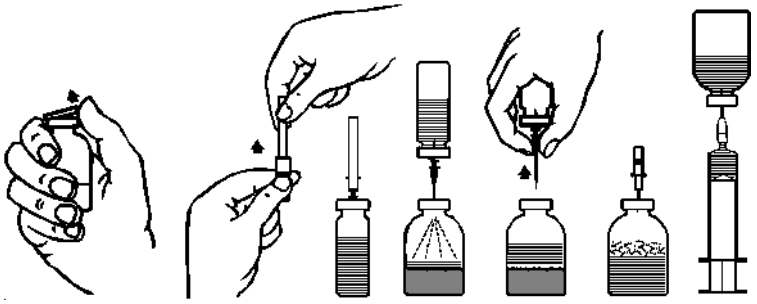

Fig. A Fig. B Fig. C Fig. D Fig. E Fig.F Fig. G

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.

Document each administration of Prothromplex TOTAL in the case history, using the enclosed self-adhesive label.