

Package leaflet: Information for the patient

Prothromplex TOTAL 1500 IU Powder and solvent for solution for injection 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 or pharmacist.
- 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
2. What you need to know before you use Prothromplex TOTAL
3. How to use Prothromplex TOTAL
4. Possible side effects
5. How to store Prothromplex TOTAL
6. Contents of the pack and other information

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

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.

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.

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 this medicine is used.

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 204 mg sodium in each vial or 0.14 mg sodium (main component of cooking/table salt) per International Unit. This is equivalent to 10.2% 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 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, alert your doctor immediately. He/she will discontinue the infusion at once. 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).

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

- 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 50 ml sterilized water for injections [IU/ml]
Human coagulation factor II	1125-2125	22.5 – 42.5
Human coagulation factor VII	1250	25
Human coagulation factor IX	1500	30
Human coagulation factor X	1500	30

One vial contains at least 1000 IU protein C co-purified with the blood coagulation factors.

The other ingredients are sodium chloride, sodium citrate, heparin sodium (0.2 – 0.5 IU/IU factor IX) and antithrombin III 37.5-75IU per vial (0.75-1.5IU/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 mosmol/kg. The solution is clear or slightly opalescent.

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

Contents of the pack

- 1 vial with Prothromplex TOTAL 1500 IU powder for solution for injection
- 1 vial with 50ml sterilized water for injections
- 1 Mix2vial for reconstitution

Pack size

1 x 1500 IU

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder

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This leaflet was last revised in April 2026


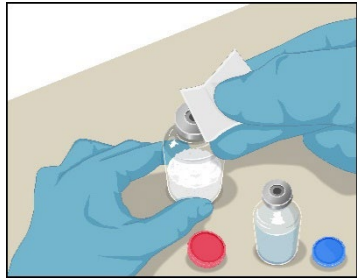
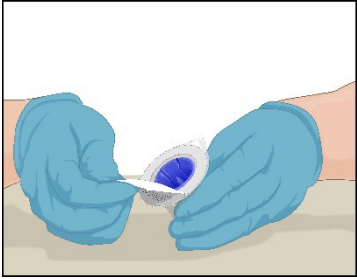
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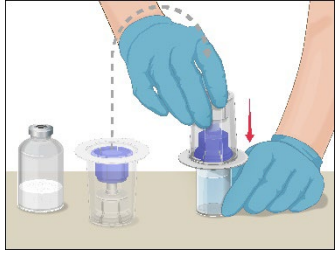
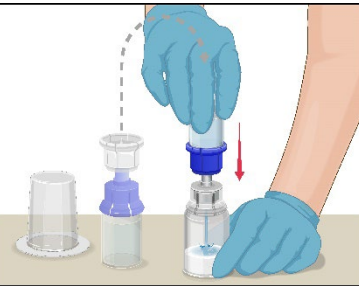
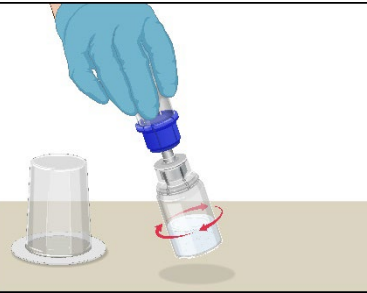
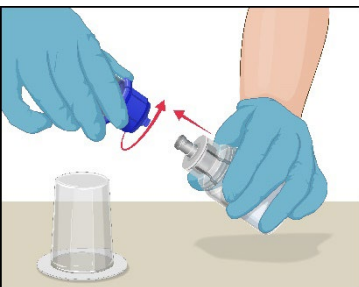
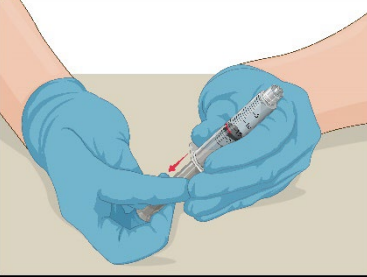
Instructions for preparation and administration

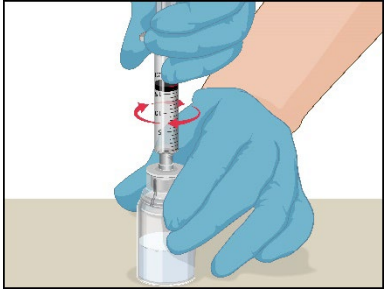
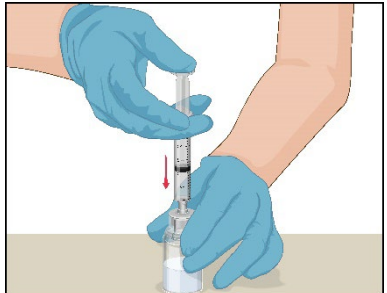
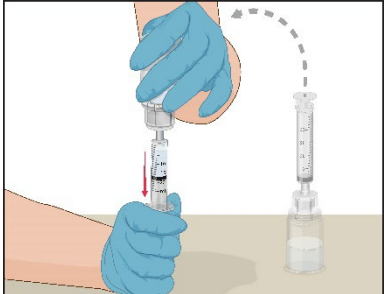
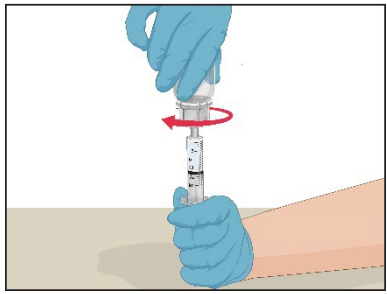
General Instructions

- Only the enclosed reconstitution set is to be used for reconstitution.
- Check the expiry date and ensure that the Prothromplex TOTAL powder and water for injections (solvent) are at room temperature prior to preparation. Do not use after the expiry date stated on the labels and carton.
- Use aseptic technique (clean and low-germ conditions) and a flat work surface during the reconstitution procedure. Wash your hands and put on clean exam gloves (the use of gloves is optional).
- Warm the unopened vial containing the solvent (sterilized water for injections) to room or body temperature (maximum 37 °C).
- Prothromplex TOTAL 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.

Instructions for reconstitution of the powder for solution for injection:

	Steps	Image
1	<ul style="list-style-type: none"> • Remove protective caps from the powder vial and the solvent vial. 	
2	<ul style="list-style-type: none"> • Disinfect each stopper with a separate sterile alcohol swab (or other suitable sterile solution) by wiping the stopper for several seconds. • Allow the rubber stopper to dry. Place the vials on a flat surface. 	
3	<ul style="list-style-type: none"> • Open the Mix2Vial device package by completely peeling away the lid, without touching the inside of the package. • Do not remove the Mix2Vial device from the package. 	

	Steps	Image
4	<ul style="list-style-type: none"> • Turn the package with the Mix2Vial device upside down and place it over the top of the solvent vial. • Firmly insert the blue plastic spike of the device into the centre of the solvent vial stopper by pushing straight down. Grip the package at its edge and lift it off the Mix2Vial device. • Be careful not to touch the clear plastic spike. • The solvent vial now has the Mix2Vial device connected to it and is ready to be connected to the Prothromplex TOTAL vial. 	
5	<ul style="list-style-type: none"> • To connect the solvent vial to the Prothromplex TOTAL vial, turn the solvent vial over and place it on top of the vial containing Prothromplex TOTAL powder. • Fully insert the clear plastic spike into the Prothromplex TOTAL vial stopper by firmly pushing straight down. This should be done right away to keep the liquid free of germs. • The solvent will flow into the Prothromplex TOTAL vial by vacuum. Check that all the solvent has transferred. • Do not use if the vacuum has been lost and the solvent does not flow into the Prothromplex TOTAL vial. 	
6	<ul style="list-style-type: none"> • Gently and continuously swirl the connected vials until dissolved or allow the reconstituted product to stand for 5 minutes then gently swirl to ensure the powder is completely dissolved. • Do not shake. Shaking will adversely affect the product. Do not refrigerate after reconstitution. 	
7	<ul style="list-style-type: none"> • Disconnect the two sides of the Mix2Vial from each other by holding the clear plastic side of the Mix2Vial device attached to the Prothromplex TOTAL vial with one hand and the blue plastic side of the Mix2Vial device attached to the solvent vial with the other hand. • Turn the blue plastic side counterclockwise and gently pull the two vials apart. • Do not touch the end of the plastic connector attached to the Prothromplex TOTAL vial containing the dissolved product. • Place the Prothromplex TOTAL vial on a flat work surface. Discard the empty solvent vial. 	
8	<ul style="list-style-type: none"> • Draw air into an empty, sterile disposable plastic syringe by pulling back on the plunger. • The amount of air should equal the amount of reconstituted Prothromplex TOTAL that you will withdraw from the vial. 	

	Steps	Image
9	<ul style="list-style-type: none"> Leaving the Prothromplex TOTAL vial (containing the reconstituted product) on your flat work surface, connect the syringe to the clear plastic connector and turn the syringe clockwise. 	
10	<ul style="list-style-type: none"> Hold the vial with one hand and use the other hand to push all the air from the syringe into the vial. 	
11	<ul style="list-style-type: none"> Flip connected syringe and Prothromplex TOTAL vial, so the vial is on top. Be sure to keep the syringe plunger pressed in. Draw the Prothromplex TOTAL into the syringe by pulling plunger back slowly. Do not push and pull solution back and forth between syringe and vial. Doing so may harm the medicine. 	
12	<ul style="list-style-type: none"> When ready to infuse, disconnect the syringe by turning it counterclockwise. Inspect the syringe visually for particulate matter; the solution should be clear and slightly opalescent. If the solution is cloudy or with deposits, do not use the solution. 	

Instructions for Administration

Inspect the prepared solution in the syringe for particulate matter and discoloration prior to administration (the solution should be clear, colourless and free from particles). The filter included in the Mix2Vial device removes those particles completely. Filtration does not influence dosage calculations. **The solution in the syringe** should not be used if it is cloudy or contains flakes or particles after filtration.

1. Attach the infusion needle to a syringe containing Prothromplex TOTAL solution. For comfort, a winged (butterfly) infusion set is recommended. Point the needle up and remove any air bubbles by gently tapping the syringe with your finger and slowly and carefully pushing air out of the syringe and needle.

2. Apply a tourniquet and get the infusion site ready by wiping the skin well with a sterile alcohol swab (or other suitable sterile solution suggested).
3. Insert the needle into the vein and remove the tourniquet. Slowly infuse Prothromplex TOTAL. Do not infuse any faster than 2 mL per minute. Disconnect the empty syringe.

Note:

Do not remove butterfly needle until all syringes have been infused and do not touch the Luer port that connects to the syringe.

4. Take the needle out of the vein and use sterile gauze to put pressure on the infusion site for several minutes.

Do not recap the needle. Place the needle, syringe, and empty Prothromplex TOTAL and solvent vial in a hard-walled sharps container for proper disposal. Do not dispose of these supplies in ordinary household trash.

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. 2001¹.

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

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.**

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/ml².

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 clinical trials.

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.

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.

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.

Name and batch number of the medicinal product.

It is strongly recommended that every time that Prothromplex TOTAL 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.