Prothromplex® TOTAL 500 IU
(human prothrombin complex)

Guideline development support for the use of Prothromplex® TOTAL 500 IU

(human prothrombin complex)

Purpose: This document has been designed to assist healthcare professionals or other relevant decision makers in developing their own guidelines for the use of Prothromplex® TOTAL 500 IU. This document does not replace the Summary of Product Characteristic (SmPC) for Prothromplex® TOTAL 500 IU. Please read the Summary of Product Characteristic before using this medicine.

Adverse events should be reported. Reporting forms and information can be found at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

Adverse events should also be reported to Takeda via: AE.GBR-IRL@takeda.com.

Takeda UK Limited, 1 Kingdom Street, London, W2 6BD, United Kingdom.

Prescribing information can be found at the end of this document

Job code: C-APROM/GB/PROT/0040

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1. Background

Warfarin and other coumarin derivatives exert their anticoagulant affect by preventing the production of biologically active Vitamin K dependent co-factors (II, VII, IX and X).[(Yee et al, 2019)] These effects can be reversed by the administration of Vitamin K with peak effects on international normalized ratio (INR) after 4-6 hours.[(Yee et al, 2019)]

Therefore, in situations where more rapid reversal of anticoagulation is required and where the thrombotic risks of complete reversal are less than the risks of continued bleeding, the use of a Prothrombin Complex Concentrate (PCC) should be considered.

2. Indications for use

As Prothromplex® TOTAL 500 IU is used for the emergency treatment of life-threatening haemorrhage, please seek advice from the Consultant Haematologist on call if there is any doubt regarding its use.

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.[(Prothromplex® TOTAL 500 IU SmPC)]

Treatment and perioperative prophylaxis of haemorrhages in congenital deficiency of vitamin K-dependent coagulation factors, when purified specific coagulation factor concentrate is not available.[(Prothromplex® TOTAL 500 IU SmPC)]

Prothromplex® TOTAL 500 IU is indicated in adults. There are insufficient paediatric data to recommend the administration of Prothromplex® TOTAL 500 IU in children.[(Prothromplex® TOTAL 500 IU SmPC)]

3. Contraindications

- Hypersensitivity to the active substance or to any of the excipients
- Known allergy to heparin or history of heparin-induced thrombocytopenia

4. Special warnings and precautions

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

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 500 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, disseminated intravascular coagulation, fibrinolysis[(Prothromplex® TOTAL 500 IU SmPC)]

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 500 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 500 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 DIC

In each of these situations, the potential benefit of treatment should be weighed against the risk of these complications.

Virus safety *(Prothromplex® TOTAL 500 IU SmPC)*

When medicinal products prepared from human blood or plasma are administered, infectious diseases due to transmission of infective agents cannot be totally excluded.

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

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Sodium *(Prothromplex® TOTAL 500 IU SmPC)*

Prothromplex® TOTAL 500 IU contains 68 mg sodium per vial or 0.14 mg sodium per International Unit equivalent to 3.4% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Heparin *(Prothromplex® TOTAL 500 IU SmPC)*

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 *(Prothromplex® TOTAL 500 IU SmPC)*

There are insufficient data to recommend the administration of Prothromplex® TOTAL 500 IU in children.

Fertility, pregnancy and lactation *(Prothromplex® TOTAL 500 IU SmPC)*

The effects of Prothromplex® TOTAL 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 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 should be used during pregnancy and lactation only if clearly indicated.

5. Adverse events

Tabulated list of adverse reactions[(Prothromplex® TOTAL 500 IU SmPC)]

System Organ Class	Undesirable effect	Frequency
Blood and lymphatic system disorders	Disseminated intravascular coagulation Inhibitors to one or more of the prothrombin complex factors (Factors II, VII, IX, X)*	Common (≥1/100 to <1/10)
Immune system disorders	Anaphylactic shock Anaphylactic reaction Hypersensitivity	Common (≥1/100 to <1/10)
Nervous system disorders	Cerebrovascular accident Headache	Common (≥1/100 to <1/10)
Cardiac disorders	Heart failure Acute myocardial infarction** Tachycardia	Common (≥1/100 to <1/10)
Vascular disorders	Arterial thrombosis Venous thrombosis** Hypotension Flushing	Common (≥1/100 to <1/10)
Respiratory thoracic and mediastinal disorders	Pulmonary embolism Dyspnoea Wheezing	Common (≥1/100 to <1/10)
Gastrointestinal disorders	Vomiting Nausea	Common (≥1/100 to <1/10)
Skin and subcutaneous tissue disorders	Urticaria Rash erythematous Pruritus	Common (≥1/100 to <1/10)
Renal and urinary disorders	Nephrotic syndrome	Common (≥1/100 to <1/10)
General and administration site conditions	Pyrexia**	Common (≥1/100 to <1/10)

* Development in patients with congenital deficient factors.
** Reported from the clinical study.

Class reactions[(Prothromplex® TOTAL 500 IU SmPC)]

- Skin and subcutaneous tissue disorders: angioedema, paraesthesia
- General disorders and administrative site conditions: infusion site reaction
- Nervous system disorders: lethargy
- Psychiatric disorders: restlessness

6. Constituents

Prothromplex® TOTAL 500 IU is a powder for solution for intravenous application. Each vial contains the following human coagulation factors:(Prothromplex® TOTAL 500 IU SmPC)

- Factor II
- Factor VII
- Factor IX
- Factor X

The specific activity of the product is 0.6 IU/ml, in relation to the factor IX activity.

One vial contains at least 333 IU Protein C co-purified with the blood coagulation factors.

Excipients with known effect:(Prothromplex® TOTAL 500 IU SmPC)

Each vial of Prothromplex® TOTAL 500 IU contains:

- Sodium 68 mg
- Heparin sodium (max. 0.5 IU/IU factor IX)

7. Dose

Treatment should be initiated under the supervision of a physician experienced in the treatment of coagulation disorders.(Prothromplex® TOTAL 500 IU SmPC)

Each vial contains Prothromplex® TOTAL 500 IU

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.(Prothromplex® TOTAL 500 IU SmPC)

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.(Prothromplex® TOTAL 500 IU SmPC)
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).(Prothromplex® TOTAL 500 IU SmPC)

Bleeding and perioperative prophylaxis of bleeding during vitamin K antagonist treatment:(Prothromplex® TOTAL 500 IU SmPC)

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 500 IU administration is based on the INR measurement the dose will depend on the INR before treatment and the targeted INR.(Prothromplex® TOTAL 500 IU SmPC)

Dosing of Prothromplex® TOTAL 500 IU according to initial INR measurement*(Prothromplex® TOTAL 500 IU SmPC)*

Dosing of Prothromplex® TOTAL 500 IU according to initial INR measurement	
INR	Dose (IU/kg) (IU refers to Factor IX)
2.0 - 3.9	25
4.0 - 6.0	35
>6.0	50

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:(Prothromplex® TOTAL 500 IU SmPC)

The calculated required dosage for treatment is based on the empirical finding that approximately 1 international unit of factor IX per kg body weight raises the plasma factor IX activity by about 0.015 international units/ml; and 1 international unit of factor VII per kg body weight raises the plasma factor VII activity by about 0.024 international units/ml. One international unit of factor II or X per kg body weight raises the plasma factor II or X activity by 0.021 international units /ml.(Prothromplex® TOTAL 500 IU SmPC)

The dose of a specific factor administered is expressed in international units, 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 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 of factor X per kg body weight raises the plasma factor X activity by 0.017 international unit/ml. The required dosage is determined using the following formula:

Required units = body weight (kg) x desired factor X rise (international units/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:(Prothromplex® TOTAL 500 IU SmPC)

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

8. Reconstitution

Nature and contents of container(Prothromplex® TOTAL 500 IU SmPC)

The powder is supplied in vials made of surface treated, colourless glass (hydrolytic class II), the solvent in vials made of surface treated, colourless 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 500 IU powder for solution for injection
- 1 vial with 17 ml sterilised water for injections
- 1 Mix2vial® for reconstitution

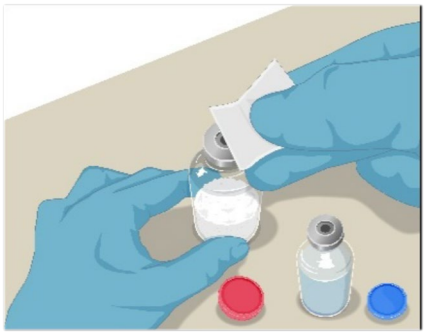
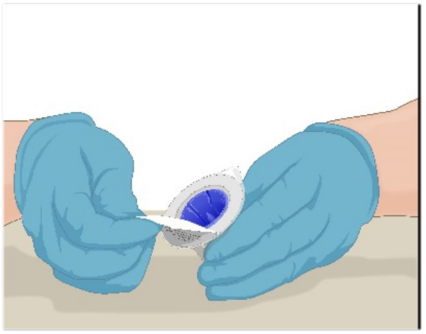
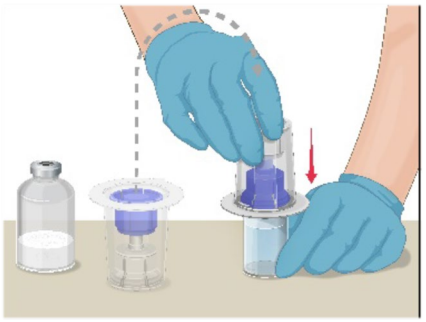
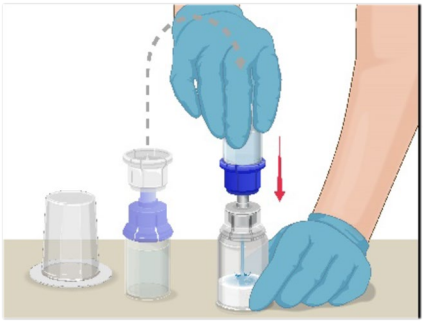
Pack size

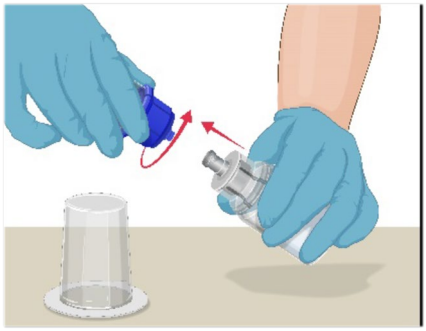
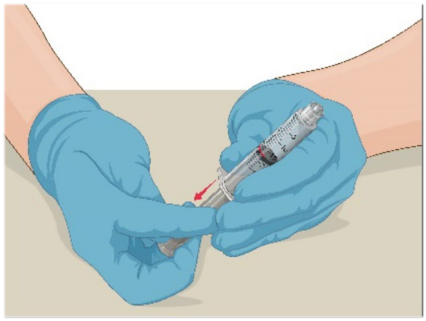
1 x 500 IU

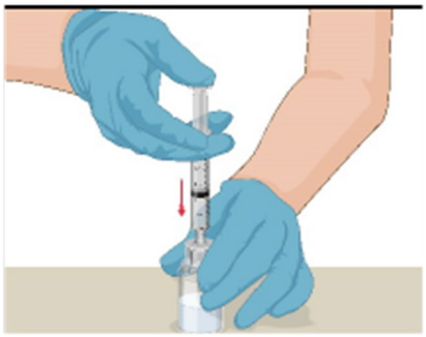
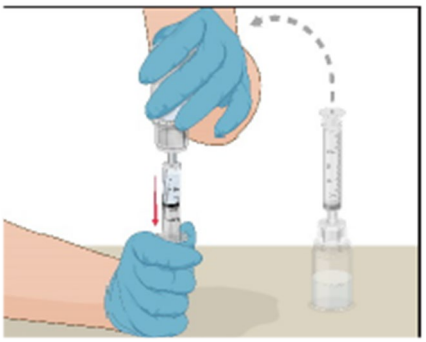
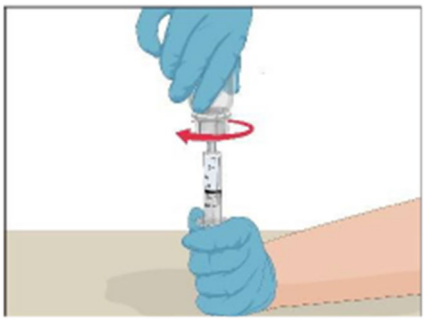
Reconstitution of the powder for solution for injection:(Prothromplex® TOTAL 500 IU SmPC)

- Only the enclosed reconstitution set is to be used for reconstitution.
- Prothromplex® TOTAL 500 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.
- Use aseptic non-touch 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).

	1. Remove protective caps from the powder vial and the solvent vial.

	2. 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. 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
	4. 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. 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. 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. 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. 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.
	9. 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. Hold the vial with one hand and use the other hand to push all the air from the syringe into the vial.
	11. 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. 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.

9. Administration

This medicinal product must not be mixed with other medicinal products except those mentioned in the reconstitution section. Only the enclosed reconstitution set should be used and for reconstitution.

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.**

Injection/infusion:

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.

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

1. Attach the infusion needle to a syringe containing Prothromplex® TOTAL solution. For comfort, 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).
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.

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

10. Monitoring

Monitoring of INR during treatment is mandatory[(Prothromplex® TOTAL 500 IU SmPC)]

Please monitor INR every [placeholder for Trust/hospital consideration]

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.[(Prothromplex® TOTAL 500 IU SmPC)]

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).[(Prothromplex® TOTAL 500 IU SmPC)]

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.[(Prothromplex® TOTAL 500 IU SmPC)]

11. Obtaining Prothromplex® TOTAL 500 IU

[Placeholder for local adaptation, e.g. information relating to ordering/location of supply, emergency/out of hours access, patient safety etc.]

12.References

Prothromplex® TOTAL 500 IU. SmPC. Available at https://www.medicines.org.uk/emc/product/15237/smpc. Access date: November 2023

Yee, J. *et al.* Emergency Reversal of Anticoagulation. *West J Emerg Med* 2019;**20**(5)**:**770-783

13.Prescribing Information

PROTHROMPLEX TOTAL (human prothrombin complex) 500 IU powder and solvent for solution for injection
PRESCRIBING INFORMATION FOR GREAT BRITAIN (ENGLAND, SCOTLAND, WALES)
Refer to the Summary of Product Characteristics (SmPC) before prescribing.
Presentation: The total protein content per vial is 250 – 625 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 333 IU protein C co-purified with the blood coagulation factors.
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 haemorrhages in congenital deficiency of vitamin K-dependent coagulation factors, when purified specific coagulation factor concentrate is not available. Prothromplex TOTAL is indicated in adults. There are insufficient paediatric data to recommend the administration of Prothromplex TOTAL in children.
Dosage and administration: Treatment should be initiated under the supervision of a physician experienced in the treatment of coagulation disorders. Posology: 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 (refer to SmPC). 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). 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 in paediatric patients have not been established in clinical trials. Method of administration: To be administered via the intravenous route slowly. It is recommended not to administer more than 2 ml per minute (60 IU/min). For instructions on reconstitution of the medicinal product before administration, please refer to the SmPC.
Contraindications:
Hypersensitivity to the active substance or to any of the excipients. Known allergy to heparin or history of heparin-induced thrombocytopenia.
Warnings and precautions: Traceability: In order to improve the traceability of biological medicinal products, the name, and the batch number of the administered product should be clearly recorded. 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 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. 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, 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. 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 (foetal infection) and for individuals with immunodeficiency or increased erythropoiesis (e.g., haemolytic anaemia). 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. When a medicinal product prepared from human blood or plasma is administered regularly/repeatedly, appropriate vaccinations (hepatitis A and B) must be considered. Sodium content: This medicinal product contains 68 mg sodium per vial or 0.14 mg sodium per International Unit equivalent to 3.4 % of the WHO recommended maximum daily intake of 2g 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. Paediatric population: There are insufficient data to recommend the administration of Prothromplex TOTAL in children.

Interactions: 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. **Fertility, pregnancy and lactation:** The effects of Prothromplex TOTAL 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 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 should be used during pregnancy and lactation only if clearly indicated. Refer to the SmPC for information on the risk of Parvovirus B19 infection in pregnant women.

Undesirable effects: *Common* (≥1/100 to <1/10): Disseminated intravascular coagulation inhibitors to one or more of the prothrombin complex factors (factors II, VII, IX, X), Anaphylactic shock, Anaphylactic reaction, Hypersensitivity, Cerebrovascular accident, Headache, Heart failure, Acute myocardial infarction, Tachycardia, Arterial thrombosis, Venous thrombosis, Hypotension, Flushing, Pulmonary embolism, Dyspnoea, Wheezing, Vomiting, Nausea, Urticaria, Rash erythematous, Pruritus,
Nephrotic syndrome and Pyrexia.

Refer to the SmPC for details on full side effect profile and interactions.

UK basic NHS price: £255.00 per vial.

Legal Classification: POM. **Marketing authorisation (MA) number:** PL 34078/0037.

Business responsible for sale and supply: Takeda UK Limited, 1 Kingdom Street, London, W2 6BD, United Kingdom.

PI approval code: pi-02715

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PROTHROMPLEX TOTAL (human prothrombin complex) 500 IU powder and solvent for solution for injection

PRESCRIBING INFORMATION FOR NORTHERN IRELAND

Refer to the Summary of Product Characteristics (SmPC) before prescribing.

Presentation: The total protein content per vial is 250 – 625 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 333 IU protein C co-purified with the blood coagulation factors.

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 haemorrhages in congenital deficiency of vitamin K-dependent coagulation factors, when purified specific coagulation factor concentrate is not available. Prothromplex TOTAL is indicated in adults. There are insufficient paediatric data to recommend the administration of Prothromplex TOTAL in children.

Dosage and administration: Treatment should be initiated under the supervision of a physician experienced in the treatment of coagulation disorders. Posology: 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 (refer to SmPC). 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). 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 in paediatric patients have not been established in clinical trials. Method of administration: To be administered via the intravenous route slowly. It is recommended not to administer more than 2 ml per minute (60 IU/min). For instructions on reconstitution of the medicinal product before administration, please refer to the SmPC.

Contraindications:

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

Warnings and precautions: Traceability: In order to improve the traceability of biological medicinal products, the name, and the batch number of the administered product should be clearly recorded. 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 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. 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, 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. 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 (foetal infection) and for individuals with immunodeficiency or increased erythropoiesis (e.g., haemolytic anaemia). 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. When a medicinal product prepared from human blood or plasma is administered regularly/repeatedly, appropriate vaccinations (hepatitis A and B) must be considered. Sodium content: This medicinal product contains 68 mg sodium per vial or 0.14 mg sodium per International Unit equivalent to 3.4 % of the WHO recommended maximum daily intake of 2g 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. Paediatric population: There are insufficient data to recommend the administration of Prothromplex TOTAL in children.
Interactions: 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. **Fertility, pregnancy and lactation:** The effects of Prothromplex TOTAL 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 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 should be used during pregnancy and lactation only if clearly indicated. Refer to the SmPC for information on the risk of Parvovirus B19 infection in pregnant women.
Undesirable effects: *Common* (≥1/100 to <1/10): Disseminated intravascular coagulation inhibitors to one or more of the prothrombin complex factors (factors II, VII, IX, X), Anaphylactic shock, Anaphylactic reaction, Hypersensitivity, Cerebrovascular accident, Headache, Heart failure, Acute myocardial infarction, Tachycardia, Arterial thrombosis, Venous thrombosis, Hypotension, Flushing, Pulmonary embolism, Dyspnoea, Wheezing, Vomiting, Nausea, Urticaria, Rash erythematous, Pruritus, Nephrotic syndrome and Pyrexia.
Refer to the SmPC for details on full side effect profile and interactions.
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