***Formulary Support Pack***

**Prothromplex® TOTAL 500 IU**

**powder and solvent for solution for injection
(human prothrombin complex)**

Therapeutic indications:(Prothromplex® TOTAL 500 IU SmPC)

* 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 500 IU is indicated in adults. There are insufficient paediatric data to recommend the administration of Prothromplex® TOTAL 500 IU in children

**Adverse events should be reported. Reporting forms and information can be found at:** [**www.mhra.gov.uk/yellowcard**](http://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.**

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**Prescribing information can be found at the end of this document**

 Job code: C-APROM/GB/PROT/0038

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# Purpose of this document

This document has been designed to assist healthcare professionals (HCP) or other authorised persons in producing their own formulary applications for Prothromplex® TOTAL 500 IU.

It is provided as a resource in a final and approved format. Once it has been accessed Takeda take no responsibility for (i) any changes to the document by any third party, or (ii) how the document or parts thereof are used by third parties.

This document is intended to support HCPs in the completion of formulary application forms for Prothromplex® TOTAL 500 IU for:(Prothromplex® TOTAL 500 IU SmPC)

* 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 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 is a rank 1\* awarded product for prothrombin complex concentrate in the NHS framework agreement 2022 for the supply of products for the treatment**

## of bleeding disorders(NHS England, July 2022)

The information provided is not intended as a substitute for local data regarding patients and services, but to provide additional, background information to support and supplement cases for local implementation.

NICE has produced Good Practice Guidance on ‘Developing and updating local formularies’ (last updated October 2015).(NICE, 2015) This includes how clinicians should apply to their local formulary decision making group, as well as what information their application should contain. This application support document is intended to contain the information to meet these NICE recommendations, in a way which can be adapted for local use.

It is worthwhile noting that the NICE guidance makes the following points:(NICE, 2015)

* *Publish all relevant local formulary information online, in a clear, simple and transparent way. Applications should be submitted by a health professional, although* ***manufacturers may support evidence gathering***
* *Provide information to the applicant to explain how the process will operate and ensure application forms are readily available. Consider inviting the applicant to a meeting to allow for constructive discussion*
* *Ensure the following information is included in application forms to consider a medicine or new indications:*
* *Details of the health professional making the application, including a declaration of interests*
* *Local patient population*
* *Details of the medicine, including strength, formulation, therapeutic drug class, indication, monitoring requirements and cost*
* *Evidence submission with relevant supporting literature, including efficacy, safety and
cost effectiveness*
* *Comparison with existing treatments*
* *Likely place in therapy*
* *Recommendation for the decommissioning of a current formulary medicine, if applicable*
* *Resource impact*

\*Based on the Most Economically Advantageous Tender (MEAT) according to the following criteria: Eligibility Pass/Fail; Price/Cost to Treat (75%); Security of Supply (15%) and Ease of Use (10%).

## Key to document layout and text

**The headings and the questions in bold grey are to help guide you to the most relevant information for your local application.**

The text in plain grey is prepared for you to use to help support your application and potentially requires checking/amending for local relevance. All data are referenced, and the reference list is found at the end of document. Full reference citations should accompany your application.

# Executive Summary

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| **Burden of disease**  | **Bleeding due to vitamin K antagonists** The incidence of major bleeding in patients receiving long-term anticoagulation with a vitamin K antagonist is 1–3% per year.(Linkins, 2013)**Perioperative prophylaxis of bleeding** In patients undergoing elective surgery, vitamin K antagonists such as warfarin should be stopped five days before surgery.(BNF, 2023)In patients requiring emergency surgery, if it can be delayed by 6-12 hours, intravenous phytomenadione can be given. Where surgery cannot be delayed, dried prothrombin complex is indicated.(BNF, 2023) However, delays to surgery have been associated with negative outcomes for patients, including higher complication rates,(Ong et al, 2015, Klestil et al, 2018), and increased mortality risk.(Klestil et al, 2018)**Congenital deficiency of vitamin K-dependent coagulation factors** Congenital deficiency of vitamin K-dependent coagulation factors is a rare disease affecting approximately 30 families worldwide.(Napolitano et al, 2010) |
| **Product**  | Prothromplex® TOTAL 500 IU powder and solvent for solution for injection(Prothromplex® TOTAL 500 IU SmPC) |
| **Licensed indication**  | * 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) |
| **Therapeutic drug class / Pharmacology**  | Antihaemorrhagics, coagulation factors IX, II, VII and X in combination.(Prothromplex® TOTAL 500 IU SmPC)The prothrombin complex consists of the coagulation factors II, VII, IX and X which are synthesised in the liver with the help of vitamin K. The administration of human prothrombin complex concentrates provides an increase in plasma levels of the vitamin K-dependent coagulation factors and can temporarily correct the coagulation defect of patients with deficiency of one or several of these factors.(Prothromplex® TOTAL 500 IU SmPC) |
| **Available formulation**  | Powder and solvent for solution for injection(Prothromplex® TOTAL 500 IU SmPC) |
| **Dosage and administration**  | Except for the therapy of bleeding and perioperative prophylaxis of bleeding during vitamin K antagonist treatment, only general dosage guidelines are given below.(Prothromplex® TOTAL 500 IU SmPC)Treatment should be initiated under the supervision of a physician experienced in the treatment of coagulation disorders.(Prothromplex® TOTAL 500 IU SmPC)**Dosage, frequency and duration**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.(Prothromplex® TOTAL 500 IU SmPC)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. 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, international normalised ratio (INR), prothrombin time (PT)) 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:**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 international unit (IU) factor IX/kg body weight raises the Quick's time value by about 1%.(Prothromplex® TOTAL 500 IU SmPC)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)The dosing below should be followed according to the recommendation made in the publication Makris et al 2001.(Makris et al, 2001)

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

International units (IU) refer to factor IXThe 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.(Prothromplex® TOTAL 500 IU SmPC)**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 IU of factor IX per kg body weight raises the plasma factor IX activity by about 0.015 IU/ml; and 1 IU of factor VII per kg body weight raises the plasma factor VII activity by about 0.024 IU /ml. One IU of factor II or X per kg body weight raises the plasma factor II or X activity by 0.021 IU/ml.(Prothromplex® TOTAL 500 IU SmPC)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).(Prothromplex® TOTAL 500 IU SmPC) One international unit of a coagulation factor activity is equivalent to the quantity in one ml of normal human plasma.(Prothromplex® TOTAL 500 IU SmPC)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 units/ml. The required dosage is determined using the following formula:(Prothromplex® TOTAL 500 IU SmPC)*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:**In order to correct the INR, it is not necessary to exceed the dose of 50 international units/kg. If the severity of bleeding requires a higher dose the risk /benefit has to be evaluated by the treating physician. (Prothromplex® TOTAL 500 IU SmPC)**Method of administration** **Intravenous use** Prothromplex® TOTAL 500 IU should be administered via the intravenous route slowly. It is recommended not to administer more than 2 ml per minute (60 IU/min).(Prothromplex® TOTAL 500 IU SmPC) |
| **Proposed** **place in therapy** | Prothromplex® TOTAL 500 IU is indicated in adults for:(Prothromplex® TOTAL 500 IU SmPC)* The 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
* The treatment and perioperative prophylaxis of haemorrhages in congenital deficiency of vitamin K-dependent coagulation factors, when purified specific coagulation factor concentrate is not available
 |
| **Impact on patient care**  | Prothromplex® TOTAL 500 IU is indicated in treatment of bleeding and perioperative prophylaxis of bleeding in acquired deficiency of prothrombin complex coagulation factors when rapid correction of the deficiency is required.(Prothromplex® TOTAL 500 IU SmPC)In an international, open-label, non-randomised clinical trial, all subjects (59/59) met the primary endpoint with an INR to ≤ 1.3 achieved within 30 minutes.(Altorjay et al, 2015)Prothromplex® TOTAL 500 IU was well tolerated and effective in reversal of oral anticoagulation in 48 subjects who were treated prophylactically with Prothromplex® TOTAL 500 IU before undergoing interventional procedures and in 13 subjects (11 of whom were included in the full analysis dataset) who received Prothromplex® TOTAL 500 IU to stop acute bleeding episodes.(Altorjay et al, 2015) With pre-treatment INRs ranging from 1.9 to 7.5, a single infusion of Prothromplex® TOTAL 500 IU rapidly normalised INR to ≤ 1.3 in all subjects. No subjects required a second dose of Prothromplex® TOTAL 500 IU (N=61). The rapid normalisation of INR was accompanied by ‘excellent’ overall haemostatic efficacy in 60/61 (98.4%) subjects, as assessed by the treating physicians.(Altorjay et al, 2015)All 12 subjects treated with Prothromplex® TOTAL 500 IU for acute bleeding episodes had satisfactory resolution of bleeding accompanied by an overall haemostatic efficacy rated as 'excellent', which is similar to what has been observed with other products.(Altorjay et al, 2015) |
| **Impact on patient safety**  | Please consult the Summary of Product Characteristics (SmPC) before prescribing Prothromplex® TOTAL 500 IU, particularly in relation to dosing and treatment monitoring Prothromplex® TOTAL 500 IU.(Prothromplex® TOTAL 500 IU SmPC)During the 15-day safety follow-up period of the Altorjay et al., 2015 trial, approximately 60% (N=61) of subjects treated with Prothromplex® TOTAL 500 IU did not experience any adverse events (AEs). Out of 66 AEs occurring in 24 subjects, the majority were mild, non-serious events; eight were serious adverse events (SAEs) and occurred in 3 subjects (2 fatal, neither of which was treatment-related) and two of these SAEs (acute myocardial infarction and deep vein thrombosis) were considered possibly related to treatment. The two subjects that experienced the two thrombotic SAEs both had several comorbidities and potential risk factors. The observed possibly related serious thrombotic adverse events (2/61, 3.3%) reported in this study are comparable to rates observed in other studies on prothrombin complex concentrate (PCC) products. (Altorjay et al, 2015) |
| **Cost / resource impact**  | List price: 1 vial (500 international units) = £255.00 There is a confidential agreement available offering a discount to the list price.Please contact your Regional Pharmacy Procurement unit for details.**Rank 1\* awarded product for prothrombin complex concentrate in the NHS framework agreement 2022 for the supply of products for the** **treatment of bleeding disorders(NHS England, July 2022)****\*Based on the Most Economically Advantageous Tender (MEAT)** **according to the following criteria: Eligibility Pass/Fail; Price/Cost to Treat (75%); Security of Supply (15%) and Ease of Use (10%).** |

# Burden of disease

**Bleeding due to vitamin K antagonists**

The incidence of major bleeding in patients receiving long-term anticoagulation with a vitamin K antagonist is 1–3% per year.(Linkins, 2013)

**Perioperative prophylaxis of bleeding**

In patients undergoing elective surgery, vitamin K antagonists such as warfarin should be stopped five days before surgery. In patients requiring emergency surgery, if it can be delayed by 6-12 hours, intravenous phytomenadione can be given. Where surgery cannot be delayed, prothrombin complex is indicated.(BNF, 2023)

Delays to surgery have been associated with negative outcomes for patients, including higher complication rates,(Ong et al, 2015, Klestil et al, 2018) and increased mortality risk.(Klestil et al, 2018)

**Congenital deficiency of vitamin K-dependent coagulation factors**

Congenital deficiency of vitamin K-dependent coagulation factors is a rare disease affecting approximately 30 families worldwide.(Napolitano et al, 2010)

# Product information

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| **Product**  | Prothromplex® TOTAL 500 IU powder and solvent for solution for injection.(Prothromplex® TOTAL 500 IU SmPC) |
| **Licensed indication**  | * 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) |
| **Therapeutic drug class / Pharmacology**  | Antihaemorrhagics, coagulation factors IX, II, VII and X in combination.(Prothromplex® TOTAL 500 IU SmPC)The prothrombin complex consists of the coagulation factors II, VII, IX and X which are synthesised in the liver with the help of vitamin K. The administration of human prothrombin complex concentrates provides an increase in plasma levels of the vitamin K-dependent coagulation factors and can temporarily correct the coagulation defect of patients with deficiency of one or several of these factors.(Prothromplex® TOTAL 500 IU SmPC) |
| **Available formulation**  | Powder and solvent for solution for injection.(Prothromplex® TOTAL 500 IU SmPC) |
| **Dosage and administration**  | Except for the therapy of bleeding and perioperative prophylaxis of bleeding during vitamin K antagonist treatment, only general dosage guidelines are givenbelow.(Prothromplex® TOTAL 500 IU SmPC)Treatment should be initiated under the supervision of a physician experienced in the treatment of coagulation disorders.(Prothromplex® TOTAL 500 IU SmPC)**Dosage, frequency and duration(Prothromplex® TOTAL 500 IU SmPC)**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 halflives 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:(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 international unit 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. The dosing below should be followed according to the recommendation made in the publication Makris et al 2001.(Makris et al, 2001)

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

International units (IU) refer to factor IXThe 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. |

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|  | **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 international units/ml; and 1 IU of factor VII per kg body weight raises the plasma factor VII activity by about 0.024 IU/ml. One IU of factor II or X per kg body weight raises the plasma factor II or X activity by 0.021 IU/ml.(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 IU/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 international units/kg. If the severity of bleeding requires a higher dose the risk/benefit has to be evaluated by the treating physician.**Method of administration** **Intravenous use(Prothromplex® TOTAL 500 IU SmPC)**Prothromplex® TOTAL 500 IU should be administered via the intravenous route slowly. It is recommended not to administer more than 2 ml per minute (60 IU/min). |

Contents of one pack:(Prothromplex® TOTAL 500 IU SmPC)

* 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

# Proposed place in therapy

Prothromplex® TOTAL 500 IU should be considered the preferred choice for:(Prothromplex® TOTAL 500 IU SmPC)

* 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 500 IU is indicated in adults.

# Clinical evidence

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| **Study design** Phase 4, international, multicentre, prospective, open-label, non-randomised study to collect new and additional efficacy and safety information on the use of Prothromplex® TOTAL 500 IU for oral vitamin K antagonist anticoagulant reversal in patients with acute bleeding or requiring urgent surgery.(Altorjay et al, 2015)Patients were ≥18 years old receiving oral anticoagulation with a stable dose of vitamin K antagonist, with an INR ≥2 at screening, who required reversal of oral anticoagulation for urgent surgery, a planned or urgent invasive procedure, or acute bleeding episode. The primary outcome measure was the proportion of subjects who achieved normalisation of INR to ≤1.3 within 30 ± 5 minutes after administration of Prothromplex® TOTAL 500 IU.(Altorjay et al, 2015)Prothromplex® TOTAL 500 IU was administered as a single intravenous infusion, with dosing based on INR measurements prior to initiating treatment, according to the dosage described by Makris et al.(Makris et al, 2001, Altorjay et al, 2015) Additional doses of Prothromplex® TOTAL 500 IU could be administered at any time at the discretion of the investigator.(Altorjay et al, 2015)Baseline INR determined the dosing, based on the following table:(Altorjay et al, 2015)

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

International units (IU) refer to Factor IX Blood samples were taken to determine INR, PT, additional coagulation markers and haematology before and after administration of Prothromplex® TOTAL 500 IU at 15 minutes, 30 minutes, 1 hour, 3 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours.(Altorjay et al, 2015) |
| **Primary outcome**All subjects (N=59/59) met the primary endpoint with an INR to ≤ 1.3 achieved within 30 minutes.(Altorjay et al, 2015) |
| **Other efficacy outcomes** Most subjects (N=57/59; 96.6%) reached an INR ≤ 1.3 within 15 minutes after infusion and the majority (47/59; 79.7%) maintained an INR at or below 1.3 for at least 6 hours. The median (range) INR value fell from 4.0 (1.9-7.5) at baseline to 1.0 (1.0-1.3) within 15 minutes.(Altorjay et al, 2015)**Rapid normalisation of coagulation activity**Confirmed by the PT analysis with a rise in median (range) PT from 15% of normal (2%-46%) at baseline, indicating prolonged PT due to anticoagulant therapy, to 83% of normal (60%-150%) at 15 minutes and 84% of normal (59%-150%) at 30 minutes after infusion with Prothromplex® TOTAL 500 IU.(Altorjay et al, 2015)***In-vivo* recovery of coagulation factors II, VII, IX and X at 30 minutes after administration of Prothromplex**® **TOTAL 500 IU**Thirty minutes after infusion with Prothromplex® TOTAL 500 IU, a marked increase from baseline activities of coagulation factors II, VII, IX and X was observed with median *in-vivo* recoveries of 2.03, 1.76, 1.12, and 1.85 IU/dL:IU/kg, respectively.(Altorjay et al, 2015) |
| **Tolerability**Of the 61 patients infused with Prothromplex® TOTAL 500 IU, 24 (39.3%) experienced a total of 66 adverse events during the 15-day safety follow-up period. A total of 3 adverse events were considered to be due to Prothromplex® TOTAL 500 IU, two of which were serious (acute myocardial infarction and deep vein thrombosis), and one which was considered non-serious where pyrexia occurred 2 hours after infusion. The two subjects that experienced the two thrombotic SAEs both had several comorbidities and potential risk factors. The observed possibly related serious thrombotic adverse events (2/61, 3.3%) reported in this study are comparable to rates observed in other studies on prothrombin complex concentrate (PCC) products. (Altorjay et al, 2015) |
| **Study conclusions*** Prothromplex® TOTAL 500 IU produces rapid normalisation of INR coupled with haemostatic efficacy, immediately reversing the effects of oral anticoagulant therapy and restoring levels of vitamin K dependent procoagulants(Altorjay et al, 2015)
* Excessive bleeding was effectively prevented in subjects undergoing interventional procedures and bleeding was decreased or stopped in subjects presenting with acute bleeding

episodes(Altorjay et al, 2015)* The well-established safety profile of Prothromplex® TOTAL 500 IU was confirmed, with no new

safety concerns raised(Altorjay et al, 2015) |

# Tolerability

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| **Contraindications(Prothromplex® TOTAL 500 IU SmPC)*** Hypersensitivity to the active substance or to any of the excipients
* Known allergy to heparin or history of heparin-induced thrombocytopenia

**Special warnings and precautions for use(Prothromplex® TOTAL 500 IU SmPC)*****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 500 IU should only be used when rapid correction of the prothrombin complex levels is necessary, such as major bleeding or emergency surgery. In other cases, reduction of the dose of vitamin K antagonist and/or administration of vitamin K is usually sufficient. Patients receiving a vitamin K antagonist may have an underlying hypercoagulable state and infusion of human prothrombin complex may exacerbate this. In congenital deficiency of any vitamin K-dependent factors, specific coagulation factor product should be used when available. Allergic-type hypersensitivity reactions including anaphylactic reactions and anaphylactic shock have been reported with Prothromplex® TOTAL 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***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 FVII deficiency, since the other vitamin K-dependent coagulation factors, with longer half-lives, may accumulate to levels considerably higher than normal. Patients given human prothrombin complex concentrates should be observed closely for signs and symptoms of intravascular coagulation or thrombosis. Because of the risk of thromboembolic complications, 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, or
* 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*** 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, hepatitis B and hepatitis C as well as against 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 (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*** This medicinal product contains the calculated value of 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*** 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.***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.***Undesirable effects:(Prothromplex® TOTAL 500 IU SmPC)*** ***Summary of the safety profile******Immune system disorders(Prothromplex® TOTAL 500 IU SmPC)***Replacement therapy with human prothrombin complex concentrates, including therapy with Prothromplex® TOTAL 500 IU, may result in the formation of circulating antibodies inhibiting one or more of the human prothrombin complex factors. If such inhibitors occur, the condition will manifest itself as a poor clinical response.Allergic or anaphylactic-type reactions have been commonly observed.***General disorders and administration site conditions(Prothromplex® TOTAL 500 IU SmPC)***Increase in body temperature has been commonly observed.***Vascular disorders(Prothromplex® TOTAL 500 IU SmPC)***There is a risk of thromboembolic episodes, following the administration of human prothrombin complex.***List of adverse reactions(Prothromplex® TOTAL 500 IU SmPC)***The acute myocardial infarction, venous thrombosis and pyrexia presented in the list of adverse reactions below have been reported in one clinical study with Prothromplex**®** TOTAL 500 IU in oral anticoagulant reversal in patients (N=61) with acquired prothrombin complex coagulation factors (II, VII, IX, X) deficiency. The other adverse reactions listed have been reported from post-marketing experience only.Very common (1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data) **Common:** 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, pyrexia\*\*.\* Development in patients with congenital deficient factors.\*\* Reported from one clinical study (n=61).(Altorjay et al, 2015, Prothromplex® TOTAL 500 IU SmPC) |

# 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

# Cost/resource impact

The list price for 1 vial of Prothromplex® TOTAL\* 500 IU is £255.00.

There is a confidential agreement available offering a discount to the list price.

Please contact your Regional Pharmacy Procurement Unit for details.

**Rank 1\* awarded product for prothrombin complex concentrate in the NHS framework agreement 2022 for the supply of products for the treatment of bleeding disorders.(NHS England, July 2022)**

**\*Based on the Most Economically Advantageous Tender (MEAT)** **according to the following criteria: Eligibility Pass/Fail; Price/Cost to Treat (75%); Security of Supply (15%) and Ease of Use (10%).**

# References

Altorjay, Á*. et al.* An international, multicenter, prospective study of a prothrombin complex concentrate, Prothromplex Total®, in anticoagulant reversal. *Thrombosis Research* 2015;**135**(3)**:**485-491

BNF. 2023. Oral anticoagulants. Available at <https://bnf.nice.org.uk/treatment-summaries/oral-anticoagulants/>. Access date: November 2023

Klestil, T*. et al.* Impact of timing of surgery in elderly hip fracture patients: a systematic review and meta-analysis. *Scientific Reports* 2018;**8**(1)**:**13933

Linkins, LA Bleeding risks associated with vitamin K antagonists. *Blood Rev* 2013;**27**(3)**:**111-118

Makris, M*. et al.* The management of coumarin-induced over-anticoagulation Annotation. *Br J Haematol* 2001;**114**(2)**:**271-280

Napolitano, M*. et al.* Hereditary combined deficiency of the vitamin K-dependent clotting factors. *Orphanet Journal of Rare Diseases* 2010;**5**(1)**:**21

NHS England. July 2022. NHS Framework Agreement for the supply of products for the treatment of bleeding disorders including Haemophilia B Offer reference number: CM/PHS/19/5576 – Award Debrief – Bleeding Disorders including Haemophilia B. Available at <https://www.contractsfinder.service.gov.uk/Notice/b9703bc2-cc0f-4908-9288-687a4338bf71>. Access date: November 2023

NICE. 2015. Developing and updating local formularies Medicines practice guideline [MPG1]. Available at <https://www.nice.org.uk/guidance/mpg1>. Access date: November 2023

Ong, M*. et al.* Impact of surgical delay on outcomes in elderly patients undergoing emergency surgery: A single center experience. *World J Gastrointest Surg* 2015;**7**(9)**:**208-213

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

# 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

**Date of preparation:** September 2023

Adverse events should be reported. Reporting forms and information can be found at [www.mhra.gov.uk/yellowcard](http://www.mhra.gov.uk/yellowcard). Adverse events should also be reported to Takeda UK Ltd at: AE.GBR-IRL@takeda.com

**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.**

**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-02716

**Date of preparation:** September 2023

Adverse events should be reported. Reporting forms and information can be found at [www.mhra.gov.uk/yellowcard](http://www.mhra.gov.uk/yellowcard). Adverse events should also be reported to Takeda UK Ltd at: AE.GBR-IRL@takeda.com