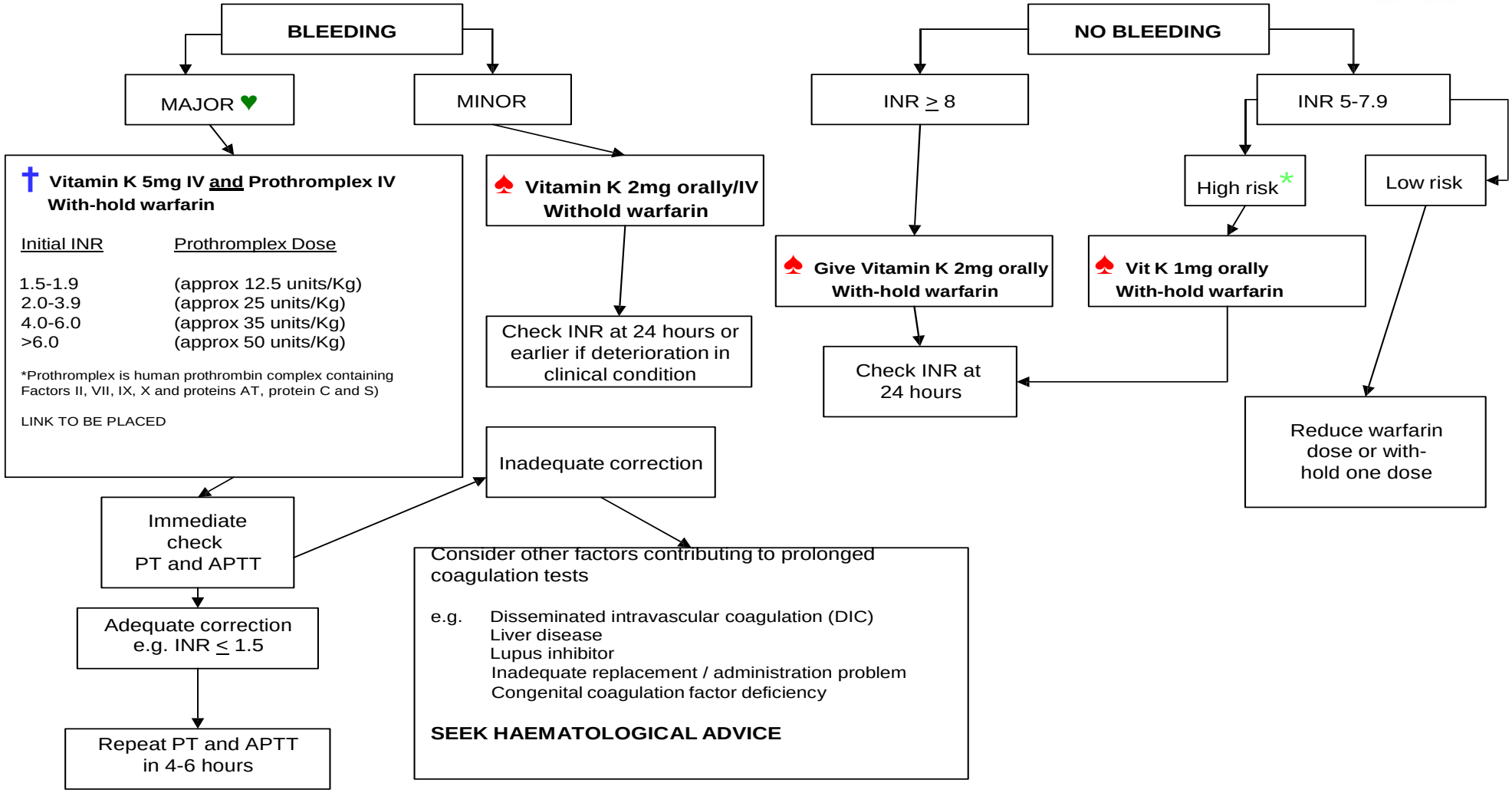
NHS LOTHIAN GUIDE TO REVERSAL OF ORAL ANTICOAGULATION ON WARFARIN
CLASSIFICATION OF BLEEDING COMPLICATIONS



Authors: J Oldham, J Anderson, K Yu
Version 1.0 Nov 2025
Date of approval by D/T Committee: Oct 2025 – comments to be confirmed
Date for revision: June 2030

Classification of Haemorrhage

Fatal
Death due to haemorrhage (Demonstrated at autopsy, radiologically or clinically obvious)

Major ♥
Intracranial (CT / MRI proven)

Retroperitoneal (CT / MRI proven)

Intra-ocular (excludes conjunctival)

Spontaneous muscle haematoma associated with compartment syndrome

Pericardial tamponade

Non-traumatic intra-articular

Any invasive procedure to stop bleeding

Active bleeding from any orifice plus BP≤90mmHg systolic, or oliguria or ≥20g/l fall in haemoglobin

Minor
Any other bleeding that would not influence your decision to anticoagulate a patient

INTERIM GUIDANCE PENDING APPROVAL
by NHSL D&T Committee ;

Reviewed Oct 2025; awaiting full comments
Next review Oct 2030

Cautions

- ◆ Prothromplex contains heparin and is contraindicated in patients with heparin induced thrombocytopenia (present or previous). Contact Haematology to discuss alternatives e.g. FFP.

Prothromplex is also relatively contraindicated in patients with:

1. An increased risk of thrombosis
2. Angina pectoris and after recent myocardial infarction

In all clinical situations assess the likely risks & benefits of administration.

In disseminated intravascular coagulation, prothrombin complex-preparations (e.g. Prothromplex) may only be administered after termination of the consumptive state.

† Intravenous vitamin K (phytomenadione) may rarely cause anaphylaxis. The Konakion MM 10mg/mL should be used for intravenous administration. Administration should be:

By slow IV bolus (see IV Manual for directions for administration)
http://intranet.lothian.scot.nhs.uk/NHSLothian/Healthcare/A-Z/MedicinesManagement/DrugsTherapeutics/Documents/Guidelines/NHS%20Lothian%20UK%20IV%20Guide.pdf
Withheld in patients with a history of previous severe allergic reaction to vitamin K

♠ Oral Vitamin K – preparation used is Konakion MM Paediatric, which comes in a concentration of 2mg/0.2mL. The oral syringes provided with each pack should be used to measure the required volume to be given orally. These syringes explicitly state 1mg and 2mg on the markings.

Standard risk patients do not require INR reversal at INR 5.0 – 7.9 but correction should be considered in “high risk” patients whose risk of bleeding is approximately 15 fold higher.

* ***Patients at high risk of warfarin associated bleeding***:

Elderly and frail (>65 years)
Previous GI bleed
Previous CVA (haemorrhagic or ischaemic)
Anaemia (Hb <10g/L)
Renal failure (CrCl <30ml/min)
Diabetes mellitus
Previous MI

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PROTHROMPLEX TOTAL (PROTHROMBIN COMPLEX CONCENTRATE) (ADULTS) ADVICE ON ADMINISTRATION

Takeda Prothromplex TOTAL 500 units PREPARATION, RECONSTITUION AND DOSING GUIDE PDF

What is Prothromplex TOTAL?

Prothromplex Total, a prothrombin complex concentrate (PCC), is licensed for use in acquired deficiencies of factors II, VII, IX and X that occur following treatment with vitamin K antagonists such as warfarin and acenocoumarol.

Prothromplex Total is a pooled plasma-derived product. The batch number of the Prothromplex MUST be recorded in order to maintain a link between the patient and the batch of the product. It is good practice to avoid mixing different batches in the same syringe, in case there is a reaction to an individual batch of product.

When is Prothromplex TOTAL indicated?

Prothromplex Total is indicated if rapid correction of the deficiency is required, such as in situations of major bleeding or when immediate emergency surgery is required.

Dosing and prescription

Prothromplex Total is prescribed on HEPMA, ICCA or a paper drug chart in "international units" (specifically for units of factor IX per kilogram body weight). Do NOT record as "IU" but write "units" to avoid prescription errors.

The dose should be calculated on an individual patient basis and will depend on the INR before treatment and the targeted INR, and the patient's weight in kilograms (kg):

Initial INR	Prothromplex TOTAL dose
1.5 – 1.9* (off label)	Approx 12.5 units / kg* (off label)
2.0 – 3.9	Approx 25 units / kg
4.0 – 6.0	Approx 35 units / kg
> 6.0	Approx 50 units / kg

It is recommended that the maximum single dose should not exceed 50 international units/Kg.

Once the appropriate dose for the patient has been calculated, this should be rounded to the nearest 500 international units (Prothromplex Total is only available in 500 international unit vial sizes). If a calculated dose falls at the midpoint between two rounded doses, the dose should be rounded up rather than down, for example:

Calculated dose: 2125 units = rounded dose 2000 units
Calculated dose: 2800 units = rounded dose 3000 units
Calculated dose: 1750 units = rounded dose 2000 units

The rounded dose is then ordered from the transfusion laboratory.

It is the rounded dose that is prescribed for the patient.

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Where and how to obtain Prothromplex TOTAL

Prothromplex TOTAL issue does not require the authorisation of a haematologist.

Royal Infirmary (telephone ext 27501/2):
Prothromplex TOTAL is obtained from the Blood Bank / transfusion laboratory upon telephone request.

Western General Hospital (telephone ext 31912):
Prothromplex TOTAL is obtained from the transfusion laboratory via provision of a completed transfusion request form (no sample required). It is recommended that the clinician brings the completed request form in person to the transfusion laboratory as the Prothromplex TOTAL can then be issued immediately. If the Prothromplex TOTAL is collected some time after the request, the collector is asked to bring patient identification details with them (full name, date of birth and CHI) – this does not have to be a blood collection slip.

St John's Hospital (telephone ext 53354):
Prothromplex TOTAL is obtained from the transfusion laboratory via provision of a completed transfusion request form (no sample required). It is recommended that the clinician brings the completed request form in person to the transfusion laboratory as the Prothromplex TOTAL can then be issued immediately. If the Prothromplex TOTAL is collected some time after the request, the collector is asked to bring patient identification details with them (full name, date of birth and CHI) – this does not have to be a blood collection slip.

A helpful hints guide will be issued from the transfusion laboratory with the product (see page 7).

Reconstitution

General instructions for the reconstitution of the product and its administration are provided by the manufacturer, Takeda, and should be followed carefully.

A step-by-step product reconstitution guide is given in the link at the top page 3, and also in the Appendix. A copy of the same will be issued from the laboratory with the product. Full manufacturer's instructions are enclosed along with the product. **Please follow the step-by-step reconstitution guidance to ensure swift and effective reconstitution and reduce risk of delay.**

The product must not be mixed with other medicinal products, diluents or solvents.

Administration

It is good practice to avoid mixing different batches in the same syringe, in case there is a reaction to an individual batch of product.

The reconstituted product should be administered immediately. **The reconstituted solution should be administered intravenously (slow intravenous injection) at a rate of not more than 2 mL/minute.**

The method of administration in elderly people (defined in the Summary of Product Characteristics as "over 65 years") is equivalent to general recommendations. There is no experience in children or neonates.

The effect of Prothromplex TOTAL and general requirement to administer concurrent vitamin K

The correction of the vitamin K antagonist-induced impairment of haemostasis is achieved within 30 minutes[1] after the injection and will persist for approximately 4-6 hours. Repeated treatment with human prothrombin complex is not usually required when vitamin K has been administered.

Therefore administer 5 mg IV vitamin K along with Prothromplex TOTAL and check the PT and APTT 30 minutes following administration, as per the NHS Lothian Guide to Reversal of Oral Anticoagulation on Warfarin (based on National Plasma Product Expert Advisory Group protocol)

If there is lack of correction further discussion is necessary with the on call haematologist.

Contraindications

There is a risk of thrombosis and caution should be taken if there is a history of previous thrombosis, angina pectoris, thrombotic stroke or recent myocardial infarction when the risks of administration of the product must be weighed against the correction of life-threatening bleeding.

Prothrombin complex concentrate should not be given in disseminated intravascular coagulation.

The product contains a trace of heparin and is contra-indicated if there is a known history of heparin-induced thrombocytopenia.

Infusion of prothrombin complex concentrate may worsen an underlying hypercoagulable state.

Special warnings

In patients receiving warfarin or vitamin K antagonists, Prothromplex TOTAL should only be used when rapid correction of the anticoagulant effect is required, such as emergency bleeding or emergency surgery. In other cases, reduction of the dose of vitamin K antagonist and / or administration of vitamin K is usually sufficient.

If allergic or anaphylactic-type reactions occur, the administration of Prothromplex TOTAL has to be stopped immediately.

There is a risk of thrombosis or disseminated intravascular coagulation (DIC) when patients are treated with human prothrombin complex concentrate, and particularly with repeated dosing. Patients given human prothrombin complex concentrate should be closely observed for signs or symptoms of DIC or thrombosis.

Close monitoring should be exercised when administering Prothromplex TOTAL to patients with liver disease, patients in the post-operative period and those at increased risk of thrombosis.

Prothromplex TOTAL 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.

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.

Further advice and resources

For more advice regarding the administration of Prothromplex TOTAL please contact the haematologist on call.

Local policies:

The NHS Lothian Guide to Reversal of Oral Anticoagulation on Warfarin is found on the intranet at Directory > Haematology > Thrombosis & Anticoagulation Policies > Warfarin Reversal (Prothromplex TOTAL)

Advice on the Administration of Prothromplex TOTAL is found on the intranet at the bottom of the homepage Application and Links > Select Homepage Link > Adult Intravenous medicines > Search "Prothomplex Total"

*Note: subject to FAF3 application approval.

REFERENCES:

[1] 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

Prothromplex TOTAL Administration – Helpful Tips

This plasma-derived blood product has been issued for your patient because they either have life / limb threatening bleeding or require emergency surgery.

Prothromplex must be administered to the patient as a priority.
Maximal reversal of anticoagulation will be achieved within around 30 minutes of administration.

1. The number of vials of Prothromplex TOTAL issued for your patient will have been calculated based on the patient's INR and body weight.

2. Please refer to the step-by-step guidance on how to reconstitute Prothromplex TOTAL which will accompany each issue of the product (instructions are also found within each vial box).

3. Once reconstituted, Prothromplex TOTAL should be withdrawn from the vials into an empty syringe using the Luer lock fitting supplied.

4. 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.

5. Prothromplex TOTAL should be administered by slow intravenous bolus (**not more than 2 mL / minute**)

   In many cases the volume required may result in more than one syringe load needing to be administered.

6. It is usually appropriate for intravenous vitamin K 5 – 10 mg to be prescribed at the same time as Prothromplex TOTAL to prevent a rebound rise in the INR once the effect of the Prothromplex TOTAL has worn off.

7. Repeat coagulation screen and INR should be checked at 30 minutes and 4-6 hours post Prothromplex TOTAL administration. In some cases additional doses of Prothromplex TOTAL or vitamin K may be required if the INR remains elevated. As this is unusual please consult the duty haematologist.

8. Contact the duty haematologist if further advice is required.

9. Local policies:

   The NHS Lothian Guide to Reversal of Oral Anticoagulation on Warfarin is found on the intranet at Directory > Haematology > Thrombosis & Anticoagulation Policies > Warfarin Reversal (Prothromplex TOTAL)

   Advice on the Administration of Prothromplex TOTAL is found on the intranet at the bottom of the homepage Application and Links > Select Homepage Link > Adult Intravenous medicines > Search "Prothomplex Total"

The authors acknowledge NHS Forth Valley Haematology Department whose original document these 'Helpful Tips' are based on.

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Appendix

Prothromplex TOTAL Reconstitution Guide

Preparation

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.

Remove the package from the Mix2Vial® device. Do not touch the clear plastic spike.

Getting started

- Remove the protective caps from both vials
- Disinfect the rubber stoppers and allow to dry
- Peel the lid from the Mix2Vial® device package
- Do not remove from packaging

Reconstitution

Turn the solvent vial over and place it on top of the vial containing Prothromplex® TOTAL powder.

Firmly insert the clear plastic spike into the centre of the Prothromplex® TOTAL vial stopper.

Check that all the solvent has transferred. Do not use if the vacuum has been lost and the solvent does not flow into the vial.

Reconstitution

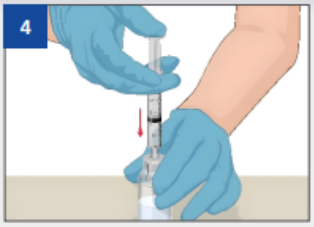
Gently swirl the connected vials until completely dissolved.

Do not shake. Do not refrigerate after reconstitution.

Reconstitution

Disconnect the two sides of the Mix2Vial® device by turning the blue plastic side counterclockwise and gently pulling the two sides apart. Do not touch the end of the plastic connector attached to the vial containing the dissolved product.

Reconstitution

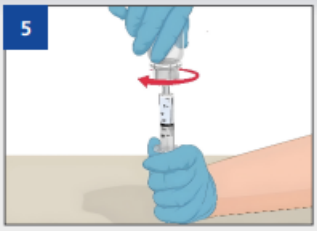


Pull back the plunger of a sterile disposable plastic syringe to the required volume. This should equal the amount of reconstituted Prothromplex® TOTAL withdrawn from the vial.

Connect the syringe to the clear plastic connector by turning the syringe clockwise.

Push down on the plunger to pressurize the vial.

Reconstitution



Flip so the vial is on top, keeping plunger pressed in, then draw the solution into the syringe by pulling plunger back slowly. Do not push and pull solution back and forth.

Disconnect the syringe by turning it counterclockwise.

Solution may be clear or slightly opalescent, do not use if cloudy or contains deposits.