Beriplex® (Human prothrombin complex) guideline for neonatal and paediatric patients

1.Purpose and scope

The purpose of this document is to provide guidance on the prescription and administration of Beriplex® (Human prothrombin complex) at the Royal Children's Hospital (RCH) in patients who are receiving anticoagulant therapy and are either actively bleeding, at risk of bleeding or require urgent surgical care.

2.Definitions

Term/Abbreviation	Explanation
Major bleeding	Bleeding in a critical site (intracranial, intraspinal, intra-ocular, pericardial, intra-articular, intramuscular with compartment syndrome, and retroperitoneal), bleeding associated with a decrease in haemoglobin >20g/L or requiring transfusions of ≥2 units of blood. [5]
Clinically relevant non-major bleeding (CRNM)	Bleeding that does not meet the criteria for major bleeding, but requires medical intervention, unscheduled contact with a physician, cessation of an anticoagulant (temporary), and discomforts such as pain or impairment of daily life activities.
CVAD	Central venous access device
DIC	Disseminated intravascular coagulation
DOAC	Direct-Acting Oral Anticoagulants
PCC	Prothrombin Complex Concentrate
VAD	Ventricular Assist Device
VKA	Vitamin K Antagonist
VKDB	Vitamin K deficiency bleeding
VTE	Venous thromboembolism

3.Guideline

3.1 Background

Beriplex® is prepared from human plasma and contains human coagulation factors II, VII, IX and X as well as Protein C and Protein S. (see appendix 1)

The CSL Beriplex® Product Information states:

The safety and efficacy of Beriplex® in the paediatric population has not been established in clinical studies.

Due to the need to provide some pragmatic guidance to paediatric clinicians, the following document has been created to provide local dosing guidance for warfarin and DOAC reversal and dosing for post cardiopulmonary bypass bleeding.

3.2 Beriplex®

Beriplex®	Details
CSL Indications	- Treatment of bleeding due to acquired deficiency of the prothrombin complex coagulation factors (II, VII, IX and X). - Reversal of vitamin K antagonists (e.g., warfarin) when rapid reversal required in perioperative setting or bleeding context. - Treatment of vitamin K antagonist overdose
RCH indications	- Emergency DOAC reversal - Cardiopulmonary bypass bleeding - Vitamin K deficiency bleeding of newborn - Patient/family refuse whole blood products. See **Blood refusal – management of procedure**.
Pharmacokinetics	- Peak plasma concentrations occur within five minutes of infusion - Elimination half-life of coagulation factors: factor II - 60 hours, factor VII - 4.2 hours, factor IX - 17 hours, and factor X - 31 hours
Contraindications	- Hypersensitivity to any components of the product. - History of Heparin Induced Thrombocytopenia (HIT). Beriplex® contains Heparin. - In DIC, Beriplex® should only be considered after resolution of the consumptive state.
Cautions	- Children with a history of thrombosis - Prothrombotic state at increased risk of thrombosis. - Patients with liver disease, patients in active DIC, the presence of a CVAD and neonates.
Consent	- Blood transfusion consent should be sought (where possible).
Presentation	- 500 IU vials with 20 mL water for injection
Ordering and approval	- Requires Haematologist approval - The Haematologist will contact the RCH Blood bank to confirm approvals. - Prescribe via the EMR
Dosing	- Based on weight up to but not exceeding 100kg. - >15 kg round to the nearest vial size - ≤15 kg, consider rounding to nearest 25 IU or 50 IU - Consider the clinical indication, current INR, target INR, need for re-anticoagulation and patient weight.
Availability	- Collect from RCH blood bank, must provide patient identification (e.g., blood bank release form)
Administration	- Reconstitute using provided diluent and according to the product instructions including **Mix2Vial™**

	- If multiple vials of Beriplex® are required they may be pooled into a single infusion. - Do not further dilute Beriplex®. - Slow IV push, do not exceed 3 IU/kg body weight/minute, maximum 210 IU/minute, approximately 8 mL/minute. - Do not mix with other medicinal products, administer via a separate IV line.
Stability	- Store below 25°C - Beriplex® does not contain antimicrobial preservative. - CSL recommends using immediately after reconstitution.
Monitoring	- INR check within 30 minutes post warfarin reversal

3.3 Beriplex® dosing for warfarin reversal

Beriplex® – warfarin reversal dosing guidance		
	Pre-treatment INR	**Beriplex® dose IU/kg**
Major bleeding that is critical organ or life threatening	Any INR ≥1.5 Or Recent dose of warfarin even if INR <1.5	50 IU/kg (Maximum 5000 IU)
Urgent peri-operative reversal **Or** **Major bleeding on warfarin**	INR 2.0 – 3.9	25 IU/kg (Maximum 2500 IU)
	INR 4.0 – 6.0	35 IU/kg (Maximum 3500 IU)
	INR ≥6.0	50 IU/kg (Maximum 5000 IU)

3.4 Vitamin K dosing for warfarin reversal

- Where Beriplex ® is administered in the context of Warfarin reversal and major bleeding, vitamin K should be considered.
- IV vitamin K has a shorter onset of action than oral vitamin K (1-3 hours vs. 4-6 hours), however has a greater chance of over-correcting the INR and leading to Warfarin resistance.
- Partial reversal is likely to be achieved with vitamin K dosing at doses ≤30mcg/kg (0.03mg/kg). If complete reversal is required doses 300mcg/kg (0.30mg/kg) should be considered, noting this may lead to Warfarin resistance for a period of up to two weeks.
- When administering vitamin K via the IV route, it should be delivered over at least 30 seconds. Rarely, anaphylaxis can occur.

Vitamin K dosing when warfarin reversal is required (non-VAD patients)		
	Type of warfarin reversal	**Vitamin K dose**
Major bleeding irrespective of INR	Complete	300 mcg/kg PO Or IV (max 10 mg)

INR >4.5-10 and bleeding risk is high OR INR >10 and no bleeding OR any INR >4.5 with minor bleeding	Complete	300 mcg/kg PO Or IV (max 10 mg)
	Partial	30mcg/kg PO or IV

3.4 Beriplex® dosing for warfarin reversal in VAD patients

- Any plan for anticoagulant reversal (either partial or complete) should be discussed prior with the RCH Cardiology (VAD) service.
- Bleeding risk needs careful balancing against thrombosis risk.
- The impact of single (or dual) anti-platelet therapy should be considered.

Beriplex® dosing for warfarin reversal guidance in VAD patients			
	Pre-treatment INR	**Approximate Beriplex® dose IU/kg**	**Vitamin K dose**
Major bleeding requiring complete reversal of warfarin	Any INR ≥1.5	50 IU/kg (Maximum 5000 IU)	Consider 300mcg/kg PO or IV (maximum dose 10mg)
CRNM bleeding requiring partial reversal	INR <7.5	10 IU/kg (Maximum 1000 IU)	Consider 15-30mcg/kg PO or IV (maximum dose 2mg)
	INR 7.5 - 10	15 IU/kg (Maximum 1500 IU)	
	INR >10	25 IU/kg (Maximum 2500 IU)	
Trivial or no bleeding	INR <7.5	NA	NA
	INR 7.5 - 10	10 IU/kg (Maximum 1000 IU)	NA
	INR >10	15 IU/kg (Maximum 1500 IU)	Consider 15-30mcg/kg PO or IV (maximum dose 2mg)

Dosing is based on body weight up to but not exceeding 100 kg.

3.5 Beriplex® dosing for DOAC reversal

Beriplex® dosing for DOAC reversal guidance

	INR	Approximate Beriplex® dose IU/kg
Major bleeding where specific reversal agent not available [6-9]	NA Check Anti-Xa drug level	50 IU/kg (Maximum 5000 IU)

3.6 Beriplex® dosing for post cardiopulmonary bypass bleeding

Beriplex® dosing guidance in Cardiac surgery patient	
	Approximate Beriplex® dose IU/kg
Bleeding post cardio-pulmonary bypass with prolonged R time (TEG) after cryoprecipitate and platelet administration.	15 IU/kg
	Additional doses (15 IU/kg) may be administered ~15 minutes if haemostasis not achieved. (Maximum 60 IU/kg)
	CAUTION: If haemostasis is not achieved use Novoseven with caution and avoid doses >90mcg/kg, due to thromboembolic risk. (Consider 45mcg/kg dose)

3.7 Beriplex® dosing for Vitamin K deficiency bleeding in infants

Beriplex® dosing for Vitamin K deficiency bleeding in infants		
	INR	**Approximate Beriplex® dose IU/kg**
VKDB in infants with major bleeding or refractory to standard treatment#	Any INR ≥1.5	50 IU/kg

In severe cases and for very-low-birth-weight infants, there may be insufficient utilisation of delivered vitamin K due to impaired (or immature) liver function.

3.8 Vitamin K dosing for Vitamin K deficiency bleeding in infants

VKDB in infants with major bleeding or refractory to standard treatment	Vitamin K Dose
	1mg

4.Key aligned documents

- RCH Warfarin guideline for clinicians (haematology intranet resources)
- THANZ Warfarin reversal guidelines (published in MJA – anticipated June 2024)

- RCH DOAC reversal clinical decision tool (haematology departmental use only)
- RCH VAD guidelines (cardiology intranet resources)
- Published guidelines for antithrombotic therapy in neonates and children[3-4]

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5.Appendices

Appendix 1

Comparative table of active ingredient composition – Prothrombinex-VF vs. Beriplex P/N

	Active ingredients content per vial comparison	
	Beriplex ® P/N 500	**Prothrombinex-VF**
Factor II	400-960 IU	~ 500 IU
Factor IX	400-620 IU	500 IU
Factor X	440-1200 IU	~ 500 IU
Factor VII	200-500 IU	
Protein C	300-900 IU	
Protein S	240-760 IU	

Appendix 2

Special patient cohorts: DOAC therapy or in accidental overdose

Rivaroxaban

Rivaroxaban is an oral direct factor Xa inhibitor with a plasma half-life of 7-9 hours.

It is metabolised 25% renally, and 75% hepatically.

There is currently no specific reversal agent available at RCH for this anticoagulant.

For minor bleeding, consider delaying or withholding the next dose (or discontinue use altogether where appropriate).

Other considerations include: fluid replacement to maintain adequate urine output, transfusion support where appropriate (including cryoprecipitate), IV Tranexamic acid, and local/surgical measures.

Of note, standard coagulation studies cannot be reliably measured in the presence of Rivaroxaban. Consideration should be given to measuring an anti-Xa drug level in consultation with Royal Melbourne Hospital (RMH).

For major bleeding or where urgent reversal is required, Beriplex 50u/kg (maximum 5000 units) can be given (see table 4) (off license use)

Apixaban

Apixaban is an oral direct factor Xa inhibitor, with a half-life of approximately 12 hours.

It is metabolised 25% renally, and 75% hepatically.

There is currently no specific reversal agent available at RCH for this anticoagulant.

For minor bleeding, consider delaying or withholding the next dose (or discontinue use altogether where appropriate).

Other considerations include: fluid replacement to maintain adequate urine output, transfusion support where appropriate (including cryoprecipitate), IV Tranexamic acid, and local/surgical measures.

Of note, standard coagulation studies cannot be reliably measured in the presence of Apixaban. Consideration should be given to measuring an anti-Xa drug level in consultation with Royal Melbourne Hospital (RMH).

For major bleeding or where urgent reversal is required, Beriplex 50u/kg (maximum 5000 units) can be given (see table 4) (off licence use)

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