NSW Health

Prothrombin complex concentrate transition to Beriplex®: clinical considerations

SAFETY NOTICE 017/24

Issue date:	1 July 2024
Content reviewed by:	NSW Blood Management Clinical Advisory Committee, NSW Medication Safety Team, CEC Medication Safety Expert Advisory Committee (MSEAC)
Distributed to:	Chief Executives; Directors of Clinical Governance; Director, Regulation and Compliance Unit
KEY MESSAGE:	NSW Health clinicians need to be aware that all three products involved in the staged transition from Prothrombinex to BeriPLEX are not interchangeable and take appropriate action as outlined in this Safety Notice.
ACTION REQUIRED BY:	Clinicians and pathology providers
REQUIRED ACTION:	1. Distribute this Safety Notice to all relevant staff, committees and departments where prothrombin complex concentrate is held, prescribed, and administered, and include this Safety Notice in relevant handovers and safety huddles. 2. Undertake a local risk assessment and incorporate the below recommendations to manage this transition. 3. Ensure a system is in place to document actions taken in response to this Safety Notice. 4. Escalate any concerns to: CEC-BloodWatch@health.nsw.gov.au. 5. Report any incidents associated with prothrombin complex concentrate via the local incident management system (e.g., ims+), to the supplier and TGA. 6. Confirm receipt and distribution of this Safety Notice within 72 hours to: CEC-BloodWatch@health.nsw.gov.au.
DEADLINE:	4 July 2024
We recommend you also inform:	Directors, Managers and Staff of: • Blood Management Committees • Surgical, Anaesthetics, and Emergency Departments • Pharmacy Services • Nursing/Midwifery Services • Medical Services • Drug and Therapeutics Committees
Website:	https://www.health.nsw.gov.au/sabs/Pages/default.aspx http://internal.health.nsw.gov.au/quality/sabs/index.html
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Situation

Australia will soon transition from the currently available brand of prothrombin complex concentrate (PCC) *Prothrombinex®VF* to *BeriPLEX®AU*. The staged transition will begin with the interim use of *BeriPLEX® P/N*, an imported product from July 2024. This will be followed by a final transition planned for 2025 to *BeriPLEX®AU*, an Australian manufactured PCC.

It is important to note that these PCC products; *Prothrombinex VF, BeriPLEX P/N* and *BeriPLEX AU* are **NOT** interchangeable. *Prothrombinex VF* contains three human coagulation factors: II, IX and X. Both BeriPLEX products contain four human coagulation factors: II, VII, IX and X.

There is a similarly named product BeriNERT, with look-alike packaging and a sound-alike name.

Background

PCCs are indicated for patients requiring urgent reversal of anticoagulation. The Patient Blood Management (PBM) guidelines and current NSW guidance references the Thrombosis and Haemostasis Society of Australia and New Zealand (THANZ) guidelines, *for warfarin reversal.* Revised THANZ reversal of anticoagulation guidelines which will include guidance on the use of *BeriPLEX* products, are pending publication. It is expected that the revision will provide important information about management based on INR thresholds, vitamin K_1 co-administration, and specific clinical indications.

Assessment

The transition to *BeriPLEX* offers additional clinical benefits but also requires careful consideration of potential risks and need for practice changes, including:

- Risk of prescription and administration errors due to availability of multiple products during the transition period. These can only be distinguished by the trade names.
- The staged transition timings pose product inventory risks.
- The presence of heparin in all PCC products may also pose risks, particularly for patients with history of Heparin Induced Thrombocytopenia (HIT). The use of PCC products in these patients is **contraindicated**, and specialist haematology advice should be sought for alternative management options.
- There are many differences between the two products – see table 1 for a summary of differences. The simultaneous administration of vitamin K1 (phytomenadione) should be considered in patients receiving both BeriPLEX PCC products for urgent reversal of vitamin K antagonists as vitamin K usually takes effect within 4–6 hours.
- The INR initial dosing thresholds for BeriPLEX are different to Prothrombinex – see table 2.

Additionally, concerns have also been raised that there is a potential for errors involving BeriPLEX and BeriNERT (C1 esterase inhibitor 500 units) due to the similar presentation and naming (or “look-alike sound-alike [LASA]” nature) of these products. Clinicians involved in the prescribing, dispensing and administration of BeriPLEX should be made aware of this potential risk for selection error, and local risk mitigation strategies should be employed.

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Table 1 - Summary of differences

Differences	Prothrombinex VF	BeriPLEX P/N	BeriPLEX AU
Dosing	Initial dosing differences between PROTHROMBINEX®-VF and BERIPLEX® include the dosing algorithm INR ranges, target INR and related dose, maximum single dose by INR range and inclusion of approximate dosing in mL/kg body weight. Note, for BeriPLEX the weight used for calculating doses should not exceed 100 kg. Please see table 2.		
Rate of administration	Approximately 3 mL per minute or as tolerated by patient	**Not exceeding 3 IU/kg body weight/minute, max. 210 IU/minute, approximately 8 mL per minute**	
Storage	Store 2–8°C (do not freeze) Can be stored below 25°C for a single period of 6 months	**Store below 25°C (do not freeze)**	
Packaging	 Note: the reconstitution method of all three brands using the Mix2Vial™ system remains the same.		

Table 2 - BeriPLEX initial dosing – see further information for detailed advice on dosing

Initial INR	Approximate dose mL/kg body weight	Approximate dose IU (factor IX) / kg body weight (not exceeding 100 kg)
2.0–3.9	1	25
4.0-6.0	1.4	35
>6.0	2	50

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Recommendations

- Assess the status and availability of PCCs in each facility, ensuring all locations of stock are identified:
    - Using this information, local laboratories should coordinate the transitions between brands and set an appropriate day and time to transition from one brand to another.
    - Ensure stock available outside of laboratories is considered during transitions.
    - Ensure clinicians in clinical areas where PCCs are utilised are informed of the transition plan.
- Prescriptions for PCCs are to include the **full trade name**. Changes may need to be made to electronic Medication Management (eMM) system configurations to accommodate this.
- Patients should **never** receive a combination of the three PCC products to achieve their dose.
- Ensure clinicians are aware of the presence of heparin in both Prothrombinex VF and the BeriPLEX branded products and consider contraindications including history of Heparin Induced Thrombocytopenia (HIT).
- Paediatric Haematology advice should be sought for urgent reversal of anticoagulation in children.
- Product inventory and transition timings must be managed by local NSW Health Pathology laboratories (or contracted pathology provider).
- Inform clinicians involved in the prescribing, dispensing and administration of BeriPLEX and BeriNERT of the potential risk for selection error because of their look-alike, sound-alike presentation. Local risk mitigation strategies should be employed to minimise the risk of selection errors, in conjunction with the requirements of the NSW Health Medication Handling *Policy Directive* (PD2022_032), and the NSW Health *High Risk Medicines Management* Policy Directive (PD2024_006) and related standards. These strategies may include but are not limited to:
    - Ensure clinicians adhere to the 5 Rights (right patient, right drug, right dose, right time, and right route) and independent second person checks
    - Ensuring each medicine is prepared and labelled separately in accordance with the Australian Commission on Safety and Quality in Health Care's *National Standard for User-applied Labelling of Injectable Medicines Fluids and Lines*. The label on the ampoule/vial should be checked and matched to that on the syringe/bag.
    - The use of Mixed-Case lettering in the eMM.

References

1. CSL Behring, Beriplex® P/N Human prothrombin complex Australia Product Information, 2024. https://www.cslbehring.com.au/products/products-list
2. Thrombosis and Haematology Society of Australia and New Zealand, An Update of Consensus Guidelines for Warfarin Reversal. Medical Journal of Australia, 2013. 198(4).

Further Information

CSL Behring Product Transition Information Booklet – BERIPLEX
CSL Behring Product Characteristics Card – BERIPLEX
CSL Behring Frequently Asked Questions – BERIPLEX

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