NSW Health

# UPDATED: Prothrombin complex concentrate transition to Beriplex®: clinical considerations

## SAFETY NOTICE SN:033/24

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| Issue date: | 11 December 2024 |
| Replaces: | SN:017/24 |
| Content reviewed by: | NSW Blood Management Clinical Advisory Committee, NSW Medication Safety Team |
| Distributed to: | Chief Executives; Directors of Clinical Governance; Director, Regulation and Compliance Unit |
| KEY MESSAGE: | NSW Health clinicians need to be aware of the update to the transition to BeriPLEX, note the altered requirements for co-administration of fresh frozen plasma and, take appropriate action as outlined in this Safety Notice. |
| ACTION REQUIRED BY: | Clinicians and pathology providers |
| REQUIRED ACTION: | 1. Distribute this updated 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.<br>2. Undertake a local risk assessment and incorporate the below recommendations to manage this transition.<br>3. Ensure a system is in place to document actions taken in response to this Safety Notice.<br>4. Escalate any concerns to: CEC-BloodWatch@health.nsw.gov.au.<br>5. Report any incidents associated with prothrombin complex concentrate via the local incident management system (e.g., ims+), to the supplier and TGA.<br>6. Confirm receipt and distribution of this Safety Notice within **7 days** to: CEC-BloodWatch@health.nsw.gov.au. |
| DEADLINE: | |
| We recommend you also inform: | Directors, Managers and Staff of:<br>• Blood Management Committees<br>• Surgical, Anaesthetics, and Emergency Departments<br>• Pharmacy Services<br>• Nursing/Midwifery Services<br>• Medical Services<br>• Drug and Therapeutics Committees |
| Website: | https://www.health.nsw.gov.au/sabs/Pages/default.aspx<br>http://internal.health.nsw.gov.au/quality/sabs/index.html |
| Review date: | July 2025 |

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02 9269 5500
CEC-BloodWatch@health.nsw.gov.au

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**SN:033/24**

## What is updated in this Safety Notice from SN017/24

This Safety Notice replaces *SN017/24 Prothrombin complex concentrate transition to BeriPLEX®: clinical considerations*, which has now been rescinded. The Safety Notice has been updated to:

- note the status of the stock transition;
- acknowledge the revised Thrombosis and Haemostasis Society of Australia and New Zealand (THANZ) recommendations for warfarin reversal; and
- include an amendment to the recommendation about stock of *Prothrombinex®VF held* outside of laboratories.

## Situation

Australia continues the transition from the previously available brand of prothrombin complex concentrate (PCC) *Prothrombinex®VF* to *BeriPLEX®AU*. The staged transition began with the interim use of *BeriPLEX® P/N*, an imported product in July 2024. The final transition to *BeriPLEX®AU*, an Australian manufactured PCC is expected to begin from March 2025.

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 Thrombosis and Haemostasis Society of Australia and New Zealand (THANZ) have published revised guidance and updated recommendations for warfarin reversal in the setting of four-factor prothrombin complex concentrate.

NSW Guidelines on Periprocedural Management of Anticoagulant and Antiplatelet Agents are being updated to reflect this revised guidance.

## 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 management risks.
- There are many differences between the two products – see Table 1 for a summary of differences. Importantly the co-administration of fresh frozen plasma with four factor PCC products is NOT required for urgent warfarin reversal.
- The simultaneous administration of vitamin K1 (phytomenadione) continues to be recommended in patients receiving PCC products for urgent reversal of vitamin K antagonists as vitamin K usually takes effect within 4–6 hours.
- To reverse warfarin anticoagulation in a non-bleeding patient – see Table 2.
- 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.

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 key differences for management of patients on warfarin therapy with bleeding*[2]

| Differences | Prothrombinex VF | BeriPLEX P/N | BeriPLEX AU |
|---|---|---|---|
| **Dosing and Co-administration of FFP** | Co-administration of FFP in addition<br>and<br>INR ≥2 with clinically significant bleeding: 35-50 units/kg | No FFP requirement<br><br>INR ≥2 with clinically significant bleeding: 25-50 units/kg***** <br><br>Note, for BeriPLEX the weight used for calculating doses should not exceed 100 kg.<br><br>***** *See THANZ guidelines for full recommendations* | |
| **Rate of administration** | Approximately 3 mL per minute or as tolerated by patient | **Not exceeding 3 units/kg body weight/minute, max. 210 units/minute, approximately 8 mL per minute** | |
| **Storage** | Store 2–8°C (do not freeze)<br>Can be stored below 25°C for a single period of 6 months | **Store below 25°C (do not freeze)** | |
| **Packaging** |  <br>Note: the reconstitution method of all three brands using the Mix2Vial™ system remains the same. | | |

*Table 2 – Suggested dosing to reverse warfarin anticoagulation in a non-bleeding patient (e.g. before surgery)*[2]*

| | Initial INR | | | |
|---|---|---|---|---|
| Target INR | **1.5-2.5** | **2.6-3.5** | **3.6-10** | **>10** |
| **0.9-1.3** | 30units/kg | 35units/kg | 50units/kg | 50units/kg |
| **1.4-2.0** | 15units/kg | 25units/kg | 30units/kg | 40units/kg |
| *Outside of surgery, BeriPLEX should only be considered if INR >10 and there is a high risk of bleeding | | | | |

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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. Particularly, stock of *Prothrombinex®VF* must be identified, removed and returned to the laboratory.
  - Ensure clinicians in clinical areas where PCCs are utilised are informed of the transition plan.
- Product inventory and transition timings must be managed by local NSW Health Pathology laboratories (or contracted pathology provider).
- Local procedures should be updated to align with the revised guidance about the co-administration of fresh frozen plasma with four factor PCC products for urgent warfarin reversal.
- 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.
- Different PCC products **MUST NOT** be combined together in a single 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.
- 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, Updated recommendations for warfarin reversal in the setting of four-factor prothrombin complex concentrate. Medical Journal of Australia, 2024.

## Further Information

Australian Red Cross Lifeblood Factor concentrates

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