15 January 2018

BIOSTATE® (human coagulation Factor VIII/VWF complex) Advisory Statement

This Advisory Statement has been prepared jointly by CSL Behring, the Australian Haemophilia Centre Director's Organisation (AHCDO) and the Australian Red Cross Blood Service to provide information for healthcare professionals and treatment centres when prescribing or ordering BIOSTATE during the transition to BIOSTATE inventory with new labelling reflecting a 1 : 2.4 ratio of factor VIII (FVIII) to von Willebrand Factor (VWF).

CSL Behring routinely monitors FVIII and VWF levels in plasma supplied to CSL Behring for manufacturing, and over recent years there has been a gradual decline in FVIII levels with minimal change in VWF levels in the plasma from which Australia's BIOSTATE is manufactured. As a result, the ratio of FVIII to VWF in BIOSTATE, historically approximately 1 : 2.0, has gradually risen to approximately 1 : 2.4. In order to improve the alignment of BIOSTATE labelling with the current product content, CSL Behring has obtained TGA approval to update the product labelling (vial Label, Carton, Product Information) to reflect a 1 : 2.4 ratio of FVIII : VWF.

BIOSTATE inventory with the updated labelling is planned to commence release into the Australian market from late January 2018. The first product with the updated labelling to be released into the Australian market will be BIOSTATE 1,000 IU FVIII. The 500 IU and 250 IU FVIII product presentations with the updated label will be released once remaining inventory of existing product label falls. Consequently, there will be a transition period during which product received may have existing labelling or updated labelling depending on remaining inventory and the presentation ordered.

Note that <u>all</u> BIOSTATE product delivered via the *CSL Behring Delivers* home delivery program will be product with updated labelling, irrespective of strength.

The image below highlights the changes to the BIOSTATE vial Label and Carton.

Updated BIOSTATE Label and Carton

Updated VWF content on each carton and label

Please note that the manufacturing process for BIOSTATE is unchanged, as are the FVIII levels in each BIOSTATE presentation.

Recommendation
Given previous reports of incorrect BIOSTATE dosing resulting from BIOSTATE prescriptions being issued in international units (IU) without specifying an active ingredient (FVIII or VWF), it is recommended that all centres that stock or administer BIOSTATE should check to ensure that:

- Clinical Practice Guidelines used by haematologists and in haemophilia treatment centres, and
- Dispensing protocols for BIOSTATE used in Blood Banks and/or Pharmacies

clearly state the following information:

- BIOSTATE contains both FVIII and VWF in a 1 : 2.4 ratio, and is approved for use in both haemophilia A and von Willebrand disease

- Each order for BIOSTATE should specify the 'active entity' of the ordered dose:
  Examples: 'BIOSTATE – 1000 IU of FVIII'
  'BIOSTATE – 2400 IU of VWF'

- Any order for BIOSTATE that does not specify the 'active entity' of the ordered dose should be clarified before the order is processed.

Prescribing notes in respect of BIOSTATE with the updated label

- When haematologists prescribe in FVIII units, the updated label should have no impact on the number of vials dispensed.

- When haematologists prescribe in VWF units, should they wish the dose to be the same number of vials, an adjustment in the number of VWF units prescribed will be required. For example: a person currently being prescribed 2000 IU VWF will require 2400 IU VWF to be prescribed in order to avoid an effective change from their current BIOSTATE dose.

Given there will be a transition period of mixed products with existing labelling and updated labelling, care should be taken when prescribing, dispensing and infusing BIOSTATE, in particular if prescribing in VWF units.

Please do not hesitate to contact any of the following people regarding this statement:

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BIOSTATE Presentations with updated labelling (staggered release to commence from late January 2018 – first to be released will be the BIOSTATE 1,000 IU FVIII presentation)

BIOSTATE Presentation	Final Concentration[1] FVIII	VWF	Colour Wedge on Carton & Vial	WFI Volume	Item number
BIOSTATE 250 IU FVIII / 600 IU VWF	50 IU/mL	120 IU/mL		5mL	33000185
BIOSTATE 500 IU FVIII / 1,200 IU VWF	50 IU/mL	120 IU/mL		10mL	33000192
BIOSTATE 1,000 IU FVIII / 2,400 IU VWF	100 IU/mL	240 IU/mL		10mL	33100194

[1] nominal