INTERCEPT® Blood System for Cryoprecipitation Package Insert

For the manufacturing of Pathogen Reduced Cryoprecipitated Fibrinogen Complex

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Rx Only

Caution: Federal law restricts this device to sale by or on the order of a licensed healthcare practitioner.

May 2, 2024

INTENDED USE

The INTERCEPT Blood System for Cryoprecipitation is intended to provide a functionally closed system for the production of Pathogen Reduced Cryoprecipitated Fibrinogen Complex.

Pathogen Reduced Cryoprecipitated Fibrinogen Complex is indicated for:

- Treatment and control of bleeding, including massive hemorrhage, associated with fibrinogen deficiency.
- Control of bleeding when recombinant and/or specific virally inactivated preparations of factor XIII or von Willebrand factor (vWF) are not available.
- Second-line therapy for von Willebrand disease (vWD).
- Control of uremic bleeding after other treatment modalities have failed.

Limitations of Use

Pathogen Reduced Cryoprecipitated Fibrinogen Complex should not be used for replacement of factor VIII.

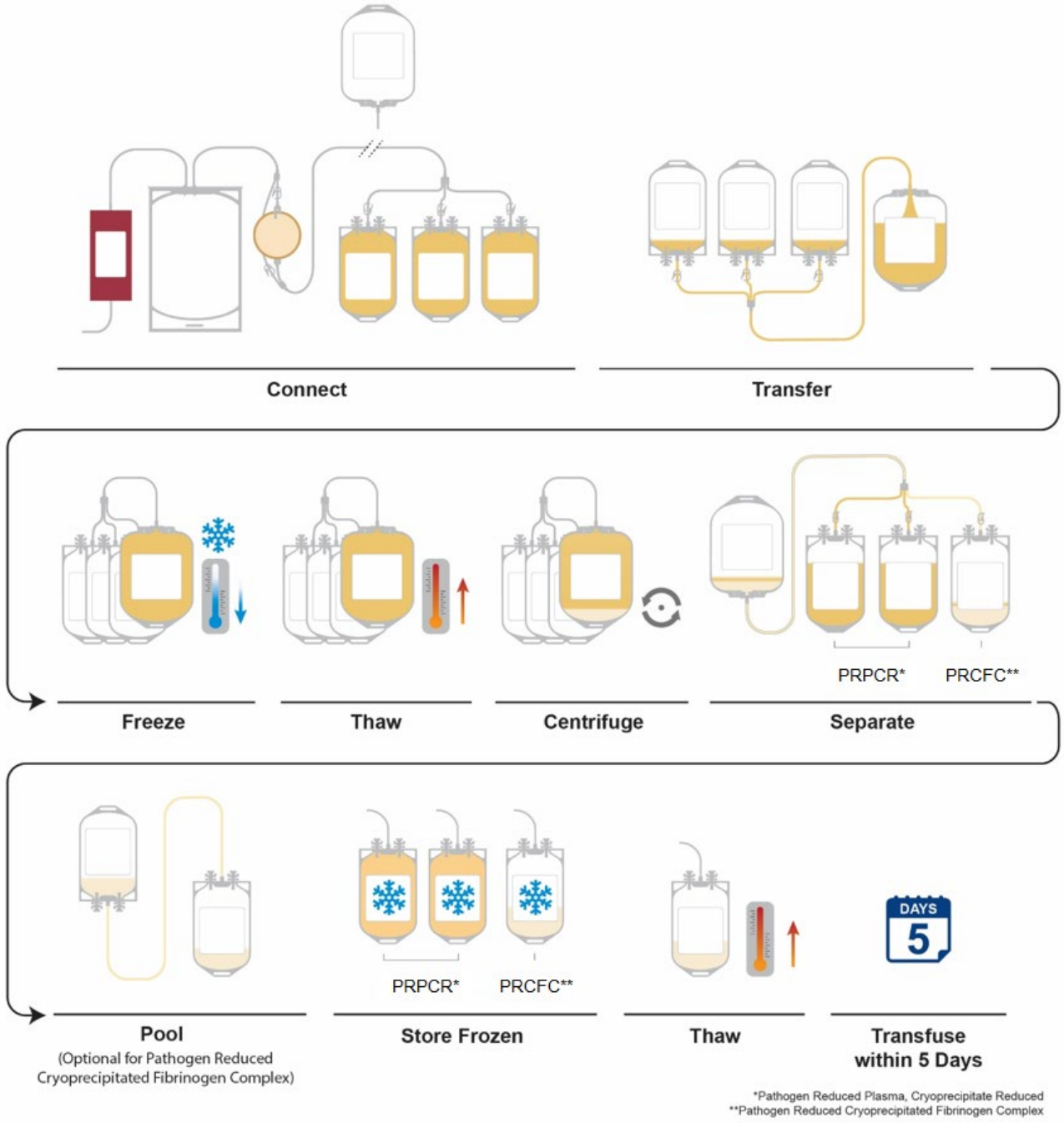
DEVICE DESCRIPTION

The INTERCEPT Blood System for Cryoprecipitation contains a sterile, non-pyrogenic, single-use, fluid path processing container – the FIBRICEPT™ Processing Container – (INT3230) for use in production of Pathogen Reduced Cryoprecipitated Fibrinogen Complex.

The operating principle for the INTERCEPT Blood System for Cryoprecipitation is illustrated in **Figure 1**. INTERCEPT Blood System processed plasma is transferred to the INT3230 processing container and frozen at -18°C or colder within 24 hours of blood draw for pooled whole blood-derived plasma, or within 8 hours of apheresis collection. The INT3230 processing container remains frozen for up to 30 days, at which time the INTERCEPT processed plasma is thawed and centrifuged. After centrifugation, the supernatant is transferred to two of the three final storage containers and the cryoprecipitate pellet is reconstituted into remaining supernatant and transferred to the third final storage container. All three blood components may be frozen and stored at -18°C or colder until thaw prior to transfusion. Components of the INTERCEPT Blood System for Cryoprecipitation may be pooled into a single final storage container using sterile docking up to a maximum of 325 mL prior to freezing.

Pathogen inactivation of plasma using the INTERCEPT Blood System, and processing in a functionally closed system, enables up to 5 days of post-thaw storage of Pathogen Reduced Cryoprecipitated Fibrinogen Complex at room temperature.

Figure 1 Illustration of the INTERCEPT Blood System for Cryoprecipitation



DEVICE PERFORMANCE

Pathogen Reduced Cryoprecipitated Fibrinogen Complex is prepared using the INTERCEPT Blood System for Cryoprecipitation from plasma that has been processed with the INTERCEPT Blood System for Plasma.[1] The INTERCEPT Blood System inactivates a broad spectrum of viruses, gram-positive and gram-negative bacteria, spirochetes, parasites and leukocytes (see **Table 1**).[1-8] There is no pathogen inactivation process that has been shown to eliminate all pathogens. Certain non-enveloped viruses (e.g., hepatitis A virus (HAV), hepatitis E virus (HEV), parvovirus B19 and poliovirus) and *Bacillus cereus* spores have demonstrated resistance to the INTERCEPT process.

Table 1 Pathogen Inactivation Efficacy of INTERCEPT Processed Plasma Used to Prepare Pathogen Reduced Cryoprecipitated Fibrinogen Complex

Pathogen	Log Reduction
Virus (Enveloped)[1-4]	
HIV-1 IIIB, cell-associated	≥6.2
HIV-1 IIIB cell-free	≥6.1
DHBV[a]	4.4 to 4.5
BVDV[b]	>4.3
HTLV-I	≥4.1
HTLV-II	≥4.7
West Nile virus	>5.5
SARS-Associated Coronavirus	≥4.0
Chikungunya virus (CHIKV)	6.5
Influenza A virus (H_5N_1 Avian Influenza)	≥5.7
Virus (Non-Enveloped)[1,4]	
Parvovirus B19	1.8
Bluetongue virus	4.2
Adenovirus 5	≥5.6
Bacteria[1,5]	
Klebsiella pneumoniae	>6.0
Enterobacter cloacae	≥6.7
Pseudomonas aeruginosa	>6.8
Yersinia enterocolitica	≥6.6
Staphylococcus epidermidis	>6.8
Staphylococcus aureus	>6.2
Treponema pallidum	≥5.4
Borrelia burgdorferi	≥9.9
Anaplasma phagocytophilum (HGE agent)	≥3.6
Protozoan Parasite[6,7]	
Plasmodium falciparum	>6.5
Babesia microti	≥4.9
Trypanosoma cruzi	>6.7

[a] DHBV model virus for HBV

[b] BVDV model virus for HCV

Using a limiting dilution assay (LDA), plasma processed with the INTERCEPT Blood System exhibited a 4 $\log_{10}$ reduction of viable T cells.[9] Using a DNA modification assay, plasma processed with the INTERCEPT Blood System demonstrated an average of one amotosalen adduct every 83 base pairs in leukocytes.[10]

Pathogen Reduced Cryoprecipitated Fibrinogen Complex serves as an enriched source of fibrinogen, factor XIII, vWF, and other constituents. The focus of the evaluation for Pathogen Reduced Cryoprecipitated Fibrinogen Complex was based on retention of critical functional activities, including 5 days post thaw, that have shown a high level of correlation with therapeutic efficacy. Fibrinogen, vWF, and factor XIII are key constituents in effective hemostasis and functional levels correlate with risk of bleeding, morbidity and mortality.[11-13]

The average (±SD) fibrinogen content (mg) in a unit of Pathogen Reduced Cryoprecipitated Fibrinogen Complex from 2 whole blood-derived plasma units immediately post thaw, and after 120 hours of storage at 20 – 24°C, were 740 ±166 mg, and 686 ±165 mg, respectively (**Table 3**). Functional fibrinogen activity was retained during the 5-day post-thaw storage.

Assessment of thrombin generation by measurement of endogenous thrombin potential (ETP) demonstrated 99 ±4% conservation of thrombin generation, an integrated assessment of overall hemostatic capacity. ETP was retained during 120 hours of storage post thaw. Fibrin clot quality was assessed by viscoelastography (ROTEM) after activation of Pathogen Reduced Cryoprecipitated Fibrinogen Complex. Pathogen Reduced Cryoprecipitated Fibrinogen Complex retained Maximum Clot Firmness (mm) measured by a modified, non-whole blood, ROTEM assay (**Table 2**).

In Vitro Characterization of Pathogen Reduced Cryoprecipitated Fibrinogen Complex from 2 Units of Whole Blood-Derived Plasma

In an n=80 *in vitro* study, two ABO-matched whole blood-derived plasma units were combined per replicate and processed with the INTERCEPT Blood System for Plasma within 18 to 22 hours of collection. The INTERCEPT processed plasma was frozen at -18°C or colder. After 26-28 days of storage, the INTERCEPT processed plasma was thawed, centrifuged, and the Pathogen Reduced Cryoprecipitated Fibrinogen Complex was recovered and frozen at -18°C or colder for 14-23 days before final thaw. The thawed components were stored at 20-24°C for 120 hours.

In vitro characterization of the thawed Pathogen Reduced Cryoprecipitated Fibrinogen Complex components is presented in **Table 2** and **Table 3**.

Table 2 *In Vitro* Factor Concentration Characterization of Pathogen Reduced Cryoprecipitated Fibrinogen Complex, per 2 Whole Blood-Derived Plasma Inputs

Characteristic	Result at Thaw	Result at 120 hours Post Thaw
Fibrinogen (mg/mL)	9.22 ± 2.26 [4.75 - 16.65]	8.59 ± 2.39 [4.20 - 17.25]
Factor VIII (IU/mL)	2.83 ± 0.80 [1.12 - 5.09]	2.58 ± 0.72 [0.99 - 4.52]
vWF ristocetin cofactor activity (IU/dL)	622 ± 233 [250 - 1610]	574 ± 206 [200 - 1160]
vWF Antigen (IU/dL)	647 ± 208 [260 - 1260]	659 ± 213 [260 - 1340]
Viscoelastography (ROTEM) Maximum Clot Firmness (mm)*	55 ± 10 [31 - 76]	56 ± 10 [34 - 79]

*Modified, non-whole blood, ROTEM analysis
Mean ±SD [range], n = 80

Table 3 *In Vitro* Factor Content Characterization of Pathogen Reduced Cryoprecipitated Fibrinogen Complex, per 2 Whole Blood-Derived Plasma Inputs

Characteristic	Result at Thaw	Result at 120 hours Post Thaw
Volume (mL)	81 ± 8 [60 - 102]	ND
Fibrinogen content (mg)	740 ± 166 [405 - 1349]	686 ± 165 [369 - 1311]
Factor VIII content (IU)	226 ± 57 [103 - 375]	206 ± 51 [91 - 315]
vWF ristocetin cofactor activity (IU)	494 ± 159 [255 - 1095]	456 ± 144 [204 - 916]
vWF Antigen (IU)	514 ± 141 [248 - 964]	523 ± 142 [248 - 898]

Mean ±SD [range], n = 80
ND = not done

In Vitro Characterization of Pathogen Reduced Cryoprecipitated Fibrinogen Complex from Pooled Whole Blood-Derived Plasma

In two *in vitro* studies, two ABO-matched whole blood-derived plasma units were combined per replicate and processed with the INTERCEPT Blood System for Plasma within 18 to 22 hours of collection. The INTERCEPT processed plasma was frozen at -18°C or colder. After 1-25 days of storage, the INTERCEPT processed plasma was thawed, centrifuged, the Pathogen Reduced Cryoprecipitated Fibrinogen Complex was recovered and frozen at -18°C or colder before final thaw. Pooled components were prepared from 2 or 4 single Pathogen Reduced Cryoprecipitated Fibrinogen Complex components (sourced from 4 or 8 whole blood-derived plasma units, respectively). The thawed components were stored at 20-24°C for 120 hours.

In vitro characterization of the thawed pooled Pathogen Reduced Cryoprecipitated Fibrinogen Complex components is presented in **Table 4** and **Table 5**.

Table 4 *In Vitro* Factor Concentration Characterization of Pooled Pathogen Reduced Cryoprecipitated Fibrinogen Complex: Pools of 2 and 4 Components

Characteristic	Result at Thaw		Result at 120 hours Post Thaw	
	Pool of 2	Pool of 4	Pool of 2	Pool of 4
Input units of WB derived plasma	4	8	4	8
Fibrinogen (mg/mL)	10.53 ±1.38 [8.70–12.84]	9.92 ±2.07 [7.41–14.17]	9.74 ±1.30 [8.12–11.81]	9.14 ±1.80 [6.75–12.45]
Factor VIII (IU/mL)	2.76 ±0.47 [2.16–3.73]	2.69 ±0.67 [1.72–3.65]	2.49 ±0.47 [1.79–3.41]	2.60 ±0.62 [1.68–3.68]
Factor XIII Antigen (mg/dL)	11.7 ±2.0 [9.8–16.3]	10.3 ±2.2 [6.8–14.3]	10.9 ±1.3 [8.9–12.5]	10.7 ±3.1 [6.2–16.0]
vWF ristocetin cofactor activity (IU/dL)	486 ±133 [302–630]	525 ±179 [303–820]	474 ±136 [285–620]	490 ±198 [245–770]
vWF Antigen (IU/dL)	663 ±72 [593–819]	677 ±120 [499–852]	668 ±87 [578–856]	688 ±117 [496–812]
Viscoelastography (ROTEM) Maximum Clot Firmness (mm)[a]	63 ±5 [55–70]	58 ±6 [49–67]	63 ±5 [56–70]	59 ±7 [50–71]

Mean ±SD [range]

n = 8 of each pool size which were derived from different plasma inputs

[a] Modified, non-whole blood, ROTEM analysis

Table 5 *In Vitro* Factor Content Characterization of Pooled Pathogen Reduced Cryoprecipitated Fibrinogen Complex: Pools of 2 and 4 Components

Characteristic	Result at Thaw		Result at 120 hours Post Thaw	
	Pool of 2	Pool of 4	Pool of 2	Pool of 4
Input units of WB derived plasma	4	8	4	8
Volume (mL)	147 ± 7 [136–155]	286 ± 16 [265–304]	ND ND	ND ND
Fibrinogen content (mg)	1556 ± 248 [1209–1913]	2845 ± 618 [2016–3868]	1435 ± 206 [1129–1760]	2625 ± 562 [1836–3399]
Factor VIII content (IU)	407 ± 78 [333–567]	777 ± 229 [456–1100]	367 ± 78 [276–518]	751 ± 211 [445–1119]
Factor XIII Antigen (mg)	17.2 ± 3.3 [13.6–24.3]	29.4 ± 6.5 [18.0–39.0]	16.0 ± 2.2 [12.4–18.8]	30.7 ± 8.7 [16.4–43.7]
vWF ristocetin cofactor activity (IU)	720 ± 210 [423–977]	1508 ± 520 [803–2239]	702 ± 215 [399 – 961]	1409 ± 583 [649–2167]
vWF Antigen (IU)	979 ± 132 [848–1269]	1943 ± 396 [1322– 2565]	985 ± 147 [869–1327]	1975 ± 387 [1314–2444]

Mean ±SD [range]
n = 8 of each pool size which were derived from different plasma inputs
ND = not done

Table 6 describes average fibrinogen content of single or pools of 2 or 4 Pathogen Reduced Cryoprecipitated Fibrinogen Complex components based on *in vitro* studies described in Device Performance section. See blood center production quality control data for additional fibrinogen content detail.

Compatibility testing is not required. ABO-compatible Pathogen Reduced Cryoprecipitated Fibrinogen Complex is preferred. Rh type need not be considered when using this product.

Table 6 Average Fibrinogen Content Per Container of Single or Pooled Pathogen Reduced Cryoprecipitated Fibrinogen Complex

Number of pooled Pathogen Reduced Cryoprecipitated Fibrinogen Complex components per container	Fibrinogen content at thaw* - mg	Fibrinogen content at the end of 5 days post thaw* - mg
1 (prepared from 2 whole blood-derived plasma units)	740 (166)	686 (165)
2 (prepared from 4 whole blood-derived plasma units)	1556 (248)	1435 (206)
4 (prepared from 8 whole blood-derived plasma units)	2845 (618)	2625 (562)

*Mean (±SD) from Pathogen Reduced Cryoprecipitated Fibrinogen Complex prepared from whole blood-derived plasma frozen within 24 hours after phlebotomy (PF24) plasma.
See *Device Performance* section for details.

One Pathogen Reduced Cryoprecipitated Fibrinogen Complex component can be prepared from single donor apheresis plasma, or a pool of two whole blood-derived plasma units, within the volume range (585-650 mL) of the INTERCEPT Blood System for Plasma. Within the volume limits of the pooling container, pools of 1 to 5 Pathogen Reduced Cryoprecipitated Fibrinogen Complex components can be prepared containing estimated fibrinogen content based on multiples of individual Pathogen Reduced Cryoprecipitated Fibrinogen Complex components. Pooling facilitates transfusion of high doses of fibrinogen delivered from a single container for administration to patients with bleeding.

Pathogen Reduced Cryoprecipitated Fibrinogen Complex may be administered empirically.

CONTRAINDICATIONS

- Contraindicated for preparation of blood components intended for patients with a history of hypersensitivity reaction to amotosalen or other psoralens.
- Contraindicated for preparation of blood components intended for neonatal patients treated with phototherapy devices that emit a peak energy wavelength less than 425 nm, or have a lower bound of the emission bandwidth <375 nm, due to the potential for erythema resulting from interaction between ultraviolet light and amotosalen.

NOTE: include information about these contraindications in the labeling provided with transfusable blood component products prepared using the INTERCEPT Blood System.

WARNINGS AND PRECAUTIONS

- Only the INTERCEPT Blood System for Cryoprecipitation is approved for use to produce Pathogen Reduced Cryoprecipitated Fibrinogen Complex.
- For management of patients with vWD or factor XIII deficiency, Pathogen Reduced Cryoprecipitated Fibrinogen Complex should not be used if recombinant or specific virally-inactivated factor preparations are available. In emergent situations, if recombinant or specific virally-inactivated factor preparations are not available, Pathogen Reduced Cryoprecipitated Fibrinogen Complex may be administered.

NOTE: include these “Warnings and Precautions” in the labeling provided with transfusable blood component products prepared using the INTERCEPT Blood System.

INSTRUCTIONS FOR USE

These instructions are for the use of the INTERCEPT Blood System for Cryoprecipitation to produce Pathogen Reduced Cryoprecipitated Fibrinogen Complex and Pathogen Reduced Plasma, Cryoprecipitate Reduced. A single 60-100 mL component of Pathogen Reduced Cryoprecipitated Fibrinogen Complex, and two components of Pathogen Reduced Plasma, Cryoprecipitate Reduced, are made from each INTERCEPT Blood System for Plasma set input defined here.

Pathogen Reduced Cryoprecipitated Fibrinogen Complex is produced from cryoprecipitation of cold, insoluble proteins from plasma that has been processed with the INTERCEPT Blood System for Plasma. Final components are produced using the INTERCEPT Blood System for Cryoprecipitation. The supernatant from this process is Pathogen Reduced Plasma, Cryoprecipitate Reduced.

Input Plasma

Input for this process requires plasma that has been processed with the INTERCEPT Blood System for Plasma but not yet frozen in the final storage containers. The plasma may be from one unit of apheresis or two units of whole blood-derived plasma.

The INTERCEPT process must be initiated to allow freezing of INTERCEPT processed plasma within 24 hours after collection of the first unit in the pool for whole blood-derived plasma or within 8 hours of apheresis collection.

Initial Setup

Equipment Provided: One (1) INTERCEPT Blood System for Cryoprecipitation

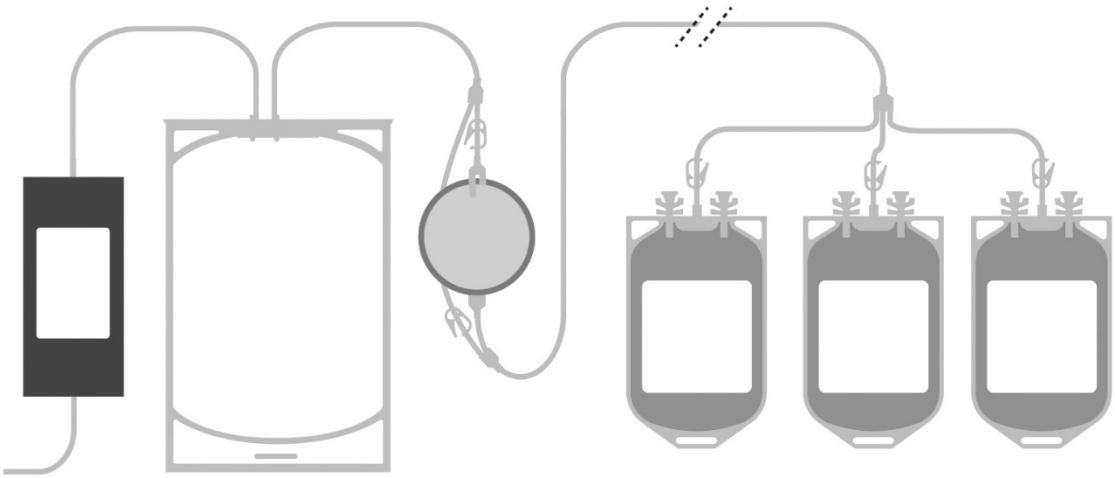
Equipment Required <u>But Not</u> Provided: sterile connecting device (SCD), tube sealer, plasma freezer, centrifuge, top-pan balance and/or scale, labels for final storage containers, label printer, temperature-controlled circulating water bath or refrigerator

Processing

I. Preparations Prior to Freezing the Plasma

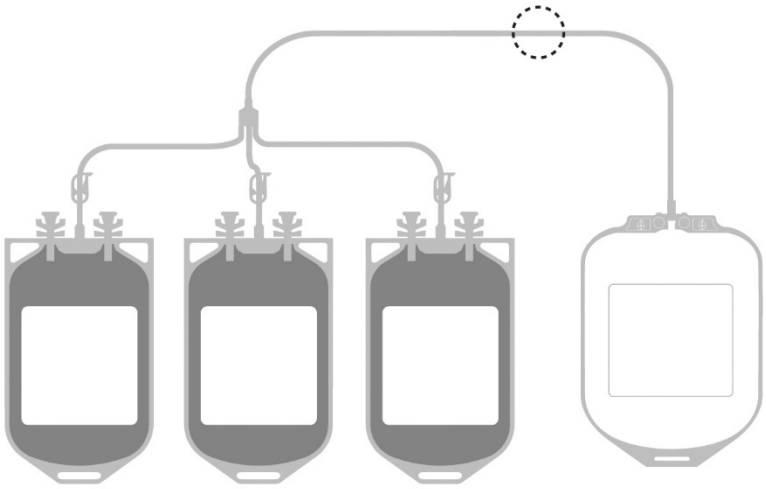
1. Refer to SPC 00818-AW, INTERCEPT Blood System for Plasma. Complete the steps for making INTERCEPT processed plasma, Section III, Step 1 through Step 11. **Do not** re-distribute plasma volume, **do not** disconnect individual storage containers, and **do not** freeze the containers. (i.e., Do not complete Step 12 through Step 16.)
2. Disconnect the storage containers from the plasma set by heat sealing above the 3-way junction of the 3 storage containers (**Figure 2)**.

Figure 2



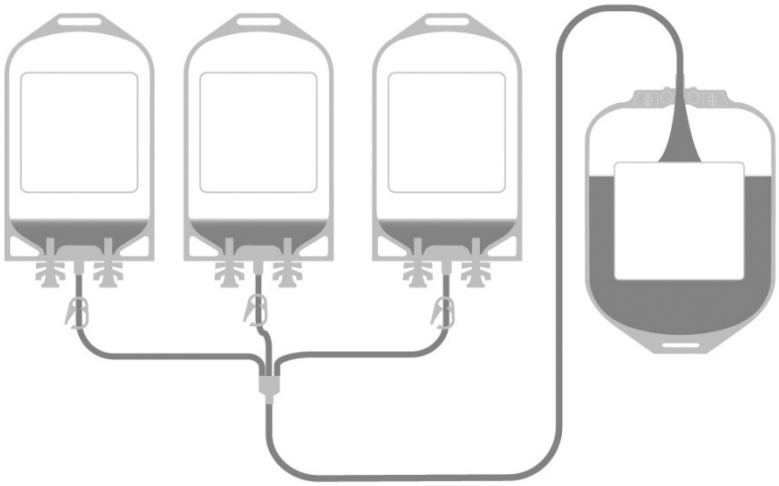
3. Remove the INTERCEPT Blood System for Cryoprecipitation from its packaging.
4. Label the INTERCEPT Blood System for Cryoprecipitation with the donation identification number (DIN).
5. Sterile connect the INTERCEPT Blood System for Cryoprecipitation to the INTERCEPT processed plasma storage containers containing INTERCEPT processed plasma (**Figure 3**).

Figure 3



6. Open the clamps and transfer the INTERCEPT processed plasma to the INTERCEPT Blood System for Cryoprecipitation via gravity flow. The tubing and 3 storage containers should remain connected (**Figure 4**).

Figure 4

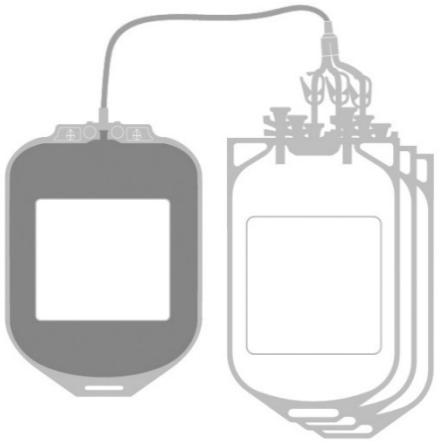


7. After the plasma is transferred, express air from the INTERCEPT Blood System for Cryoprecipitation into the 3 plasma storage containers as needed.
8. Close the clamp on the lines of each of the plasma storage containers. Do not disconnect any of the containers at this point.

II. Freezing INTERCEPT Processed Plasma in the INTERCEPT Blood System for Cryoprecipitation

1. Organize the INTERCEPT Blood System for Cryoprecipitation, tubing, and connected containers. The INTERCEPT Blood System for Cryoprecipitation and the 3 containers should remain connected during freezing (**Figure 5**).

Figure 5



2. Place tubing between the INTERCEPT Blood System for Cryoprecipitation and the connected storage containers to minimize tubing exposure and movement.
3. Place in a freezer that is -18°C or colder.
4. Store at -18°C or colder for no more than 30 days.

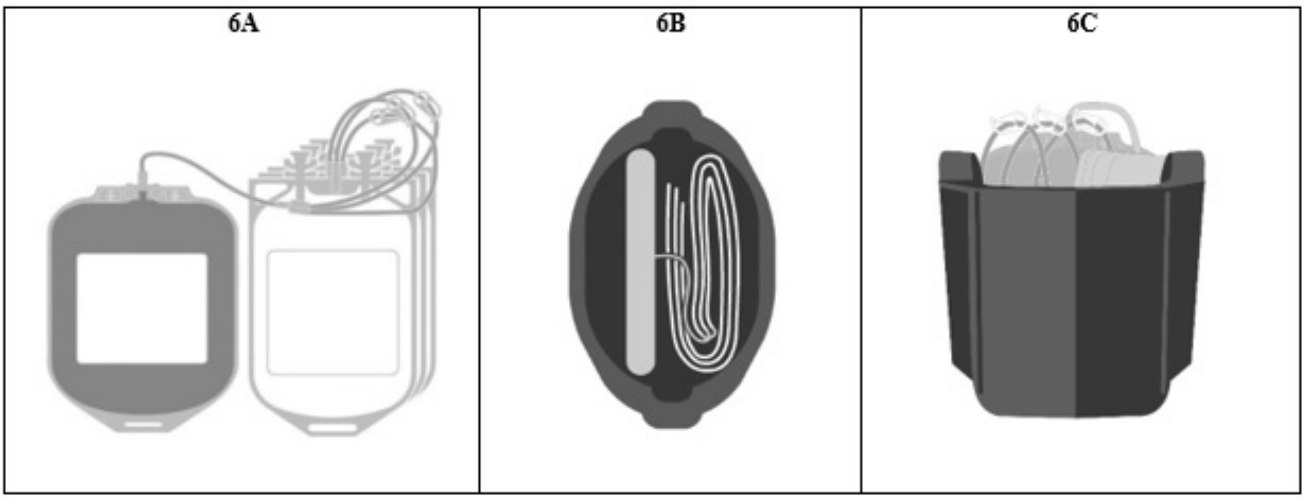
III. Thawing INTERCEPT Processed Plasma in the INTERCEPT Blood System for Cryoprecipitation

1. Carefully remove the INTERCEPT Blood System for Cryoprecipitation, tubing, and connected containers from the freezer.
2. After removal from the freezer, allow sufficient time at ambient temperature for the tubing to thaw sufficiently to regain flexibility.
3. Place the INTERCEPT Blood System for Cryoprecipitation and connected containers at 1°C to 6°C until the plasma is sufficiently thawed.
   NOTE: Thaw time and specific thawing practices must be characterized by the blood center.
4. When the plasma has completely thawed, remove the INTERCEPT Blood System for Cryoprecipitation, tubing, and connected containers from the water bath or refrigerator.

IV. Centrifugation

1. Organize and place the INTERCEPT Blood System for Cryoprecipitation, tubing, and containers in a centrifuge liner. An example is shown below of the contents (**Figure 6A**) and placement (**Figure 6B** - top view, **Figure 6C** - side view). White clamps should be positioned prior to folding to avoid compression during centrifugation (**Figure 6A**). NOTE: method of loading in the centrifuge liner and clamp placement must be established by the blood center.

Figure 6



2. Place the liner into the centrifuge bucket and balance with any other liners following centrifuge manufacturer's instructions.
3. Centrifuge at 1°C to 6°C using a hard spin. NOTE: Centrifuge time and settings must be characterized by the blood center.
4. Carefully remove the INTERCEPT Blood System for Cryoprecipitation, tubing, and connected containers from the liner.
5. Inspect to ensure cryoprecipitate pellet is visible and there are no breaks or leaks. Take care not to disturb the pellet during handling.
6. If separation is not performed immediately, store the items at 1°C to 6°C until ready for separation.

V. Separation into Components

1. Open the clamps leading to any two of the final storage containers. One clamp on the tubing leading to the third storage container will remain closed.
2. Drain or express the Pathogen Reduced Plasma, Cryoprecipitate Reduced supernatant from the INTERCEPT Blood System for Cryoprecipitation into two open final storage containers. Retain 60 mL to 100 mL of cryoprecipitate and supernatant within the INTERCEPT Blood System for Cryoprecipitation.
3. Expel air from the two final storage containers containing Pathogen Reduced Plasma, Cryoprecipitate Reduced into the INTERCEPT Blood System for Cryoprecipitation, as needed.
4. Clamp off INTERCEPT Blood System for Cryoprecipitation with hemostat or clamp.

5. Distribute the Pathogen Reduced Plasma, Cryoprecipitate Reduced evenly as needed between the two final storage containers. Each storage container can hold up to a maximum of 325 mL.
6. Disconnect the two final storage containers with the Pathogen Reduced Plasma, Cryoprecipitate Reduced by heat sealing below the 3-way junction. Allow sufficient tubing length for segments if needed. Discard the white clamps.
7. Apply blood center label for Pathogen Reduced Plasma, Cryoprecipitate Reduced to each disconnected container.
8. Resuspend the cryoprecipitate in the residual supernatant in the INTERCEPT Blood System for Cryoprecipitation.
9. Open the clamp leading to the remaining empty final storage container.
10. Transfer the Pathogen Reduced Cryoprecipitated Fibrinogen Complex from the INTERCEPT Blood System for Cryoprecipitation into the final storage container.
11. Expel air from the final storage container back into the INTERCEPT Blood System for Cryoprecipitation, as needed.
12. Disconnect the final storage container by heat sealing below the 3-way junction. Allow sufficient tubing length for segments if needed. Discard the white clamp.
13. Apply blood center label for Pathogen Reduced Cryoprecipitated Fibrinogen Complex to the final storage container or label after pooling multiple Pathogen Reduced Cryoprecipitated Fibrinogen Complex components into one final storage container. Each storage container can hold up to a maximum of 325 mL.
14. Organize components into packaging for freezing and storage.
15. Freeze immediately following blood center procedures.
16. Store all three components at -18°C or colder.
17. Discard the INTERCEPT Blood System for Cryoprecipitation as Biohazardous Waste.

NOTE: Pathogen Reduced Cryoprecipitated Fibrinogen Complex must be stored in one of the INTERCEPT Blood System for Plasma storage containers.

NOTE: Multiple Pathogen Reduced Cryoprecipitated Fibrinogen Complex components may be pooled into one INTERCEPT Blood System for Plasma storage container. Each storage container can hold up to a maximum of 325 mL of Pathogen Reduced Cryoprecipitated Fibrinogen Complex.

NOTE: Pathogen Reduced Cryoprecipitated Fibrinogen Complex may be stored at -18°C or colder for up to 12 months from the date of collection of the first donation in the input plasma pool.

STORAGE AND HANDLING

INTERCEPT Blood System for Cryoprecipitation

- The INTERCEPT Blood System for Cryoprecipitation is designed to be a functionally closed system for use with the INTERCEPT Processing Set for plasma. Pathogen Reduced Cryoprecipitated Fibrinogen Complex must be stored in one of the three final storage containers of the INTERCEPT Processing Set for plasma.
- The INTERCEPT Blood System for Cryoprecipitation is for single use only. Do not reuse.
- Do not use the INTERCEPT Blood System for Cryoprecipitation if the container or its packaging is damaged or shows any sign of deterioration.
- Protect the packaging, container, and tubing from sharp objects.
- Do not store processing set above 25°C.
- Do not freeze prior to use.

Pathogen Reduced Cryoprecipitated Fibrinogen Complex

- Pathogen Reduced Cryoprecipitated Fibrinogen Complex may be stored at -18°C (-0.4°F) or colder for up to 12 months.
- Thaw according to institutional procedures. If using a water bath for thawing Pathogen Reduced Cryoprecipitated Fibrinogen Complex, place in liquid-impermeable plastic overwrap. Do not allow product to contact water. Do not refreeze post thaw.
- Do not administer Pathogen Reduced Cryoprecipitated Fibrinogen Complex if there is evidence of container breakage or of thawing during frozen storage.
- If Pathogen Reduced Cryoprecipitated Fibrinogen Complex is pooled or aliquoted post thaw without using an FDA-cleared sterile connection device, transfuse within 4 hours of pooling or aliquoting.
- Pathogen Reduced Cryoprecipitated Fibrinogen Complex may be stored at room temperature for up to 5 days post thaw.
- Discard unused, thawed Pathogen Reduced Cryoprecipitated Fibrinogen Complex at the end of 5 days post thaw as medical waste according to institutional and local regulations.

NONCLINICAL TOXICOLOGY

Nonclinical toxicology studies have not been performed with the INTERCEPT Blood System for Cryoprecipitation.

Pathogen Reduced Cryoprecipitated Fibrinogen Complex is prepared from INTERCEPT processed plasma. *In vitro* studies using whole blood-derived plasma frozen within 24 hours after phlebotomy (PF24) were used to evaluate the concentration of amotosalen in precursor plasma Pathogen Reduced Cryoprecipitated Fibrinogen Complex fractions. The average concentrations in precursor plasma and Pathogen Reduced Cryoprecipitated Fibrinogen Complex were comparable and demonstrate that there is no enrichment of amotosalen in any fraction; and thus, the safety data from the nonclinical, clinical, and post-marketing studies with INTERCEPT processed plasma are informative about the safety of Pathogen Reduced Cryoprecipitated Fibrinogen Complex.

Nonclinical studies were conducted in mice, rats, and dogs to evaluate the potential toxicity of single and repeated exposures to amotosalen, the synthetic psoralen derivative used in the INTERCEPT process to cross-link DNA and RNA. A single, intravenous injection of amotosalen alone resulted in mortality in rats at doses equal to or greater than 35,000-fold the anticipated human exposure from INTERCEPT Blood System processed plasma, on a dose per kilogram body weight basis. Lower doses (4,000- or 20,000-fold greater than the human exposure in dogs and rats, respectively) were not lethal, and resulted in transient clinical signs of toxicity (i.e., piloerection, inactivity, hunched posture and abnormal breathing in rats, and excessive salivation, convulsions, and non-lethal cardiac arrhythmias in dogs). No target organ toxicities were noted at necropsy.[14]

Animal experiments provided no indication of an increased toxicological risk for the use of plasma processed with amotosalen using the INTERCEPT Blood System, as compared to dosing with equivalent volumes of either homologous unprocessed plasma, or saline or buffer control. Single-dose studies with INTERCEPT processed plasma in dogs were non-toxic at amotosalen doses of 6,000-fold the expected clinical exposure, and repeated daily dosing in rats and dogs for 28 days with homologous plasma processed with the INTERCEPT Blood System showed no evidence of toxicity at 5,000-fold the expected amotosalen clinical exposure.[14]

Amotosalen was rapidly eliminated following intravenous dosing in mice and rats, with an initial plasma $t_{½}$ of less than one hour. There was no evidence of amotosalen accumulation after repeated exposures over periods as long as 13 weeks. The primary route of excretion of amotosalen and its photo-byproducts was fecal.

No effects on fertility parameters were noted in male or female rats repeatedly dosed with amotosalen. In studies evaluating the effects of amotosalen dosing of pregnant rats or rabbits on embryo-fetal or peri-postnatal development, and in one study of neonatal rats dosed with amotosalen, there was no evidence of teratogenicity, or other reproductive or developmental toxicities.[15] No evidence of genotoxicity or mutagenicity was observed in the *in vitro* or *in vivo* mutagenicity studies of amotosalen[16]. In transgenic mice heterozygous for the p53 tumor suppressor gene, there was no evidence of carcinogenicity after repeated, three times weekly dosing for 6 months with amotosalen in plasma, at cumulative weekly

doses approximately 150 times the human exposure from a single infusion of INTERCEPT processed plasma.[14]

CLINICAL STUDIES

Pathogen Reduced Cryoprecipitated Fibrinogen Complex is intended to provide fibrinogen, factor XIII, and vWF for management of massive bleeding or risk of massive bleeding due to fibrinogen deficiency and as second-line therapy for vWD, factor XIII deficiency and bleeding associated with uremia.[17,18] No *in vivo* clinical studies have been performed with Pathogen Reduced Cryoprecipitated Fibrinogen Complex.

Efficacy of fibrinogen provided by Pathogen Reduced Cryoprecipitated Fibrinogen Complex

The primary indication for Pathogen Reduced Cryoprecipitated Fibrinogen Complex with 5-day post-thaw storage is control of massive bleeding associated with fibrinogen deficiency. The effective fibrinogen dose for transfusion of Pathogen Reduced Cryoprecipitated Fibrinogen Complex is dependent on the clinical presentation of bleeding, the clinical setting, and the risk and magnitude of bleeding associated with demonstrable or clinically suspected fibrinogen deficiency. The higher levels of fibrinogen content in pooled doses of Pathogen Reduced Cryoprecipitated Fibrinogen Complex provides feasibility to transfuse a large dose of fibrinogen in a tolerable volume (**Table 6**).

Clinical efficacy of vWF and factor XIII replacement provided by Pathogen Reduced Cryoprecipitated Fibrinogen Complex

Pathogen Reduced Cryoprecipitated Fibrinogen Complex contains therapeutic levels of vWF RCF activity and factor XIII. Each of these factors retained functional activity or antigenic levels over 5 days of post-thaw storage at room temperature.[19]

vWF RCF activity in Pathogen Reduced Cryoprecipitated Fibrinogen Complex was retained 94 ± 21% over 5 days post thaw (**Table 5**). Treatment of vWD requires doses ranging from 20 – 60 IU/kg, which for a 60 kg patient would require a total dose of 1200 to 3,600 IU. The levels in Pathogen Reduced Cryoprecipitated Fibrinogen Complex support clinically feasible dosing of vWF when other products are not available or as second-line therapy for vWD (**Table 5**).

Summary of Safety of Pathogen Reduced Cryoprecipitated Fibrinogen Complex

There are no specific clinical safety studies for Pathogen Reduced Cryoprecipitated Fibrinogen Complex.

Pathogen Reduced Cryoprecipitated Fibrinogen Complex is prepared from INTERCEPT processed plasma and contains the comparable concentrations of residual amotosalen as INTERCEPT processed plasma.

The safety data from the nonclinical, clinical, and post-marketing studies with INTERCEPT processed plasma are informative about the safety of Pathogen Reduced Cryoprecipitated Fibrinogen Complex.

Studies with Pathogen Reduced Cryoprecipitated Fibrinogen Complex in pregnant women or pediatric patients have not been conducted. Pathogen Reduced Cryoprecipitated Fibrinogen Complex is produced from INTERCEPT processed plasma, which has been used in the treatment of pregnant and pediatric patients, including neonates. No unexpected adverse events associated with transfusion of INTERCEPT processed plasma to pregnant women or children have been reported.[20] Assessment of safety for INTERCEPT processed plasma has relied on validated nonclinical studies in appropriate animal models, controlled clinical trials, and post-marketing surveillance studies, including in countries with active hemovigilance programs, such as France. The nonclinical studies in reproductive animal models and neonatal animal models established high safety margins in these populations using platelet and plasma components.

INTERCEPT processed plasma has been in clinical use in the European Union for 15 years for treatment of congenital coagulopathy including fibrinogen deficiency, acquired coagulopathy including liver transplant, and for therapeutic plasma exchange (TPE). Each of these indications was supported by clinical trials. TPE is of specific interest because this requires large volume exposure to plasma processed with amotosalen. Long-term surveillance studies of TPE patients have demonstrated no excess treatment related morbidity indicative of safety.[21-24] Post-marketing surveillance studies that have included neonatal and children to age 18 have not detected any adverse events specifically related to INTERCEPT processed plasma transfusion; and these studies have included longitudinal exposures for many of these patients including liver transplant.[25-27] On the basis of the multi-year clinical experience with INTERCEPT processed plasma, there are no safety signals indicative of excess treatment related morbidity.[20]

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