**Rx Only**

# INTERCEPT® Blood System for Plasma

## DESCRIPTION

The INTERCEPT® Blood System for plasma consists of single-use processing sets containing amotosalen solution (INTERCEPT Processing Sets) and an illumination device (INTERCEPT Illuminator), which provides a controlled dose of ultraviolet A (UVA) light for each treatment. (Plasma treated with the INTERCEPT Blood System is referred to as INTERCEPT Plasma.)

The INTERCEPT processing set is a sterile non-pyrogenic fluid path device consisting of four integrated plastic single-use components:

- One 15 mL 6 mM amotosalen solution container (Formula: Amotosalen HCl 203 mg - Sodium Chloride, USP, 924 mg - Water for Injection, USP, to 100 mL)
- Illumination container
- Compound Adsorption Device (CAD) for the reduction of residual amotosalen and free photoproducts
- Three containers for storage of treated plasma prior to transfusion

The INTERCEPT Illuminator delivers a controlled amount of UVA light (wavelength 320 to 400 nm) to the illumination container during each treatment cycle. The device has the capability of illuminating 1 or 2 INTERCEPT processing sets per treatment cycle. Each illumination container rests on a UVA transparent tray that undergoes horizontal agitation during the illumination process. UVA illumination in each chamber is provided by 2 opposing banks of fluorescent lamps mounted above and below the illumination tray, and is monitored by independent photodiode systems which quality the UVA dose. The INTERCEPT Illuminator delivers a 3 Joules/$cm^2$ (J/$cm^2$) UVA treatment within approximately 6 to 8 minutes. Upon completion of the illumination step, the illuminated plasma is transferred through the CAD by gravity flow, and divided among the three storage containers.

## PRINCIPLE OF OPERATION

During the INTERCEPT process, amotosalen (a synthetic psoralen-derivative) is added to the plasma unit and the mixture is subjected to a controlled exposure to UVA light. A compound adsorption device (CAD) is then employed to reduce the levels of unreacted amotosalen and its free photoproducts.

The principle of operation is based upon the following:

- Amotosalen is added to the plasma unit and penetrates cellular and nuclear membranes of pathogens and cells, intercalating into helical regions of DNA and RNA.
- Covalent cross links to nucleic acid base pairs form upon exposure to UVA light.
- DNA and RNA replication are permanently blocked and this prevents replication of pathogens and residual leukocytes.
- Following illumination, residual levels of unreacted amotosalen and free photoproducts are reduced by passing the plasma through the compound adsorption device (CAD).
- The plasma is transferred, by gravity, to the storage containers, and the single units of plasma are frozen and stored at -18°C or below.

## INDICATIONS AND USAGE

The INTERCEPT Blood System for plasma is intended to be used for the ex vivo preparation of pathogen-reduced, whole blood derived or apheresis plasma in order to reduce the risk of transfusion-transmitted infection (TTI).

## CONTRAINDICATIONS

- Contraindicated for preparation of plasma intended for patients with a history of hypersensitivity reaction to amotosalen or other psoralens.
- Contraindicated for preparation of plasma intended for neonatal patients treated with phototherapy devices that have peak energy wavelengths less than 425 nm due to the potential for erythema resulting from interaction between ultraviolet light and amotosalen.

## WARNINGS

This process is designed to be a closed system. Treatment with INTERCEPT Blood System does not replace applicable standards for processing in open and closed systems. If there is a leak in the set during processing, plasma product must be discarded.

Do not use INTERCEPT Plasma that is cloudy or has deposits either before or after freezing.

Amotosalen in contact with skin may result in photosensitization in the presence of ultraviolet light. If skin exposure occurs, flush exposed skin with water.

Sterile connecting device (SCD) and tube sealer should be used according to manufacturer's instructions for use.

While laboratory studies of amotosalen processing with UVA light have shown a reduction in levels of certain viruses, bacteria, and parasites; there is no pathogen inactivation process that has been shown to eliminate all pathogens.

DEHP is known to be released from polyvinyl chloride (PVC) medical devices; increased leaching can occur with extended storage or increased surface area contact. The INTERCEPT processing sets only have tubing components, container ports and, if included, an in-line filter that contain PVC; all containers and other parts are PVC-free. During use of this processing set, blood components are in contact with PVC for a brief period of time (approx. <15 minutes). Based on limited surface area contact and minimal contact time, DEHP levels in blood components after use of the processing set are estimated to be well below those resulting from other medical applications containing PVC tubing (e.g., hemodialysis, intravenous fluid administration, extracorporeal membrane oxygenation and cardiopulmonary bypass procedures). The risks associated with DEHP released to the blood components must be weighed against the benefits of therapeutic transfusion and inactivation of harmful viruses, bacteria and other pathogens.

- Amotosalen-treated plasma may cause the following adverse reaction:

  *Cardiac Events*

  In a randomized controlled trial of therapeutic plasma exchange (TPE) for TTP, five patients treated with INTERCEPT Blood System processed plasma and none with conventional plasma had adverse events in the cardiac system organ class (SOC) reported. These events included angina pectoris (n=3), cardiac arrest (n=1), bradycardia (n=1), tachycardia (n=1) and sinus arrhythmia (n=1). None of these events resulted in documented myocardial infarction or death. Monitor patients for signs and symptoms of cardiac events during TPE for TTP.

## PRECAUTIONS

The INTERCEPT processing sets are intended for single-use. Do not reuse sets or components of sets.

Do not use if: tamper-evident package has been opened; signs of deterioration are visible; fluid path closures are loose or not intact; cannulae are broken or there is no fluid in amotosalen solution container.

All the following conditions must be met for pathogen inactivation:

- Plasma volume and red blood cell (RBC) content must be within the range specified in the Instructions for Use.
- Plasma mixed with amotosalen must be exposed to UVA light dose from INTERCEPT Illuminator. No other source of UVA light may be used. Please refer to the Operator's Manual for the INTERCEPT Illuminator.
- Plasma must be passed through the CAD by gravity flow after illumination.
- Plasma processing should be in accordance with blood bank practice.

Treat all blood products as though they contain an infectious agent. Follow institutional guidelines regarding the handling of infectious agents. Dispose of all materials used in the procedure as biohazardous waste.

## CAUTIONS

The impact of combining UVA treatment and gamma-irradiation on the function of coagulation factors has not been studied.

## ADVERSE EVENTS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a product cannot be directly compared to rates in the clinical trials of another product and may not reflect the rates observed in clinical practice.

In studies of healthy volunteers, the only adverse event (regardless of relatedness to study plasma) that occurred in ≥5% of subjects was headache.

A large number of adverse events reported in the randomized clinical trials that included patients with severe liver disease (some undergoing liver transplant), as well as patients undergoing daily total plasma exchange for treatment of TTP due to morbidity of the disorders. Most events were considered to be related to the procedure and/or the underlying disease and were not reported as related to the use of study plasma. The adverse events in the prospective randomized clinical trials that were reported as possibly or probably related to the use of INTERCEPT Plasma and were observed in ≥5% of patients are recognized symptoms of transfusion reactions and included pruritis (7%) and urticaria (6%). Related adverse reactions (defined as possibly or probably related to study transfusion) that occurred in ≥ 2 subjects in either treatment group in the randomized clinical trials are summarized in **Table 1**.

**Table 1 Related Adverse Events Occurring in ≥2 Subjects Treated with INTERCEPT or Conventional Plasma in Randomized Clinical Trials**

| Event | INTERCEPT Plasma Group (N=83) | Conventional Plasma Group (N=86) | Event | INTERCEPT Plasma Group (N=83) | Conventional Plasma Group (N=86) |
|---|---|---|---|---|---|
| Any Adverse | 24 (28.9%) | 16 (18.6%) | Paraesthesia | 2 (2.4%) | 1 (1.2%) |
| Pruritus | 5 (6.0%) | 1 (1.2%) | Pyrexia | 2 (2.4%) | 0 |
| Urticaria | 5 (6.0%) | 3 (3.5%) | Rigors | 2 (2.4%) | 0 |
| Hypokalemia | 4 (4.8%) | 0 | Vomiting | 2 (2.4%) | 0 |
| Nausea | 3 (3.6%) | 0 | Fluid overload | 1 (1.2%) | 3 (3.5%) |
| Anemia | 2 (2.4%) | 0 | Haematuria | 1 (1.2%) | 2 (2.3%) |
| Dyspnea | 2 (2.4%) | 0 | Hepatic artery | 1 (1.2%) | 2 (2.3%) |
| Hypotension | 2 (2.4%) | 0 | Epistaxis | 0 | 2 (2.3%) |

Similarly, many of the related adverse reactions (possibly or probably related to study transfusion) that were observed in the small study of patients with congenital coagulation factor deficiencies are related to transfusion reactions and reflect the higher prior exposure of these patients to plasma. Adverse events (grouped in MedDRA high level group terms) reported in 2 or more subjects with congenital coagulation deficiencies treated with INTERCEPT Plasma are displayed by relationship to the study transfusion in the following **Table 2.**

**Table 2 Subjects with Congenital Coagulation Factor Deficiencies (n = 34): Adverse Events Occurring in ≥2 Subjects Treated with INTERCEPT Plasma[a]**

| Events [b] | INTERCEPT Plasma Group (N=34) | | | |
|---|---|---|---|---|
| | Total | Probable | Possible | Not Related |
| Any Adverse Event | 29 (85.3%) | 17 (50.0%) | 4 (11.8%) | 8 (23.5%) |
| Allergic conditions | 14 (41.2%) | 14 (41.2%) | 0 (0%) | 0 (0%) |
| Bleeding disorders | 5 (14.7%) | 1 (2.9%) | 1 (2.9%) | 3 (8.8%) |
| Body temperature conditions | 9 (26.5%) | 5 (14.7%) | 2 (5.9%) | 2 (5.9%) |
| Bronchial disorders (exc neoplasms) | 3 (8.8%) | 2 (5.9%) | 1 (2.9%) | 0 (0%) |
| Cardiac arrhythmias | 2 (5.9%) | 1 (2.9%) | 0 (0%) | 1 (2.9%) |
| Cardiac disease symptoms and signs | 2 (5.9%) | 0 (0%) | 1 (2.9%) | 1 (2.9%) |
| Electrolyte and fluid balance conditions | 2 (5.9%) | 0 (0%) | 0 (0%) | 2 (5.9%) |
| Epidermal and dermal conditions | 3 (8.8%) | 3 (8.8%) | 0 (0%) | 0 (0%) |
| Gastrointestinal motility and defecation conditions | 4 (11.8%) | 0 (0%) | 0 (0%) | 4 (11.8%) |
| Gastrointestinal symptoms and signs | 12 (35.3%) | 3 (8.8%) | 1 (2.9%) | 8 (23.5%) |
| General system symptoms and signs | 8 (23.5%) | 1 (2.9%) | 0 (0%) | 7 (20.6%) |
| Headaches (all forms) | 17 (50.0%) | 2 (5.9%) | 4 (11.8%) | 11 (32.4%) |
| Hematological disorders NOS | 2 (5.9%) | 2 (5.9%) | 0 (0%) | 0 (0%) |
| Hematology investigations including blood groups | 2 (5.9%) | 0 (0%) | 2 (5.9%) | 0 (0%) |
| Increased blood pressure | 4 (11.8%) | 0 (0%) | 3 (8.8%) | 1 (2.9%) |
| Infections – pathogen class unspecified | 3 (8.8%) | 1 (2.9%) | 0 (0%) | 2 (5.9%) |
| Neurological signs and symptoms | 3 (8.8%) | 0 (0%) | 0 (0%) | 3 (8.8%) |
| Respiratory symptoms and signs | 6 (17.6%) | 1 (2.9%) | 3 (8.8%) | 2 (5.9%) |

[a] Open-label study, no control arm.

[b] MedDRA high level group term.

## Immunogenicity

No antibodies to amotosalen or amotosalen associated neoantigens were detected in a total of 90 subjects for whom post-baseline samples were tested in the prospective clinical studies.

**Post Market Experience**

Because post-marketing reporting of adverse reactions is voluntary and from a population of uncertain size, it is not always possible to reliably estimate the frequency of these reactions or establish a causal relationship product exposure.

An active hemovigilance study conducted by Cerus included data for 57,171 INTERCEPT Plasma components transfused to 9,669 patients in 22,101 transfusion episodes. The primary endpoint of the post-market hemovigilance study was the number of transfusion episodes with at least one acute transfusion reaction (ATR) during routine use of INTERCEPT Plasma. Thirty-two subjects (0.3%) experienced an ATR following 41 separate transfusion episodes (0.2%); including 5 subjects (0.05%) who experienced an ATR following more than one transfusion episode. The most common signs/symptoms of those ATR were urticaria, chills, rash, and pruritus. Most ATRs were considered to be mild. Six ATRs were assessed as serious and possibly or probably related to study transfusion; the symptoms of these reactions were consistent with recognized transfusion reactions and included three instances of allergic reaction or symptoms of allergic reaction (e.g. rash, tachycardia, hypotension, respiratory symptoms, chills), two instances of fluid overload and one report of respiratory distress.

**Post Market Experience in France**

During the 3 year period after implementation of INTERCEPT Plasma in routine use in France, the rates of acute transfusion reactions (ATR) for INTERCEPT Plasma have been comparable to other plasma components, approximately 0.4 events per 1,000 plasma components (Rapport Annuel Hemovigilance for 2009, 2010, and 2011). A single case of TRALI was reported in association with INTERCEPT Plasma. ATR frequency for IBS and other plasma types based on annual reports (2009-2011) is summarized in **Table 3**.

**Table 3 Frequency of ATR Per 1,000 Plasma Components Transfused (ANSM Annual Reports 2009-2011)**

| Year | Product | ATR | Components | ATR/$10^3$ |
|---|---|---|---|---|
| **2009** | Other Plasma[a] | 191[b] | 348,725 | 0.55[d] |
| | INTERCEPT Plasma | 12 | 22,933 | 0.52[d] |
| **2010** | Other Plasma[a] | 195[c] | 329,757 | 0.59[e] |
| | INTERCEPT Plasma | 25[c] | 52,692 | 0.47[e] |
| **2011** | Other Plasma[a] | 98 | 311,482 | 0.31[f] |
| | INTERCEPT Plasma | 21 | 68,440 | 0.31[f] |

a. Includes quarantine plasma, methylene blue treated plasma, and solvent-detergent treated plasma

b. Excluding irregular antibody (RAI: recherche d'anticorps irréguliers)

c. Excluding allo-immunization

d. ATR: Acute transfusion reaction, all grades, imputability 2-4

e. ATR: Acute transfusion reaction, all grades, imputability 1-3

f. ATR: Allergic transfusion reactions only, all grades, imputability 2-3

## NONCLINICAL TOXICOLOGY

Nonclinical studies have been conducted to evaluate the potential toxicity of exposure to amotosalen, the synthetic derivative used in the INTERCEPT process to cross-link DNA and RNA. Animal experiments with amotosalen provided no indication of an increased toxicological risk for the use of plasma treated using the INTERCEPT Blood System. Single dose studies in dogs were non-toxic at 6000 fold the clinical dose and repeated dose in rats and dogs, over 28 days, showed no evidence of toxicity at 5000 fold the clinical exposure of the plasma produced from the INTERCEPT Blood System.

In fertility studies of embryo-fetal or peri-postnatal development in rats and rabbits as well as in one study with neonatal rats, no reproductive toxicity of amotosalen was determined.

No evidence of mutagenicity and carcinogenicity was observed in the in vitro or in vivo mutagenicity and carcinogenicity studies of amotosalen.

## CLINICAL STUDIES

The safety and effectiveness of INTERCEPT Plasma were investigated in eight clinical studies, including five prospective randomized controlled clinical trials (RCT), one prospective single arm uncontrolled clinical trial, and two retrospective controlled clinical studies. A total of 704 study subjects received INTERCEPT Plasma in the clinical studies.

A single-arm, Phase 3, open-label, multi-center, intent-to-treat study was conducted in 34 male or female patients ≥2 years of age with congenital coagulation factor deficiencies requiring FFP, who were to receive at least one transfusion of INTERCEPT Plasma over a 12-month open-enrollment period. The results of recovery and half-life of each coagulation factor after one transfusion of INTERCEPT plasma are listed in **Table 4** below. This study was not powered to evaluate efficacy in specific congenital factor deficiencies. The dosing regimen for specific congenital factor deficiencies has not been established.

**Table 4 Coagulation Factor Recovery Following Transfusion of INTERCEPT Plasma**

| Deficiency | Number of Patients for Proportional Recovery | Proportional Recovery[a] (%) (mean±SD) | Recovery (%)[b] (Literature Reference) | Number of Patients for $T_{1/2}$ | $T_{1/2}$ (Hours) (mean±SD) | $T_{1/2}$ (Hours) (Literature Reference) |
|---|---|---|---|---|---|---|
| Factor I | 2 | 32.7 ± 15.5 | 50 | 1 | 31.7 | 72 – 120 |
| Factor II | 3 | 55.3 ± 3.8 | 50 – 100 | 3 | 23.3 ± 10.27 | 72 |
| Factor V | 7 | 84.1 ± 14.9 | 50 – 100 | 4 | 16.1 ± 4.39 | 15 – 36 |
| Factor VII | 3 | 37.5 ± 14.8 | 100 | 2 | 4.8 ± 0.32 | 2 – 6 |
| Factor X | 1 | 98.5 | 50 – 100 | 1 | 42.8 | 24 – 40 |
| Factor XI | 11 | 70.2 ±14.9 | 100 | 6 | 47.0 ± 8.44 | 40 – 84 |
| Factor XIII | 3 | 93.7 ± 14.4 | 50 – 100 | 3 | 99.5 ± 57.6 | 216 – 288 |
| Protein C | 3 | 37.3 ± 9.6 | N/A | 2 | 9.1 ± 2.35 | N/A |

[a] Unadjusted recovery was determined using an estimated blood volume for each patient based on body-weight, first 60 min after transfusions (post-transfusion – pre-transfusion) and expressed as the proportion of the administered dose (%).

[b] Reference values for proportional post-transfusion factor recovery were obtained from the literature (Friedman and Rodgers 2004)

A Phase 3 prospective multi-center, randomized, controlled, double-blind, intent to-treat study was conducted in patients with acquired coagulopathy associated with liver disease requiring FFP to support either a major or minor medical procedure. A total of 121 modified intention-to-treat (MITT) subjects received at least one 2-unit transfusion of study FFP (INTERCEPT Plasma or conventional FFP) during the 7-day plasma support period. The study evaluated the changes in prothrombin (PT) and activated partial thromboplastin (aPTT) times in response to initial and subsequent FFP transfusions. A total of 51 patients in the study were enrolled for plasma transfusion support associated with orthotopic liver transplantation (OLT); 22 received INTERCEPT Plasma and

29 received conventional FFP. The mean change/improvement (calculated as pre – post) in PT and aPTT was 3.4 sec and 3.0 sec, respectively, in MITT patients who received INTERCEPT Plasma, compared to 3.5 sec and 4.8 sec in MITT patients who received conventional FFP (after exclusion of one extreme PTT value from one patient who received conventional FFP). Mean recovery of Factor VII was 0.69 [IU/dl]/[IU/kg] for INTERCEPT Plasma and 0.48 [IU/dl]/[IU/kg] for conventional FFP.

Hemostatic evaluations, using the 5-point modified WHO bleeding scale for 8 potential bleeding sites, were performed at pre and post transfusion for all transfusion episodes during the 7-day period of study transfusion support. Bleeding was assessed for the 8-hour period prior to transfusion through the 8-hour period post transfusion. Both the incidence of bleeding at each potential bleeding site and an overall hemostatic grade for all bleeding sites, representing the most severe bleeding grade at any site, were determined at each time point.

Hemostatic assessments were analyzed separately for the OLT and non-OLT populations, since patients who received FFP transfusions for coagulation support associated with significant hemostatic challenges, such as OLT surgery, were likely to have more bleeding. The distribution of overall bleeding grades, representing the most severe bleeding grade at any bleeding site, preceding and following the first study transfusion is shown in **Table 5** below for MITT patients by OLT status.

**Table 5 Distribution of Overall (Maximum) Hemostatic Grade at Pre and Post First Study Transfusion by OLT Status**

| | **OLT Population (N=51)** | | **Non-OLT Population (N=70)** | |
|---|---|---|---|---|
| | **INTERCEPT Plasma Group (N=22)** | **Conventional Plasma Group (N=29)** | **INTERCEPT Plasma Group (N=38)** | **Conventional Plasma Group (N=32)** |
| **Pre transfusion** | | | | |
| Grade 0 | 17 (77%) | 17 (61%) | 14 (37%) | 12 (38%) |
| Grade 1 | 3 (14%) | 4 (14%) | 15 (40%) | 13 (41%) |
| Grade 2 | 2 (9%) | 5 (18%) | 7 (18%) | 3 (9%) |
| Grade 3 | 0 (0%) | 2 (7%) | 2 (5%) | 3 (9%) |
| Grade 4 | 0 (0%) | 0 (0%) | 0 (0%) | 1 (3%) |
| | | | | |
| **Post transfusion** | | | | |
| Grade 0 | 5 (23%) | 3 (11%) | 27 (71%) | 23 (72%) |
| Grade 1 | 3 (14%) | 2 (7%) | 4 (11%) | 1 (3%) |
| Grade 2 | 11 (50%) | 17 (61%) | 4 (11%) | 5 (16%) |
| Grade 3 | 3 (14%) | 5 (18%) | 3 (8%) | 2 (6%) |
| Grade 4 | 0 (0%) | 1 (4%) | 0 (0%) | 1 (3%) |

**Table 6** below summarizes other blood component transfusions for the OLT and non-OLT populations. Notably, the proportion of patients requiring other blood components and the mean number of each of these components transfused were higher for the OLT population compared to the non-OLT population.

**Table 6 Transfusion Exposure to Other Blood Components by OLT Status**

| | OLT Population (N=51) | | Non-OLT Population (N=70) | |
|---|---|---|---|---|
| | INTERCEPT Plasma Group (N=22) | Conventional Plasma Group (N=29) | INTERCEPT Plasma Group (N=38) | Conventional Plasma Group (N=32) |
| **RBC (units)** | | | | |
| Any (%) | 22 (100%) | 29 (100%) | 21 (55.3%) | 16 (50.0%) |
| N | 22 | 29 | 21 | 16 |
| Mean (±SD) | 11.8 ±6.1 | 13.4 ±10.2 | 3.8 ±2.2 | 4.9 ±4.9 |
| Min, max | 2, 26 | 1, 37 | 1, 9 | 1, 18 |
| **Platelets (units)** | | | | |
| Any (%) | 18 (81.8%) | 24 (82.8%) | 16 (42.1%) | 9 (28.1%) |
| N | 18 | 24 | 16 | 9 |
| Mean (±SD) | 13.4 ±11.3 | 16.5 ±17.3 | 7.6 ±17.0 | 6.1 ±7.2 |
| Min, max | 1, 40 | 1, 80 | 1, 70 | 1, 19 |
| **Cryoprecipitate (units)** | | | | |
| Any (%) | 9 (40.9%) | 8 (27.6%) | 0 (0%) | 3 (9.4%) |
| N | 9 | 8 | 0 | 3 |
| Mean (±SD) | 15.8 ±8.4 | 13.8 ±5.2 | N/A | 9.7 ±8.5 |
| Min, max | 2, 30 | 10, 20 | N/A | 1, 18 |

A Phase 3 prospective, randomized, controlled, double-blind, study of therapeutic plasma exchange (TPE) with INTERCEPT Plasma or conventional FFP was conducted in 35 subjects (17 INTERCEPT Plasma and 18 conventional FFP) with acquired auto-immune thrombotic thrombocytopenic purpura (TTP). The suggested TPE plasma dose was a 1-1.5 plasma volume exchange (PVE) per day (40-60 mL/kg/day). The primary efficacy endpoint was the proportion of subjects achieving remission (defined as platelet count >150x$10^9$/L for 2 consecutive days without deterioration in neurologic status) within 30 days of first study TPE. 82.4% of subjects transfused with INTERCEPT Plasma and 88.9% of subjects transfused with conventional FFP achieved remission within 30 days. Median time to remission was 5.5 days for INTERCEPT Plasma and 6.0 days for conventional FFP. The adverse events, that were reported by ≥2 (>10%) patients in either treatment group and were assessed as probably or possibly related, are summarized in **Table 7**.

**Table 7 Related Adverse Events Occurring in ≥2 Subjects Treated with INTERCEPT or Conventional Plasma in Phase 3 TPE Study**

| Events | INTERCEPT Plasma Group (N=17) | Conventional Plasma Group (N=18) |
|---|---|---|
| Anemia | 3 (17.6%) | 0 |
| Nausea | 2 (11.8%) | 0 |
| Hypokalemia | 4 (23.5%) | 0 |
| Hypomagnesaemia | 2 (11.8%) | 0 |
| Paraesthesia | 2 (11.8%) | 1 (5.6%) |
| Dyspnea | 2 (11.8%) | 0 |
| Pruritus | 6 (35.3%) | 1 (5.6%) |
| Urticaria | 5 (29.4%) | 3 (16.7%) |
| Hypotension | 2 (11.8%) | 0 |

In addition, a total of 5 patients (all in the INTERCEPT plasma group) had reported adverse events that mapped to the Cardiac Disorders SOC, including chest pain/tightness, bradycardia, tachycardia, and cardiac arrest.

A retrospective no-interventional analysis was conducted. INTERCEPT Plasma and conventional Plasma were used in two time periods for therapeutic plasma exchange (TPE) in patients with idiopathic thrombocytopenic purpura (TTP) in two regional centers in France. A total of 13 patients who received conventional Plasma from 1998 to 2007, and 18 patients who received INTERCEPT Plasma from 2007 to 2013 were included in the analysis. The remission rates 30 days and 60 days after initiation of TPE were 11/18 (61.1%) and 14/18 (77.8%) for INTERCEPT Plasma cohort and 6/13 (46.2%) and 10/13 (76.9%) for the conventional Plasma cohort. Among patients who received RBC components, the mean number of RBC components used was 8.7 for INTERCEPT Plasma cohort and 12.7 for conventional Plasma cohort. The proportion of patients receiving treatment with Rituximab, an anti-CD20 monoclonal antibody, as an adjunctive therapy to TPE to treat TTP, was 38.9% in the INTERCEPT Plasma cohort and 23.1% in the conventional Plasma cohort. The potential safety signal in the cardiac system organ class was not detected in this retrospective analysis in TTP.

A retrospective two period cohort analysis was performed to compare the effectiveness of INTERCEPT Plasma with conventional Plasma in patients undergoing liver transplant [Cinqualbre et al. Transfusion 2015; 55:1710-1720]. Within 7 days of the transplantation, the median volume of plasma, and the median number of RBC component and platelet transfused were 2160 mL, 8.0, 8.0 $x10^{11}$ for INTERCEPT Plasma cohort and 1969 mL, 6.0, 4.0 $x10^{11}$ for conventional Plasma cohort. On a per transplant basis, the incidence of hepatic artery thrombosis was 2.3% for INTERCEPT plasma cohort and 5.0% for conventional plasma cohort, and the mortality within 7 days of transplantation was 4.6% for INTERCEPT plasma cohort and 3.7% for conventional plasma cohort.

## DEVICE PERFORMANCE

### Pathogen Inactivation

The INTERCEPT pathogen inactivation process has been validated to effectively inactivate a broad spectrum of enveloped and non-enveloped viruses, of Gram-positive and Gram-negative bacteria, spirochetes, parasites and leukocytes. Selection of pathogens was intended to provide evidence of the broad capabilities of the inactivation process. Pathogens selected represent those associated with transfusion transmission as well as model viruses of more general applicability. **Tables 8-11** summarize the pathogen inactivation data.

**Table 8 Viral Inactivation (Enveloped)**

| Virus | Log Reduction |
|---|---|
| HIV-1 IIIB, cell-associated | ≥6.2 |
| HIV-I IIIB, cell-free | ≥6.1 |
| DHBV[a] | 4.4 to 4.5 |
| BVDV (model for HCV)[a] | ≥4.5 |
| HTLV-I | ≥4.0 |
| HLTV-II | ≥4.7 |
| West Nile virus | ≥6.7 |
| SARS-Associated Coronavirus | ≥4.0 |
| Chikungunya virus (CHIKV) | ≥7.0 |
| Influenza A virus ($H_5N_1$ Avian Influenza) | ≥5.7 |

[a.] Inactivation of this pathogen in plasma volumes > 600 mL may be impacted by 0.75 log or less.

**Table 9 Viral Inactivation (Non-Enveloped)**

| Virus | Log Reduction |
|---|---|
| Parvovirus B19 | 1.8 |
| Bluetongue virus[a] | ≥4.0 |
| Adenovirus 5 | ≥5.6 |

[a.] Inactivation of this pathogen in plasma volumes > 600 mL may be impacted by 0.75 log or less.

**Table 10 Bacterial Inactivation**

| Bacteria | Log Reduction |
|---|---|
| *Klebsiella pneumoniae* | ≥6.7 |
| *Yersinia enterocolitica* | ≥6.6 |
| *Staphylococcus epidermidis* | ≥6.6 |
| *Treponema pallidum* | ≥5.4 |
| *Borrelia burgdorferi* | >8.8 |
| *Anaplasma phagocytophilum* (HGE agent) | ≥3.6 |

**Table 11 Parasite Inactivation**

| Protozoan Parasite | Log Reduction |
|---|---|
| *Plasmodium falciparum* | ≥5.9 |
| *Babesia microti* | ≥4.9 |
| *Trypanosoma cruzi* | >5.0 |

**Leukocyte Inactivation**

Using a limiting dilution assay (LDA), the INTERCEPT Blood System has shown a 4 $\log_{10}$ reduction of viable T-cells in plasma. In addition to the LDA methodology to detect the clonal expansion of viable T-cells, the frequency of adduct formation in leukocyte DNA was assessed; one amotosalen adduct per 89 base pairs demonstrates sufficient frequency to ensure inactivation of most genes. The results of these studies in plasma indicate effective inactivation of T-cells and leukocytes. The leukocyte inactivation studies were performed using frozen PBMCs that were thawed and cultured overnight, prior to adding to plasma for the inactivation studies.

**Table 12 In vitro studies that demonstrate effective inactivation of T-cells and leukocytes**

| Assay | Extent of Inactivation |
|---|---|
| **DNA modification** | Approximately one amotosalen adduct per 89 base pairs |
| **Limiting dilution assay** | 4 $\log_{10}$ reduction of viable T-cells |

**Retention of Coagulation Function**

The impact of the INTERCEPT Blood System for plasma on the in vitro functional activity of plasma components was evaluated using paired samples of INTERCEPT and control (conventional) plasma from whole blood (62 paired samples) or from apheresis plasma collections (62 paired samples). A paired control design was used in order to minimize the impact of inter-individual variation due to the variation of coagulation protein activity among healthy blood donors. For apheresis plasma, INTERCEPT Plasma and conventional Control plasma were frozen within 8 hours of donation (FFP). In vitro functions were measured after at least 30 days of frozen storage at ≤-18°C. For whole blood-derived plasma, three ABO-matched components from qualified, healthy volunteer donors were pooled, a portion of the pools was used to prepare conventional Control components. Approximately 585 mL of the pool was treated with the INTERCEPT Blood System for plasma within 22 hours of phlebotomy. The INTERCEPT and conventional control plasma components for each replicate were frozen simultaneously, within 24 hours of collection (PF 24) and frozen at ≤-18°C for a minimum of 30 days. No studies have been performed to assess the protein levels in cryosupernatant and cryoprecipitate prepared from INTERCEPT plasma.

The in vitro characteristics and coagulation functions for INTERCEPT-treated plasma and conventional plasma after ≥30 days of frozen storage are provided in **Table 13.**

**Table 13 In Vitro Characteristics and Coagulation Function of INTERCEPT Plasma and Conventional Plasma After ≥ 30 Days of Frozen Storage**

| | FFP | | PF24 | |
|---|---|---|---|---|
| | **INTERCEPT Plasma (n=62)** | **Conventional Plasma (n = 62)** | **INTERCEPT Plasma (n = 62)** | **Conventional Plasma (n = 62)** |
| **pH** | 7.38 ±0.05 | 7.38 ±0.04 | 7.38 ±0.03 | 7.41 ±0.05 |
| **Osmolality (mOsm/kg)** | 291 ±3 | 291 ±4 | 308 ±5 | 309 ±5 |
| **Prothrombin Time (s)** | 14.6 ±1.2 | 13.4 ±1.0 | 14.4 ±0.7 | 13.1 ±0.7 |
| **Activated Partial Thromboplastin Time (s)** | 28.5 ±3.1 | 24.8 ±2.5 | 27.0 ±1.7 | 24.2 ±1.4 |
| **Thrombin Generation ETP[a] (nM/min)** | 2086 ±303 | 2189 ±328 | 2010 ±233 | 2140 ±223 |
| **Fibrinogen (mg/dL; Pacific Hemostasis)[b]** | 2.28 ±0.49 | 3.00 ±0.62 | 2.43 ±0.37 | 2.91 ±0.36 |
| **Fibrinogen (mg/dL; Stago)[c]** | 2.49 ±0.53 | 2.89 ±0.59 | 2.49 ±0.33 | 2.81 ±0.35 |
| **Factor II (IU/mL)** | 0.89 ±0.12 | 1.01 ±0.13 | 0.93 ±0.09 | 1.03 ±0.10 |
| **Factor V (IU/mL)** | 0.86 ±0.17 | 0.90 ±0.16 | 0.82 ±0.11 | 0.91 ±0.13 |
| **Factor VII (IU/mL)** | 0.77 ±0.23 | 0.97 ±0.28 | 0.81 ±0.13 | 0.99 ±0.14 |
| **Factor VIII (IU/mL)** | 0.92 ±0.35 | 1.31 ±0.46 | 0.73 ±0.20 | 0.91 ±0.25 |
| **Factor IX (IU/mL)** | 1.00 ±0.25 | 1.27 ±0.29 | 0.93 ±0.17 | 1.12 ±0.19 |
| **Factor X (IU/mL)** | 0.94 ±0.19 | 1.05 ±0.22 | 0.83 ±0.13 | 0.95 ±0.14 |
| **Factor XI (IU/mL)** | 0.92 ±0.21 | 1.08 ±0.24 | 0.90 ±0.13 | 1.02 ±0.14 |
| **vWF activity ristocetin cofactor (IU/mL)** | 0.95 ±0.38[c] | 0.96 ±0.37[c] | 0.97 ±0.24 | 1.01 ±0.25 |
| **ADAMTS-13 (Antigenic µg/dL)** | 118 ±25 | 116 ±24 | 128.8 ±20.6 | 124.7 ±17.9 |
| **ADAMTS-13 (Functional, %)** | 90 ±16 | 97 ±16 | 87.5 ±11.0 | 93.4 ±10.3 |
| **Antithrombin III** | 0.83 ±0.09 | 0.88 ±0.10 | 0.93 ±0.06 | 0.98 ±0.06 |
| **Protein C (IU/mL)** | 0.79 ±0.18 | 0.92 ±0.19 | 0.86 ±0.09 | 0.95 ±0.10 |
| **Protein S (IU/mL)** | 0.97 ±0.23 | 1.02 ±0.25 | 1.04 ±0.10 | 1.08 ±0.11 |
| **Alpha-2-plasmin inhibitor (IU/mL)** | 0.76 ±0.07 | 0.91 ±0.07 | 0.85 ±0.07 | 1.00 ±0.08 |
| **Thrombin-Antithrombin Complexes (µg/L)[d]** | 2.5 ±0.4 | 2.5 ±0.5 | 2.3 ±0.8 | 2.4 ±0.8 |
| **Factor VIIa (ng/mL)** | <3.6 | <3.6 | <3.6 | <3.6 |
| **Non-activated partial thromboplastin time (s)** | 104.2 ±17.9 | 94.0 ±11.4 | 91.8 ±11.4 | 91.8 ±10.6 |
| **C3a (ng/mL)** | 44.2 ±45.9 | 107.4 ±59.4 | 50.4 ±38.4 | 134.7 ±57.0 |

*Results are expressed as either mean ± SD, min-max.

[a] Endogenous Thrombin Potential (5 pM tissue factor)

[b] The assay for the Stago results has a higher thrombin to plasma ratio than that of the Pacific Hemostasis assay.

[c] n=61

[d] For samples below the lower limit of quantitation (LOQ), the LOQ (2.0 µg/L) was used for calculation of mean and SD.

All INTERCEPT Plasma components demonstrated retention of thrombin generation and retained sufficient levels of fibrinogen for therapeutic hemostatic efficacy. None of the INTERCEPT Plasma components exhibited excessive activation of the coagulation cascade as assessed by FVIIa levels, TAT complexes, and NAPTT values. Of note, the majority of Test plasma components demonstrated a substantial decrease in C3a activity.

## INSTRUCTIONS FOR USE

- Do not use if: tamper-evident package has been opened; signs of deterioration are visible; fluid path closures are loose or not intact; cannulae are broken or there is no fluid in amotosalen solution container.
- Do not store above 25°C. Do not vent. Do not freeze. Protect the pack and tubing from sharp objects.
- Sets removed from the aluminum foil must be used within 24 hours.
- Record the Date Opened on the foil pouch label in space provided.
- Unused sets may be kept up to 20 days at room temperature in open aluminum foil by folding and securing open end of aluminum foil. Record the Use By date on the foil pouch label in space provided.
- Keep set in light-protective package until time of use. Protect from direct sunlight and strong UVA light source.
- Set is single-use only.

This process is designed to be a closed system. Treatment with INTERCEPT Blood System does not replace applicable standards for processing in open and closed systems. If there is a leak in the set during processing, plasma product must be discarded.

Do not use previously frozen samples as input material for INTERCEPT.

**Materials and Equipment**

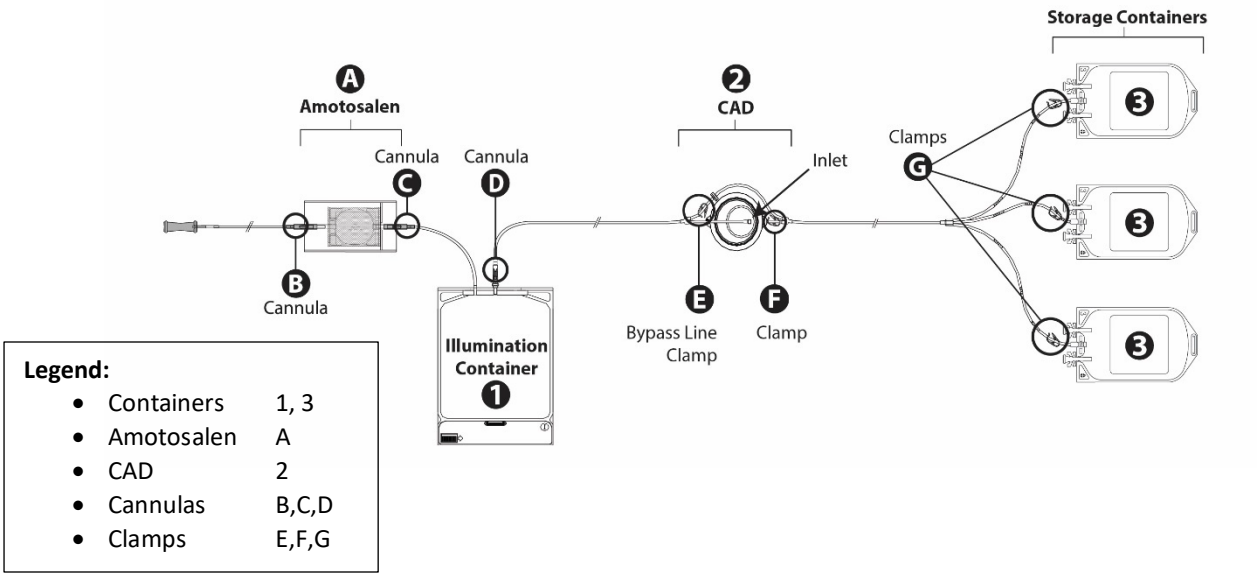
**Materials Provided**: One (1) INTERCEPT Plasma (P) Processing Set

**Equipment Available Separately**: INTERCEPT Illuminator

**Equipment Required <u>but not</u> Provided:** Sterile Connecting Device (SCD), Tube Sealer, Manual Tube Clamp (e.g., Hemostat)

Temperatures should be controlled to meet applicable regulations for plasma processing. Used and unused INTERCEPT processing sets should be discarded like any used blood containers, as biohazardous waste.

**Figure 1:** INTERCEPT Processing Set for Plasma Diagram




## Performing the INTERCEPT Treatment Process

Instructions refer to Figure 1 for labeling and identification of set components.

### I. Processing Plasma with the INTERCEPT® Blood System

Plasma products within the following ranges (**Table 1**) have been shown to be acceptable for use with this processing set.

**Table 1: Plasma Product Processing Range**

| Volume | RBC Content |
|---|---|
| 385-650 mL | $<4\times10^6$ RBC/mL |

### II. Amotosalen Addition

1. Remove set from package.
2. Weld tubing from plasma collection container to amotosalen container ( A ) tubing using SCD.
3. Disassemble set from organizer and remove rubber band. Save rubber band for assembly of CAD and storage containers during the illumination step.
4. If two plasma units will be produced by the INTERCEPT process, heat seal and remove one storage container ( 3 ).
5. Label storage containers ( 3 ) using appropriate donation identification. While labeling storage containers, separate them to ensure they do not adhere to one another.
6. Hang plasma container ensuring that the processing set containers/components do not come in contact with floor.
7. Break cannula ( C ) below amotosalen container ( A ) to let amotosalen flow into illumination container ( 1 ); visually verify amotosalen is present.
8. Break cannula ( B ) above amotosalen container ( A ) to let plasma flow through amotosalen container into illumination container ( 1 ).
9. Ensure that plasma drains completely from initial plasma container into illumination container ( 1 ).

10. Express air from the illumination container ( ❶ ) into the amotosalen container ( Ⓐ ).
11. When air is removed and plasma has fully drained back into the illumination container ( ❶ ), manually clamp tubing above illumination container. Mix illumination container thoroughly by gentle agitation to ensure complete mixing of amotosalen and plasma. (Figure 2)

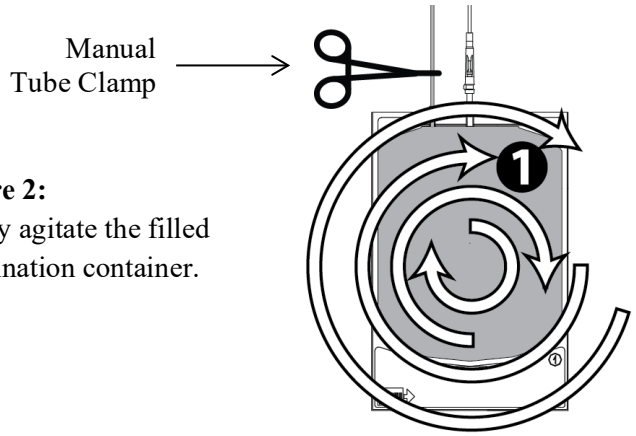
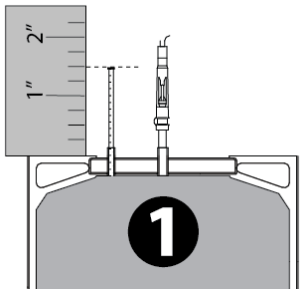



**Figure 2:**
Gently agitate the filled illumination container.

12. Open manual tube clamp and express a small amount of plasma and amotosalen mixture into tubing, filling at least 1.5 inches of tubing. Close manual tube clamp.
13. Seal tubing between illumination container ( ❶ ) and amotosalen container within the 1.5 inches of tubing (See Figure 3 below; also reference INTERCEPT Illuminator Operator's Manual for further details on loading the processing set into the Illuminator).
**<u>Warning</u>:** During illumination, tubing must be held within large compartment of illumination tray.

**Figure 3:**
Heat seal filled tubing within 1.5 inches.



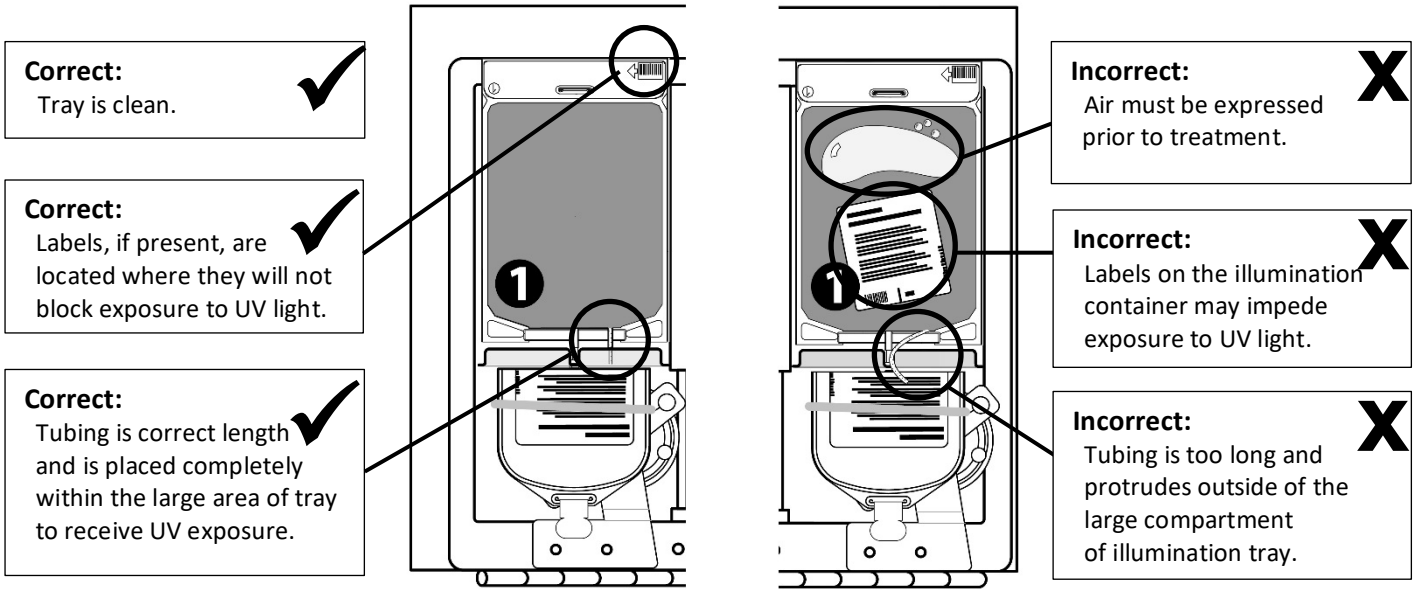

14. Remove and discard initial plasma container, amotosalen container ( Ⓐ ) and excess tubing.

## III. Illumination

Illuminate plasma.

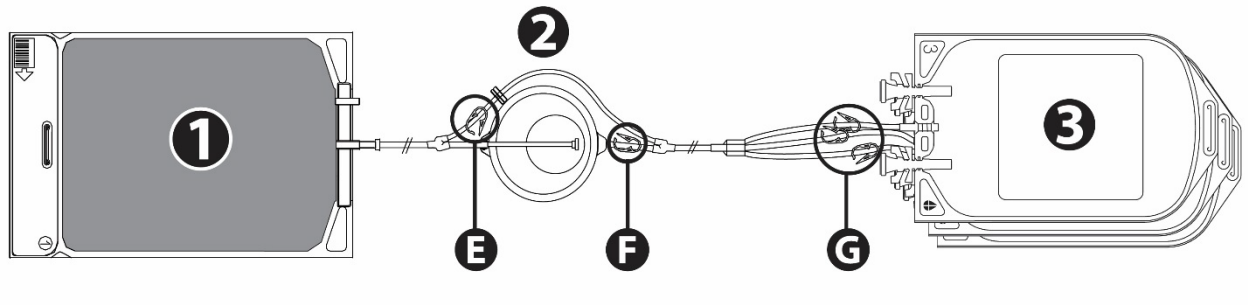
Refer to INTERCEPT Illuminator Operator's Manual for complete illumination instructions for use. **Warning:** All plasma, both in illumination container and tubing, must be within large compartment of illuminator tray in order for inactivation to occur. The process requires unimpeded light transmission through tray and illumination container with plasma. **No labels or other material should be on this area. Tray must be clean. Labels should be placed on illumination container flap only**. Illumination container should lay flat in order to ensure complete illumination.

**Figure 4:** The correct and incorrect way to load a processing set into the illuminator tray



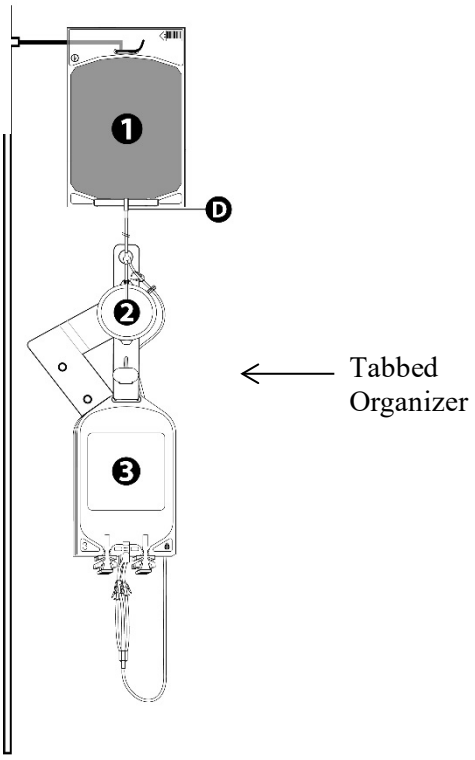
## IV. Processing with Compound Adsorption Device (CAD)

**Figure 5:** Clamps used during processing: ( Ⓔ ) bypass line clamp, ( Ⓕ ) clamp below CAD, ( Ⓖ ) clamps above storage containers ( ❸ ).




1. Hang illumination container ( ❶ ), allowing CAD ( ❷ ) to hang freely, with storage containers ( ❸ ) kept in the tabbed organizer to keep them in an inverted position. (See Figure 6)

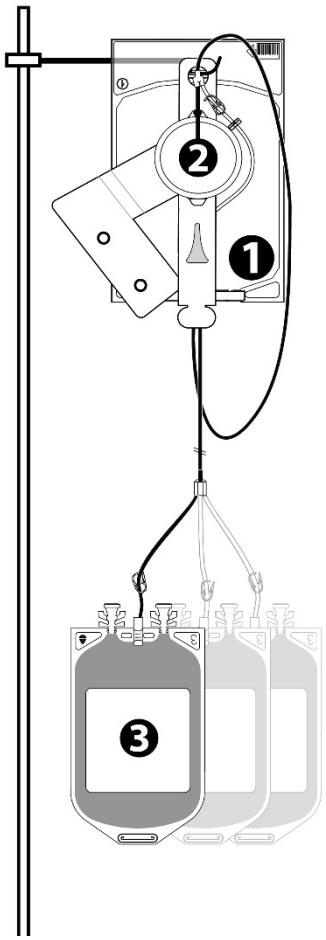
**Figure 6:**
How to hang the Illumination Container




2. Close clamp ( Ⓔ ) on bypass line; ensure all other clamps ( Ⓕ and Ⓖ ) are open.
3. Break cannula ( Ⓓ ) on illumination container and allow plasma to flow through CAD into storage containers ( ❸ ).
4. Once plasma has emptied from illumination container and passed through CAD, close clamp ( Ⓕ ) on tubing leading from the CAD.

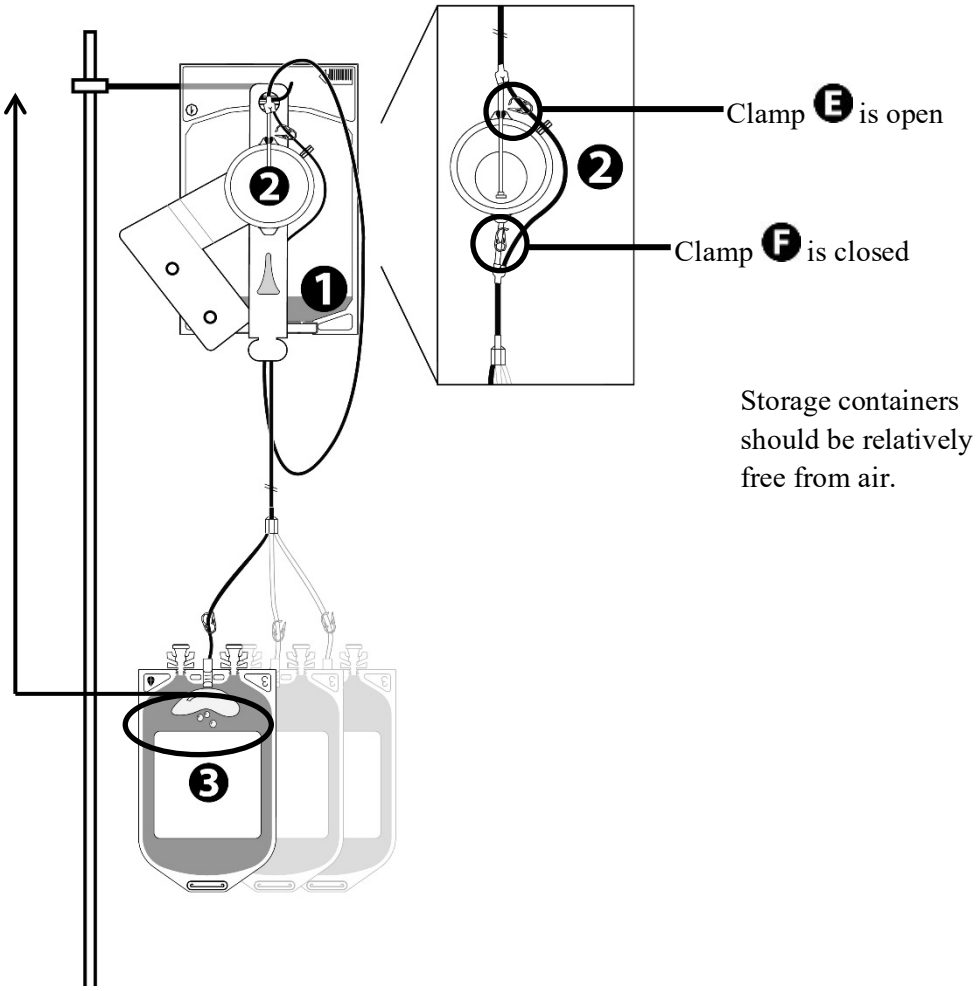
5. Hang CAD ( ❷ ) together with illumination container ( ❶ ). Remove storage containers ( ❸ ) from tabbed organizer on CAD and allow them to hang ports up. (Figure 7)

**Figure 7:**
Hanging the CAD & Illumination container



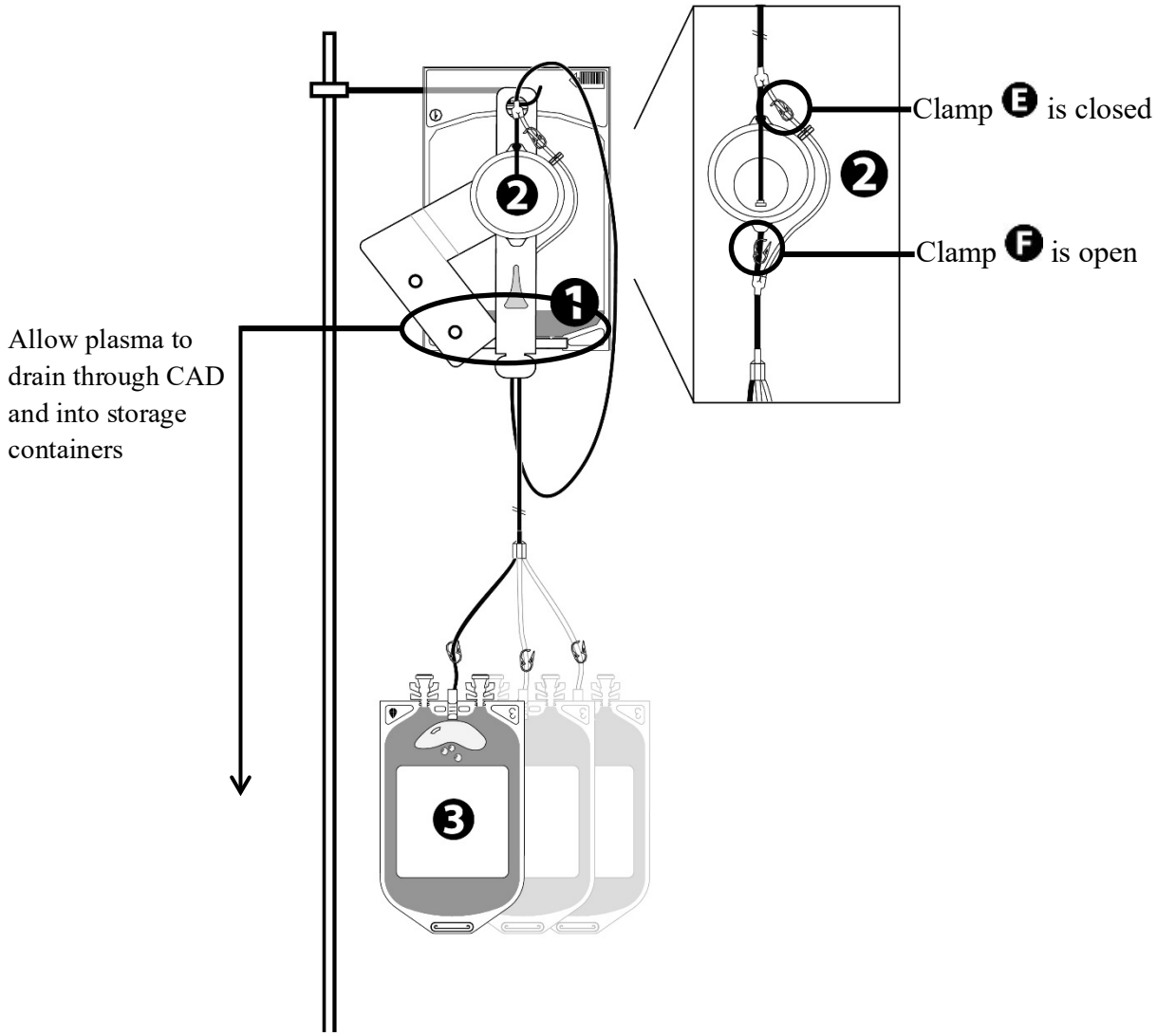

6. Open clamp ( ❺ ) on bypass line and completely express air from storage containers through bypass line into the illumination container ( ❶ ). (Figure 8) This may be done by expressing air from the first storage container into the second; then afterwards, expressing air from the second storage container into the third storage container.

**Figure 8:** Express air from storage containers into the illumination bag.




7. Close clamp ( E ) on the bypass line. (Figure 9)
8. Open clamp ( F ) below the CAD, allowing plasma to drain into storage containers ( 3 ). (Figure 9)

**Figure 9:** Drain Plasma through CAD




9. Close clamps ( G ) on storage containers.
10. Re-distribute plasma volume between storage containers, if necessary.
11. Disconnect storage containers ( 3 ) from set by heat-sealing, allowing sufficient tubing length for segments if appropriate.
12. Discard CAD, illumination container, and any excess tubing. The INTERCEPT treatment process is now complete.
13. Seal tubing as appropriate for making segments as needed.
14. Follow internal procedures for freezing plasma.

## STORAGE AND HANDLING

Processing Set

- Do not store processing set above 25°C. Do not vent. Do not freeze. Protect the processing pack and tubing from sharp objects.
- Unused processing sets may be kept up to 20 days at room temperature in open aluminum foil by folding and securing open end of aluminum foil.
- Sets removed from the aluminum foil must be used within 24 hours
- Keep set in light-protective package until time of use. Protect from direct sunlight and strong UVA light source.

INTERCEPT Plasma

- Following processing, INTERCEPT Plasma should be stored in the containers provided in the processing sets at ≤-18°C (-0.4°F) for up to 12 months from the time of collection.
- Following frozen storage at or below -18°C (-0.4°F), INTERCEPT Plasma may be thawed according to current license requirements and infused within 4 hours when kept at 20° to 25°C (68° to 77°F), or infused within 24 hours if held at 1° to 6°C (33.8° to 42.8°F), after which the component may be discarded.
- Alternatively, after 24 hours post-thaw storage at 1° to 6°C (33.8° to 42.8°F), INTERCEPT Plasma may be relabeled as Thawed Plasma, stored at 1° to 6°C (33.8° to 42.8°F) and used for up to 5 days from the original thaw date. Sterility studies were not performed after a 5-day storage period.
- Before use, INTERCEPT Plasma should be thawed according to current license requirements.
- Stability of thawed INTERCEPT fresh frozen plasma (FFP) and conventional plasma frozen within 24 hours of collection (PF24) over 5 days of storage at 1˚C – 6˚C is provided in Table 2 and 3 below.

**Table 2: Stability of Thawed INTERCEPT FFP and PF24 Over 5 Days of Storage at 1˚C – 6˚C (mean n=6)**

| Storage Condition | | pH | Osmol[a] | PT | aPTT | TGT | Fibrinogen | FII | FV | FVII | FVIII | FIX | FX |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | mOsm/kg | seconds | | nM/min | mg/dL | IU/mL | | | | | |
| FFP | Day 0 | 7.38 | 296 | 14.5 | 30.0 | 2104 | 216 | 0.92 | 0.80 | 0.86 | 0.58 | 0.75 | 0.87 |
| | Day 1 | 7.39 | 297 | 14.7 | 32.3 | 2051 | 213 | 0.92 | 0.77 | 0.84 | 0.43 | 0.73 | 0.87 |
| | Day 2 | 7.39 | 296 | 14.9 | 33.1 | 2034 | 220 | 0.93 | 0.78 | 0.86 | 0.35 | 0.70 | 0.87 |
| | Day 3 | 7.42 | 297 | 14.9 | 33.1 | 1969 | 224 | 0.92 | 0.76 | 0.85 | 0.34 | 0.71 | 0.87 |
| | Day 4 | 7.42 | 296 | 15.1 | 33.6 | 1972 | 212 | 0.93 | 0.78 | 0.88 | 0.32 | 0.71 | 0.88 |
| | Day 5 | 7.43 | 296 | 15.2 | 33.7 | 1882 | 215 | 0.94 | 0.73 | 0.88 | 0.33 | 0.69 | 0.88 |
| | Day 5 Retention of Day 0 | 101% | 100% | 104% | 113% | 90% | 100% | 101% | 92% | 102% | 57% | 92% | 100% |
| PF24 | Day 0 | 7.39 | 308 | 14.5 | 27.4 | 2070 | 232 | 0.89 | 0.83 | 0.76 | 0.65 | 0.81 | 0.85 |
| | Day 1 | 7.40 | 309 | 14.9 | 28.8 | 2051 | 231 | 0.89 | 0.75 | 0.76 | 0.46 | 0.78 | 0.84 |
| | Day 2 | 7.41 | 310 | 15.2 | 29.4 | 2060 | 244 | 0.88 | 0.74 | 0.77 | 0.41 | 0.76 | 0.83 |
| | Day 3 | 7.43 | 311 | 15.4 | 29.5 | 2047 | 244 | 0.90 | 0.70 | 0.77 | 0.40 | 0.75 | 0.83 |
| | Day 4 | 7.43 | 311 | 15.6 | 30.1 | 2038 | 237 | 0.89 | 0.68 | 0.77 | 0.37 | 0.74 | 0.83 |
| | Day 5 | 7.43 | 313 | 15.8 | 30.1 | 1927 | 229 | 0.88 | 0.68 | 0.77 | 0.39 | 0.77 | 0.83 |
| | Day 5 Retention of Day 0 | 101% | 102% | 109% | 110% | 93% | 100% | 99% | 81% | 101% | 60% | 96% | 98% |

**Table 3: Stability of Thawed INTERCEPT FFP and PF24 Over 5 Days of Storage at 1˚C – 6˚C (mean n=6)**

| Storage Condition | | FXI | vWF | ADAMTS-13 | | AT III | Protein C | Protein S | α-2 PI | TAT | FVIIa | NAPTT | C3a |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | IU/mL | | Antigen (µg/mL) | Function (%) | IU/mL | | | | µg/L | ng/mL | seconds | ng/mL |
| FFP | Day 0 | 0.79 | 0.88 | 1.21 | 97 | 0.89 | 0.79 | 0.91 | 0.90 | 2.1 | <3.6 | 117 | 64 |
| | Day 1 | 0.77 | 0.83 | 1.19 | 95 | 0.88 | 0.79 | 0.90 | 0.91 | 2.2 | <3.6 | 112 | 75 |
| | Day 2 | 0.79 | 0.89 | 1.19 | 91 | 0.88 | 0.82 | 0.87 | 0.85 | 2.2 | <3.6 | 143 | 138 |
| | Day 3 | 0.76 | 0.80 | 1.17 | 89 | 0.87 | 0.81 | 0.86 | 0.90 | 2.2 | <3.6 | 134 | 156 |
| | Day 4 | 0.77 | 0.84 | 1.17 | 93 | 0.86 | 0.79 | 0.86 | 0.86 | 2.2 | <3.6 | 131 | 158 |
| | Day 5 | 0.76 | 0.82 | 1.21 | 95 | 0.86 | 0.79 | 0.84 | 0.91 | 2.1 | <3.6 | 132 | 162 |
| | Day 5 Retention of Day 0 | 96% | 92% | 101% | 98% | 97% | 101% | 92% | 102% | 99% | 100% | 112% | 232% |
| PF24 | Day 0 | 0.84 | 0.98 | 1.07 | 96 | 0.95 | 0.78 | 0.85 | 0.92 | 2.4 | 4.1 | 93 | 46 |
| | Day 1 | 0.84 | 0.94 | 1.07 | 98 | 0.93 | 0.72 | 0.83 | 0.90 | 2.3 | 3.7 | 112 | 60 |
| | Day 2 | 0.84 | 0.97 | 1.02 | 95 | 0.93 | 0.71 | 0.82 | 0.95 | 2.3 | <3.6 | 109 | 64 |
| | Day 3 | 0.84 | 0.92 | 1.01 | 94 | 0.92 | 0.76 | 0.79 | 0.85 | 2.3 | <3.6 | 125 | 69 |
| | Day 4 | 0.86 | 1.05 | 0.99 | 91 | 0.92 | 0.81 | 0.77 | 0.90 | 2.3 | 3.8 | 126 | 91 |
| | Day 5 | 0.83 | 0.96 | 0.99 | 94 | 0.89 | 0.73 | 0.71 | 0.95 | 2.2 | <3.6 | 121 | 91 |
| | Day 5 Retention of Day 0 | 99% | 97% | 93% | 98% | 94% | 94% | 83% | 104% | 96% | 90% | 131% | 206% |

[a.] Osmol = Osmolality, PT = prothrombin time, aPTT = activated partial thromboplastin time, TGT = thrombin generation time (endogenous thrombin potential), ATIII = antithrombin III, α-2 PI = alpha-2-plasmin inhibitor, TAT = thrombin-antithrombin complexes, NAPTT = non-activated partial thromboplastin time.

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