

INTERCEPT BLOOD SYSTEM FOR PLASMA PHOTOCHEMICAL TREATMENT (PCT) OF PLASMA USING AMOTOSALEN HYDROCHLORIDE AND UVA LIGHT

The INTERCEPT Blood System for plasma is a Class III medical device that is intended for the *ex vivo* preparation and storage of pathogen inactivated plasma intended for transfusion. The INTERCEPT Blood System for plasma is used to inactivate bacteria, viruses, parasites, and leukocytes. This process for treatment of plasma products is intended to reduce the risk of transfusion-associated transmission of viruses, bacteria, and parasites, and may also reduce the risk of adverse effects due to transfusion of contaminating donor leukocytes. The device uses amotosalen HCl (a photoactive compound) and long-wavelength ultraviolet (UVA) illumination to photochemically treat plasma.

The INTERCEPT Blood System for plasma is a sterile, non-pyrogenic fluid path integrated disposable plastic processing set. The set consists of 15 mL of amotosalen solution in a plastic container, a plastic illumination container, a compound adsorption device, and three plastic storage containers, all sequentially integrated. The single-use set is manufactured from inert polyolefin PL 2411, PL 2410, and PL 269 plastics compatible with plasma.

Plasma collected by apheresis or prepared from whole blood (containing $<4 \times 10^6$ RBC/mL) is connected to the processing set using a sterile-connect device. Plasma to be treated is in a volume range of 385 mL to 650 mL, including anticoagulant and prior to addition of amotosalen. Plasma flows through the amotosalen container and into the illumination container. Prior to illumination the nominal concentration of amotosalen in plasma is 150 μ M. Illumination is provided by the INTERCEPT Illuminator. This ancillary Class I device is microprocessor controlled and is designed to deliver a target UVA treatment of 3 Joules/cm².

The INTERCEPT Plasma processing set includes a compound adsorption device (CAD), which significantly reduces the level of residual amotosalen in plasma prior to storage. The CAD consists of ground adsorbent beads and an ultra-high molecular weight polyethylene binder. The illuminated plasma flows by gravity through the CAD and into the storage containers. INTERCEPT Plasma is stored according to requirements for frozen plasma until released for transfusion.

Amotosalen Hydrochloride

Amotosalen HCl is a synthetic psoralen compound that reversibly intercalates into the helical regions of DNA and RNA. Upon illumination with UVA light at 320 to 400 nm, amotosalen forms covalent bonds with pyrimidine bases in nucleic acids. The genomes of pathogens and leukocytes cross-linked in this manner can no longer function or replicate. No pharmacological effect of residual amotosalen is intended.

INTERCEPT Plasma

Indications

INTERCEPT Plasma is indicated for support of patients requiring plasma transfusions or therapeutic plasma exchange, according to clinical practice guidelines. Clinical trials in patients have demonstrated that plasma treated with the INTERCEPT Blood System was well tolerated and retained therapeutic efficacy comparable to conventional fresh frozen plasma. INTERCEPT Plasma may be used to treat single coagulation factor or antithrombotic protein deficiencies for which no concentrates are available, as well as multiple coagulation factor and antithrombotic protein deficiencies. INTERCEPT Plasma may also be used for plasma exchange for thrombotic thrombocytopenic purpura (TTP). INTERCEPT treatment may be used as an alternative to gamma irradiation for prevention of transfusion-associated graft-versus-host disease (TA-GVHD). Plasma photochemically treated with the INTERCEPT Blood System may be stored and transfused according to standard methods for frozen plasma.

Pathogen Inactivation

In non-clinical studies, the INTERCEPT Blood System for plasma demonstrated inactivation of viruses, bacteria, parasites, and donor leukocytes.

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Viruses

The INTERCEPT Blood System for plasma has been shown to inactivate a variety of viruses. Viruses shown to be inactivated are listed below:

| Viruses Tested Using the INTERCEPT Blood System for Plasma | Extent of Inactivation* (log ₁₀ reduction) |
|---|--|
| Enveloped Viruses | |
| HIV-1 (cell-associated)** | >6.7 |
| HIV-1 (cell-free) | >6.8 |
| HBV (strain MS-2) | >4.5 |
| HCV (strain Hutchison) | >4.5 |
| HTLV-I (Human T-cell Lymphotropic Virus)** | ≥4.5 |
| HTLV-II (Human T-cell Lymphotropic Virus)** | >5.7 |
| WNV (West Nile Virus) | ≥6.8 |
| SARS-CoV (Human Corona Virus) | ≥5.5 |
| BVDV (Bovine Viral Diarrhea Virus, model virus for human HCV) | ≥6.0 |
| DHBV (Duck Hepatitis B Virus, model virus for human HBV) | 4.4 - 4.5 |
| Chikungunya virus | ≥7.6 |
| Influenza A H5N1 virus (Avian Influenza) | >5.7 |
| Non-Enveloped Viruses | |
| BTV (Bluetongue Virus) | 5.1 |
| Human Adenovirus-5 | ≥6.9 |
| Parvo (Parvovirus B19) | 1.8 |

* “>” refers to inactivation below the limit of detection of the assay

“≥” refers to inactivation at or below the limit of detection of the assay

** intracellular inoculum

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Bacteria

Although bacterial contamination is not common for plasma, studies performed using representative gram-negative and gram-positive organisms demonstrated efficacy of the INTERCEPT process for bacterial inactivation. In addition, studies demonstrated inactivation of two spirochete bacteria, *Treponema pallidum*, for which blood is currently tested, and *Borrelia burgdorferi*. Studies were carried out with these organisms because they are known to be asymptotically present in the blood during chronic infections. Bacteria, which have been shown to be inactivated, are listed below:

| Bacterial Species Tested Using the INTERCEPT Blood System for Plasma | Extent of Inactivation* (log₁₀ reduction) |
|---|---|
| Gram-Negative Bacteria | |
| <i>Klebsiella pneumoniae</i> | ≥7.4 |
| <i>Yersinia enterocolitica</i> | >7.3 |
| <i>Anaplasma phagocytophilum</i> (HGE agent) | >4.2 |
| Gram-Positive Bacteria | |
| <i>Staphylococcus epidermidis</i> | >7.3 |
| Spirochete Bacteria | |
| <i>Treponema pallidum</i> (syphilis) ** | >5.9 |
| <i>Borrelia burgdorferi</i> (Lyme disease) | >10.6 |

* “>” refers to inactivation below the limit of detection of the assay

“≥” refers to inactivation at or below the limit of detection of the assay

** intracellular inoculum

Parasites

The INTERCEPT Blood System for plasma has been shown to inactivate contaminating parasites. Various *in vitro* studies have demonstrated inhibition of parasite replication following photochemical treatment. The results of these studies are summarized below:

| Parasites Tested Using the INTERCEPT Blood System for Plasma | Extent of Inactivation* (log₁₀ reduction) |
|---|---|
| <i>Plasmodium falciparum</i> ** (malaria) | ≥6.9 |
| <i>Trypanosoma cruzi</i> (Chagas’ disease) | >5.0 |
| <i>Babesia microti</i> (babesiosis) | >5.3 |

* “>” refers to inactivation below the limit of detection of the assay

“≥” refers to inactivation at or below the limit of detection of the assay

** intracellular

Leukocytes

Because plasma is frozen under conditions that do not promote preservation of intact cells, TA-GVHD caused by leukocytes is of significantly less concern in frozen plasma than in other blood components. However, T-cells may retain functionality after freezing and TA-GVHD has been reported to result from transfusions of conventional plasma not treated with gamma irradiation. Two assays were used to evaluate inactivation of leukocytes: frequency of adduct formation in leukocyte DNA and limiting dilution assay to detect clonal expansion of viable T-cells. The results of these studies in plasma indicate effective inactivation of T-cells and leukocytes (see table below). The adduct frequency demonstrated is sufficient to ensure inactivation of most individual genes.

| Assay | Extent of Inactivation |
|-------------------------|---|
| DNA modification | Approximately one amotosalen adduct per 89 base pairs |
| Limiting dilution assay | $\geq 6.1 \log_{10}$ reduction of viable T-cells |

Clinical Use of INTERCEPT Plasma**Congenital Coagulation Factor Deficiencies**

A single-arm, open-label clinical trial was conducted to evaluate efficacy and safety of INTERCEPT Plasma in patients with congenital deficiencies of coagulation factors I (fibrinogen), II, V, VII, X, XI, and XIII as well as protein C. The results of this 34 patient trial demonstrated that, for most factors evaluated, INTERCEPT Plasma provided coagulation factor recovery and pharmacokinetics comparable to conventional plasma, as reported in the literature, and PT and aPTT responses sufficient for adequate hemostasis. The respective terminal half-lives and clearances for patients with deficiencies of coagulation factors V, VII, X, XI and protein C were comparable to literature references. Terminal half-life results for factors I, II and XIII were low relative to the medical literature. These results may have been due to the very small number of patients evaluated (n of 1-3 for each factor) and differences in the methods of analysis. Hemostasis was achieved for all therapeutic transfusions and INTERCEPT Plasma was well-tolerated.

Acquired Coagulation Factor Deficiencies

A randomized, controlled, double-blinded clinical trial was conducted to evaluate efficacy and safety of INTERCEPT Plasma compared to conventional fresh frozen plasma in patients with acquired coagulation deficiencies. The results of this 121 patient clinical trial demonstrated the efficacy of INTERCEPT Plasma for treatment of coagulopathy resulting from chronic liver disease, including a significant proportion of patients undergoing orthotopic liver transplantation. Maintenance of adequate hemostasis during orthotopic liver transplantation and other invasive procedures was similar between treatment groups. There were no significant differences in adverse events, including

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hepatic artery thrombosis, deaths, or transfusion reactions between patients treated with INTERCEPT Plasma and those treated with conventional fresh frozen plasma.

Therapeutic Plasma Exchange

A randomized, controlled, double-blinded clinical trial was conducted to evaluate efficacy and safety of INTERCEPT Plasma compared to conventional fresh frozen plasma for therapeutic plasma exchange in patients with thrombotic thrombocytopenic purpura (TTP). The results of this 35 patient clinical trial demonstrated that therapeutic response to plasma exchange with INTERCEPT Plasma was not different than response to conventional fresh frozen plasma in terms of both rates of TTP remission and relapse, and time to remission and relapse. As patients received daily plasma volume exchanges over one or two 35-day cycles of exchange, the exposure to INTERCEPT Plasma in this study represents a 10-fold higher exposure when compared to transfusion studies where patients were treated for congenital or acquired coagulopathies. The safety profile of INTERCEPT Plasma in this setting was similar to conventional fresh frozen plasma. No evidence of antibody formation to amotosalen neoantigens was observed.

Contraindications

Use of INTERCEPT Plasma is contraindicated in patients with a history of allergic response to amotosalen or psoralens.

Notes to Physicians

Neonatal patients who require plasma transfusion during phototherapy for treatment of hyperbilirubinemia should be treated with phototherapy devices that do not emit light less than 425 nm to avoid the theoretical potentiation of an interaction between UVA light and amotosalen, which may result in erythema.

While laboratory studies of photochemical treatment processing with the INTERCEPT Blood System for plasma have shown significant reduction in the infectivity of certain viruses, bacteria and parasites, no pathogen inactivation process has been shown to eliminate the infectivity of all pathogens. This pathogen inactivation process is designed as a closed system. Pathogen inactivation does not replace applicable standards that apply to processing in closed and open systems.

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