INTERCEPT **Plasma**

TECHNICAL DATA SHEET

INTERCEPT BLOOD SYSTEM

Contents

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 $<4\times10^6$ 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 µM. 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/cm^2.

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 polyethelene 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). INTERCEPT treatment may be used in place of CMV testing and leukoreduction for prevention of transfusion-transmitted CMV infection. Plasma photochemically treated with the INTERCEPT Blood System may be stored and transfused according to standard methods for frozen plasma.

Pathogen Inactivation Claims

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

Viruses

The INTERCEPT Blood System for plasma has been shown to inactivate a variety of viruses. Viruses shown to be inactivated are listed in Table 1.

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 Hutchinson)	>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.

Table 1. Inactivation Claims - Viruses

Bacterial Species Tested Using the INTERCEPT Blood System for Plasma	Extent of Inactivation* (log_{10} reduction)
Gram-Negative Bacteria	
Klebsiella pneumoniae	≥7.4
Yersinia enterocolitica	>7.3
Anaplasma phagocytophilum (HGE agent)	>4.2
Gram-Positive Bacteria	
Staphylococcus epidermidis	>7.3
Spirochete Bacteria	
Treponema pallidum (syphilis)**	>5.9
Borrelia burgdorferi (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.

Table 2. Inactivation Claims - Bacteria

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 asymptomatically present in the blood during chronic infections. Bacteria, which have been shown to be inactivated, are listed in Table 2.

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 in Table 3.

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 4). The adduct frequency demonstrated is sufficient to ensure inactivation of most individual genes.

Parasites Tested Using the INTERCEPT Blood System for Plasma	Extent of Inactivation* (log_{10} reduction)
*Plasmodium falciparum*** (malaria)	≥6.9
Trypanosoma cruzi (Chagas' disease)	>5.0
Babesia microti (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 inoculum.

Table 3. Inactivation Claims - Parasites

Assay	Extent of Inactivation
DNA modification	Approximately one amotosalen adduct per 89 base pairs
Limiting dilution assay	≥6.1 log10 reduction of viable T-cells

Table 4. Inactivation Claims - Leukocytes

Clinical Use of INTERCEPT Plasma

Tolerability and Safety in Healthy Volunteers

The tolerability, safety, and amotosalen clearance after transfusion of INTERCEPT Blood System processed plasma to healthy subjects was evaluated. This was an open label, step-wise ascending dose escalation (100, 200, 400, and 1000 mL) crossover trial; 15 healthy volunteers received autologous plasma processed with the INTERCEPT Blood System or untreated Fresh Frozen Plasma (FFP). For patients receiving the processed plasma, the peak concentration of amotosalen at 1,000 mL was 11.5 ng/mL with a mean concentration at 16-24 hours of 0.52 ±0.10 ng/mL and a terminal half-life of 138.5 minutes. Comparison of coagulation factor activity following transfusion revealed no differences between transfusion of processed plasma versus FFP. No clinically relevant adverse events were observed in subjects exposed to INTERCEPT processed plasma at doses as high as 1,000 mL.

Transfusion in Healthy Volunteers After Warfarin Sodium Anticoagulation

The transfusion of INTERCEPT processed plasma to healthy subjects anticoagulated with warfarin sodium was evaluated. The effect of processing plasma with the INTERCEPT Blood System on vitamin K dependent coagulation factors was assessed in a prospective randomized, single-blind crossover, pharmacokinetics and safety trial in 27 healthy volunteers, receiving autologous plasma. Autologous plasma samples, obtained by apheresis, were split and then either processed or frozen as FFP. Following a four day regimen (7.5 mg/day) of warfarin sodium to reduce vitamin K dependent coagulation factors, subjects received approximately 1,000 mL of processed plasma or FFP in random order. Blood samples to assess vitamin K dependent factor levels were drawn over 24 hours following transfusion. After a two-week washout period, subjects received the second transfusion with contralateral product following an identical warfarin regimen. No statistically significant differences for clearance, recovery, half-life, mean residence time, or volume of distribution for Factor VII were observed between processed plasma and FFP. Additionally, no differences in recoveries of other vitamin K dependent factors (FII, FIX, and FX) were observed. No clinically relevant adverse events were observed in subjects anticoagulated with warfarin sodium and transfused with 1,000 mL of INTERCEPT Blood System processed 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 hepatic artery thrombosis, deaths, or transfusion reactions between patients treated with INTERCEPT Plasma and those treated with conventional fresh frozen plasma.

Multiple Coagulation Factor Deficiencies

A randomized, prospective, double-blind trial was conducted to evaluate efficacy and safety of INTERCEPT Plasma compared to conventional fresh frozen plasma in patients with multiple coagulation factor deficiencies. This cohort of 13 patients (6 INTERCEPT processed plasma and 7 untreated FFP) primarily included patients with liver disease. Patients received a single transfusion of up to 2 liters of either INTERCEPT processed plasma or untreated FFP. There was no difference in the response of the prothrombin time (PT) or activated partial thromboplastin time (aPTT) at any time point after transfusion between INTERCEPT Blood System processed plasma and untreated FFP. No unexpected adverse events were observed in patients exposed to INTERCEPT Blood System processed plasma (604 to 1589 mL). One serious adverse event of pulmonary edema related to transfusion of 1589 mL of INTERCEPT processed plasma was reported. This event resolved with diuretic therapy.

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.

Therapeutic Plasma Exchange – Post Marketing Study

The post marketing experience with transfusion of INTERCEPT Blood System processed plasma to patients with TTP was evaluated in two specialized treatment centers using a two-period sequential cohort design. In a retrospective study examining patients with TTP (N=31), 61% of patients treated with INTERCEPT Blood System processed plasma and 46% of patients treated with FFP achieved remission within 30 days ($p = 0.570$). Also, 78% of patients treated with INTERCEPT Blood System processed plasma achieved remission within 60 days, with a median time to remission of 15 days. The mean total exposure to both INTERCEPT Blood System processed and untreated plasma was comparable (32 L and 28 L respectively). No significant differences in related adverse events or related serious adverse events were observed between groups. The incidence of treatment emergent adverse events in the Cardiac SOC, including electrocardiographic abnormalities, was not increased for patients treated with INTERCEPT processed plasma. The incidence of treatment emergent serious adverse events in the Cardiac SOC was similar for patients treated with processed plasma and conventional plasma, respectively (cardiac arrest 1 vs 2; arrhythmia 0 vs 1; bradycardia 0 vs 1; nodal rhythm 0 versus 1; ventricular fibrillation 0 vs 1; acute coronary syndrome 1 vs 0; and angina pectoris 1 vs 0).

Support of Liver Transplantation – Post Marketing Study

The post marketing experience with transfusion of INTERCEPT Blood System processed plasma to patients undergoing liver transplant was assessed in a regional liver transplant center using a two-period sequential cohort design. In a retrospective study of patients undergoing liver transplant secondary to acute or chronic liver disease, 335 liver transplants were performed in 328 patients with plasma transfusion support. The study examined blood product consumption, treatment differences in FFP volume transfused, total platelet dose transfused, and RBC components transfused from the time of surgery through postoperative day 7, as well as safety outcomes, such as hepatic artery thrombosis (HAT) within nine days of transplant and mortality within seven days of transplant. One hundred seventy four transplants in 171 patients were supported with INTERCEPT Blood System processed plasma, and 161 transplants in 157 patients were supported with conventional FFP. The median volume of INTERCEPT Blood System processed plasma (2,160 mL) required for transfusion support was not different from that of conventional plasma (1,969 mL). Similarly, the number of RBC and platelet components transfused to all patients supported with plasma was not different between the processed and conventional plasma cohorts. Overall, no clinically relevant differences were detected between the treatment groups in efficacy or safety measures. The only adverse events monitored in this study were hepatic artery thrombosis (HAT) up to 9 days after initial exposure to processed plasma, and mortality. The incidence of HAT was not increased after exposure to INTERCEPT Blood System processed plasma compared to conventional plasma, (2.3% vs 5.0% respectively). Likewise, mortality was similar for processed and conventional plasma, (4.6% vs 3.7%).

Hemovigilance – Post Market Experience

An observational, prospective, uncontrolled,hemovigilance study conducted by Cerus evaluated 57,171 INTERCEPT Blood System processed 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 Blood System processed plasma. Thirty-two subjects (0.3%) experienced an ATR following 41 separate transfusion episodes (0.2%), including five subjects (0.05%) who experienced an ATR following more than one transfusion episode. The most common signs/symptoms of those ATRs 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.

France

During the 3 year period after implementation of INTERCEPT Blood System processed plasma for routine use in France, the rates of acute transfusion reactions (ATR) for INTERCEPT plasma have been comparable to those of other plasma components, i.e., approximately 0.4 events per 1,000 plasma components.

Contraindications

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

Notes to Physicians

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. INTERCEPT plasma components should not be prescribed to neonatal patients treated with phototherapy devices that emit a peak energy wavelength less than 425 nm, and/or have a lower bound of the emission bandwidth <375 nm, due to the risk of erythema resulting from potential interaction between ultraviolet light (below 400 nm) and residual amotosalen.

CERUS

INTERCEPT REGULATORY APPROVALS

Brazil (ANVISA)
2015 (platelets and plasma)

United States (FDA)
2014 (platelets and plasma)

Mexico (COFEPRIS)
2014 (platelets and plasma)

Singapore (HSA)
2014 (platelets)

Switzerland (Swissmedic)
2009 (platelets), 2010 (plasma)

Germany (PEI)
2007* (platelets), 2011* (plasma)

France (ANSM)
2003 (platelets), 2006 (plasma)

CE mark, Class III
2002 (platelets), 2006 (plasma)

* First blood center marketing authorization approved.

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Use of INTERCEPT Plasma or Platelets is contraindicated in patients with a history of allergic response to amotosalen or psoralens. Consult instructions for use for indications, contraindications, warnings, and precautions.

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