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INTERCEPT™ Blood System for Plasma

Technical Data Sheet

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The INTERCEPT Blood System for Plasma consists of the INTERCEPT Processing Set for Plasma (Class III) and the INTERCEPT™ Illuminator INT200 (Class IIb) medical devices and is intended for the ex vivo preparation and storage of pathogen inactivated plasma intended for transfusion. The system is used to inactivate a broad spectrum of bacteria, viruses, parasites as well as contaminating donor leukocytes in plasma components. The device uses amotosalen (a photoactive compound) and low energy ultraviolet (UVA) illumination to photochemically treat plasma.

INTERCEPT Processing Sets for Plasma

The INTERCEPT processing set for plasma is a sterile, non-pyrogenic fluid path, single use, disposable plastic treatment set.

Each INTERCEPT Processing Set includes amotosalen solution in a polypropylene plastic container, an ethylene-vinyl acetate (EVA) blend plastic illumination container, a flow through Compound Adsorption Device (CAD) with ground adsorbent beads and a polyethylene binder in a sintered disk within an EVA/wax blend housing and three EVA blend plastic plasma storage containers.

Plasma flows through the amotosalen container and into the illumination container. Prior to illumination the nominal concentration of amotosalen in plasma is 150 µM. Photoactivation is provided by the INTERCEPT Illuminator.

Residual amotosalen and free photoproducts are reduced to low levels by exposure to a compound adsorption device before transfer of the treated plasma to the final storage container. INTERCEPT Plasma is stored according to requirements for frozen plasma until released for transfusion.

Amotosalen

Amotosalen is a synthetic psoralen compound that reversibly intercalates into the helical regions of DNA and RNA. The compound is formulated as the hydrochloride salt. Upon illumination with UVA light amotosalen forms covalent bonds with pyrimidine bases in nucleic acid. 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.

Intended Purpose

The INTERCEPT Processing Set for Plasma is used with an INTERCEPT Illuminator to inactivate a broad spectrum of viruses, bacteria, and parasites as well as contaminating donor leukocytes in plasma. This process for treatment of plasma components is intended to reduce the risk of transfusion-associated transmission of viruses, bacteria, and parasites, and the risk of adverse effects due to transfusion of contaminating donor leukocytes.

Intended Patient Population

Plasma prepared and stored using the INTERCEPT Blood System for Plasma (INTERCEPT Plasma) is intended for transfusion in all patients of all ages requiring plasma transfusions according to local, national, or regional clinical practice guidelines. No controlled clinical studies have been performed in pregnant and lactating women.

Indications for Use

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 (FFP). 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.

INTERCEPT Plasma may be stored from the time of collection for 12 months between -18°C and -25°C or for 36 months below -25°C, in compliance with applicable procedures and regulations.

Plasma photochemically treated with the INTERCEPT Blood System may be stored and transfused according to standard methods for frozen plasma. Thawed INTERCEPT Plasma that has been stored at 2-6°C can be used for up to 5 days. As with all plasma products, clinical use should consider that labile coagulation factors decline during post thaw storage. INTERCEPT Plasma may be prepared from single or pooled donations. INTERCEPT Plasma can be further processed into Cryoprecipitate, Pathogen Reduced and Plasma, Fresh frozen, Cryoprecipitate-Depleted using a validated preparation method. Thawed cryoprecipitate must be used as soon as possible and must not be re-frozen.

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 processing with the INTERCEPT Blood System for Plasma have shown a reduction in the levels of many 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.

Plasma must not be used in a patient with an intolerance to plasma proteins.

Before use, the component must be thawed in a properly controlled environment at +37°C and the integrity of the pack must be verified to exclude any defects or leakages. No insoluble cryoprecipitate must be visible on completion of the thaw procedure.

Potential adverse reactions to plasma transfusions include: (EDQM 21st edition, 2023):

- Haemolytic transfusion reaction may result from transfusion of ABO blood group-incompatible plasma.
- Non-haemolytic transfusion reaction (mainly chills, fever, and urticaria)
- Transfusion-related acute lung injury (TRALI)
- Pathogen transmission is possible as no pathogen inactivation process has been shown to eliminate all pathogens.
- Sepsis due to inadvertent bacterial contamination post pathogen inactivation treatment.
- Citrate toxicity in neonates and in patients with impaired liver function
- Transfusion-associated circulatory overload (TACO)
- Anaphylaxis and allergic reactions
- Transfusion-associated graft-versus-host disease

Clinical Benefits

INTERCEPT Plasma benefits patients by:

- Maintaining the plasma-mediated haemostatic capacity of the patient's blood.
- Reducing the risk of transfusion-transmitted infections (TTI) and of TA- GVHD.
- Serving as an alternative to gamma irradiation for prevention of transfusion-associated graft-versus-host disease (TA-GVHD).
- Use in place of CMV testing and leukoreduction for prevention of transfusion-transmitted CMV infection.

Pathogen Inactivation Claims

The INTERCEPT Blood System for Plasma has been tested against a broad spectrum of pathogens and demonstrated inactivation of viruses, bacteria, parasites, and donor leukocytes.

Pathogen inactivation data are reported as $\log_{10}$ reduction in pfu (plaque forming units) or cfu (colony forming units) per mL, $TCID_{50}$ (tissue culture infectious dose-50) per mL, ID_{50} (infectious dose-50) per mL, or CID_{50} (chimpanzee infectious dose-50) per mL depending on the assay methodology.

Cerus targets ≥ 4 $\log_{10}$ inactivation whenever possible to demonstrate the robustness of the inactivation process. Pathogens with results below this value are due to one of the following, as annotated in the tables:

- The maximum attainable input titer was < 4 $\log_{10}$ but the pathogen was fully inactivated to the achievable input titer.
- Pathogen inactivation efficacy was < 4 $\log_{10}$. For these pathogens, some protection may still be provided, however it is below the Cerus robustness target.
  - Certain non-enveloped viruses such as EMCV, PPV and Parvovirus B19 have demonstrated < 2 $\log_{10}$ inactivation with the INTERCEPT system (Table 1). HEV and HAV, similar non-enveloped viruses, are expected to be resistant to inactivation with INTERCEPT (data not shown).
  - The INTERCEPT process is not effective against *Bacillus* spores (data not shown).

Legend for Tables 1 – 4:

- Where a " > " is shown, no viable pathogen was detected in any post-treatment sample.
- Where a " ≥ " is shown, residual organisms were detected in some but not all replicates in the study.
- Where no symbol is shown, the inactivation capacity could be precisely calculated from the study results.

Caution: DEHP when used as a plasticizer, is known to be released from polyvinyl chloride (PVC) medical devices; increased leaching can occur with extended storage or increased surface area contact. The cannulas (specifically the cannula housing, which has minimal fluid contacting surfaces during storage or processing) in the INTERCEPT processing sets are the only components that contain DEHP; all containers and other components are DEHP-free. During use of this processing set, blood components are in contact with a small surface of cannula (with DEHP) for a brief period of time. 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 with DEHP components (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.

Viruses

The INTERCEPT Blood System for Plasma has been shown to inactivate a variety of viruses. The results of these studies are summarized in Table 1.

Table 1. Inactivation Claims - Viruses

Viruses Tested	Extent of Inactivation (log_{10} reduction)
Enveloped Viruses	
BVDV (bovine viral diarrhea virus, model virus for human HCV)	>5.0
CHIKV (chikungunya virus)	≥5.1
CMV	>4.4
DENV (dengue)	>6.0
DHBV (duck hepatitis B virus, model virus for human HBV)	>4.3
FLUAV (avian influenza A H5N1 virus)[f]	>5.7
HBV (hepatitis B virus, strain MS-2)[f]	>4.5
HCV (hepatitis C virus, strain Hutchinson)[f]	>4.5
HIV-1 (human immunodeficiency virus type I, cell-associated)[a,f]	>5.9
HIV-1 (human immunodeficiency virus type I, cell-free)	>4.8
HTLV-I (human T-cell lymphotropic virus) [a,b,c,f]	3.8
HTLV-II (human T-cell lymphotropic virus)[a,b,f]	4.7
SARS-CoV (human coronavirus)[f]	≥4.0
SARS-CoV-2 (human coronavirus)[c,f]	>3.3
WNV (West Nile Virus)	>7.0
ZIKV (Zika virus)[f]	>6.3
Non-Enveloped Viruses	
Ad5 (human adenovirus 5)	≥5.4
BTV (bluetongue virus, type II)	≥4.3
EMCV[e]	0.0
Parvovirus B19[d,f]	1.8
PPV[e]	0.1

[a] intracellular inoculum.

[b] inherent low-level background in non-infected indicator cells precludes ">" of HTLV.

[c] achievable input titer < 4 log_{10}. Complete inactivation up to the maximum attainable titer.

[d] Inactivation < 4 log_{10} suggests reduced pathogen reduction efficacy against this pathogen.

[e] viruses not activated

[f] performed with INT100 Illuminator.

Bacteria

The INTERCEPT Blood System for Plasma has been shown to inactivate a variety of bacteria. The results of these studies are summarized in Table 2. Studies were carried out with spirochete bacteria *Treponema pallidum* and *Borrelia burgdorferi* because these organisms are known to be asymptomatically present in the blood during chronic infections.

Table 2. Inactivation Claims - Bacteria

Bacterial Species Tested	Extent of Inactivation (log_{10} reduction)
Gram-Negative Bacteria	
Anaplasma phagocytophilum (HGE agent)[a,b,d]	>3.6
Enterobacter cloacae[d]	≥6.7
Klebsiella pneumoniae[c]	5.1
Pseudomonas aeruginosa[d]	>6.8
Pseudomonas fluorescens[c]	≥7.5
Yersinia enterocolitica[d]	>6.6
Gram-Positive Bacteria	
Clostridium perfringens (vegetative form)[c]	>6.7
Staphylococcus aureus[c]	>6.5
Staphylococcus aureus (MRSA)[d]	>6.1
Staphylococcus aureus (MSSA)[d]	>6.2
Staphylococcus epidermidis[d]	>6.8
Spirochete Bacteria	
Borrelia burgdorferi (Lyme disease)	>5.7
Treponema pallidum (syphilis)[a,d]	≥5.4

[a] intracellular inoculum.

[b] achievable input titer < 4 log_{10}. Complete inactivation up to the maximum attainable titer.

[c] WHO approved bacterial reference strain used.

[d] performed with INT100 Illuminator.

Parasites

The INTERCEPT Blood System for Plasma has been shown to inactivate parasites. The results of these studies are summarized in Table 3.

Table 3. Inactivation Claims - Parasites

Parasites Tested	Extent of Inactivation (log_{10} reduction)
Babesia microti (babesiosis)[a,b]	>4.9
Plasmodium falciparum[a] (malaria)	>7.5
Trypanosoma cruzi (Chagas disease)[b]	>6.7

[a] intracellular inoculum.

[b] performed with INT100 Illuminator.

Leukocytes

The INTERCEPT Blood System for plasma inactivates contaminating donor leukocytes, including T cells, at a log reduction factor of >5.7 log_{10} reduction of viable T-cells. The study also demonstrated that the INTERCEPT Blood System is equally effective when compared to treatment with 2,500 cGy gamma irradiation, the current standard prophylaxis for the prevention of TA-GVHD.

In Vitro Characterization of INTERCEPT Plasma

In vitro studies were performed to evaluate plasma function: fibrinogen and factor VIII, and coagulation factors II, V, VII, IX, X and XI, proteins C and S, antithrombin III, alpha-2 antiplasmin, PT, aPTT, thrombin generation, after INTERCEPT treatment and frozen storage. INTERCEPT Plasma components demonstrated retention of coagulation factors and met the EDQM requirements[1] for therapeutic plasma, following INTERCEPT treatment and frozen storage for 12 months between -18°C and -25°C or for up to 36 months below -25°C ensuring therapeutic hemostatic efficacy.

Clinical Use of INTERCEPT Plasma

Tolerability and Safety in Healthy Volunteers

The tolerability, safety, and amotosalen clearance after transfusion of INTERCEPT Plasma to healthy subjects was evaluated. This was an open label, stepwise ascending dose escalation (100, 200, 400, and 1000 mL) crossover trial; 15 healthy volunteers received autologous plasma processed with the INTERCEPT Blood System for Plasma 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 INTERCEPT Plasma versus conventional FFP. No clinically relevant adverse events were observed in subjects exposed to INTERCEPT Plasma at doses as high as 1,000 mL.

Transfusion in Healthy Volunteers After Warfarin Sodium Anticoagulation

The transfusion of INTERCEPT 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 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 FFP 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 FFP.

Multiple Coagulation Factor Deficiencies

A randomized, prospective, double-blind trial was conducted to evaluate efficacy and safety of INTERCEPT Plasma compared to conventional FFP 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 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 Plasma and untreated FFP. No unexpected adverse events were observed in patients exposed to INTERCEPT Plasma (604 to 1589 mL). One serious adverse event of pulmonary edema related to transfusion of 1589 mL of INTERCEPT 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 FFP 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 FFP
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 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 Plasma and 46% of patients treated with FFP achieved remission within 30 days ($p = 0.570$). Also, 78% of patients treated with INTERCEPT Plasma achieved remission within 60 days, with a median time to remission of 15 days. The mean total exposure to both INTERCEPT 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 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).

Post-market Clinical Follow-up (PMCF)

An observational, prospective, uncontrolled, hemovigilance study conducted by Cerus evaluated 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 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.

Agence nationale de sécurité du medicament (ANSM) Hemovigilance Program (France)[2]

National HV programs are also monitored for relevant clinical data as part of the PMCF Plan for INTERCEPT Plasma. To date, France has produced the most consistent and high quality HV data. INTERCEPT Plasma accounted for between 13.8% (2010) and 48.4% (2015) of the national plasma supply in France between 2010-2015. In 2022, INTERCEPT Plasma accounted for <10% of the supply as the country transitioned to a quarantine plasma strategy. Between 2020-2022 the annual incidence rate of transfusion reactions decreased from 146.4 to 112.3 (2022) per 100,000 plasma units issued. Since 2010 no cases of transfusion-transmitted infections (TTI) have been reported involving viruses or bacterial against which the INTERCEPT Blood System has been shown to be highly effective. Likewise, no cases of TA-GVHD have ever been associated with INTERCEPT Plasma.

References:

1) Guide to the preparation, use and quality assurance of Blood Components. EDQM 21st Edition 2023. Available at https://www.edqm.eu/en/blood-guide
2) Agence Nationale de Sécurité du Médicament et des Produits de santé (ANSM) Rapport annuel Hémovigilance 2010-2022

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