

INTERCEPT PLATELETS

TECHNICAL DATA SHEET



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INTERCEPT Blood System for Platelets Photochemical Treatment (PCT) of Platelets Using Amotosalen Hydrochloride and UVA Light

INTERCEPT Blood System for Platelets

The INTERCEPT Blood System for platelets is a Class III medical device that is intended for the ex vivo preparation and storage of whole blood-derived and apheresis platelets. The system is used to inactivate a broad spectrum of viruses, bacteria, and parasites as well as contaminating donor leukocytes in platelet components. This process is intended to reduce the risk of transfusion-associated transmission of viruses, bacteria, and parasites, prevent transfusion-associated graft versus host disease, and may also reduce the risk of other 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 platelet components.

INTERCEPT Platelet Processing Sets

The INTERCEPT Blood System for platelets is a sterile, non-pyrogenic fluid path integrated disposable plastic processing set. The INTERCEPT Platelet Processing Sets consist of small volume (SV), large volume (LV) and dual storage containers (DS) disposables. The INTERCEPT processing sets for large volume platelet concentrates and small volume platelet concentrates are each provided as four integral containers in a sealed over-wrap. The INTERCEPT platelet processing set

with dual storage containers is provided as five integral containers in a sealed over-wrap. Platelets suspended in plasma with or without additive solutions can be processed with this system. Platelets suspended in 100% plasma must be processed using only the LV processing set. When using platelet additive solutions, either the LV, DS or SV processing sets can be used and the plasma to platelet additive solution ratio in the suspension medium needs to be approximately 35%/65%. Platelets flow through the amotosalen container into the illumination container. The nominal concentration of amotosalen in the platelet mixture prior to illumination is 150 μM . Photoactivation is provided by the INTERCEPT Illuminator. This ancillary Class I device is microprocessor controlled and delivers a target UVA treatment of 3 J/cm^2 . Residual amotosalen and free photoproducts are reduced to low levels by exposure to a compound adsorption device (CAD), before transfer of the treated platelets to a storage container for release.

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 acid. The genomes of pathogens and leukocytes cross-linked in this manner can no longer function or replicate. No *in vivo* pharmacological effect of residual amotosalen is intended.

Platelet Additive Solutions

Platelet additive solutions approved for use with INTERCEPT: InterSol, SSP+. Both are provided separately.

INTERCEPT Platelets

Platelets suspended in 35% plasma and 65% additive solution that have been processed using the INTERCEPT Blood System may be stored for up to 7 days from time of collection at 20°C to 24°C with continuous gentle agitation according to applicable blood banking procedures. Any extension of platelet storage time should be evaluated and validated according to local blood bank procedures.

Platelets suspended in 100% plasma that have been processed using the INTERCEPT Blood System may be stored for up to 5 days from time of collection at 20°C to 24°C with continuous gentle agitation according to applicable blood banking procedures.

Treatment of platelet components with the INTERCEPT Blood System does not cause substantial differences in pH, lactate concentration, platelet count, mor-

phology score, glucose concentration, aggregation, secretory and total adenosine triphosphate concentration, extent of shape change, or platelet hypotonic shock response compared to untreated platelet components.

Indications

Platelet components processed using the INTERCEPT Blood System (“INTERCEPT Platelets”) are indicated for transfusion support of patients requiring platelet transfusions according to clinical practice guidelines. Any type of thrombocytopenia resulting from disease, therapy, or injury can be supported with INTERCEPT Platelets. 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 Platelets are not clinically different from untreated platelets and are infused according to standard platelet infusion methods.

Pathogen Inactivation Claims

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

Viruses

The INTERCEPT Blood System for platelets has been shown to inactivate a variety of viruses. Of viruses tested to date, only HAV and PPV were resistant to inactivation. The results of these studies are summarized in Table 1.

Table 1: Inactivation Claims – Viruses

Viruses Tested Using the INTERCEPT Blood System	Extent of Inactivation* (log ₁₀ reduction)	
	Platelets in plasma/ Additive Solution	Platelets in plasma
Enveloped Viruses		
HIV-1 (cell-associated)***	>6.1	>6.7
HIV-1 (cell-free)	>6.2	≥4.7
Clinical isolate of HIV-1	>3.4	-
Clinical isolate of HIV-2	>2.5	-
Latent proviral HIV-1	Inactivated to the limit of detection	-
HBV (strain MS-2)	>5.5	>4.5
HCV (strain Hutchison)	>4.5	>4.5
HTLV-I (Human T cell Lymphotropic Virus)***	4.7**	≥4.5
HTLV-II (Human T cell Lymphotropic Virus)***	5.1**	>5.7
Cell-associated Cytomegalovirus (CMV)***	>5.9	-
Bovine Viral Diarrhea Virus (BVDV, model virus for human HCV)	>6.0	≥5.4
Duck Hepatitis B Virus (DHBV, model virus for human HBV)	>6.2	4.4 to 4.5
PRV (Pseudorabies virus, model for CMV)	-	≥4.7
West Nile virus	>6.0	≥6.8
SARS-CoV (Human Corona virus)	-	≥5.5
Chikungunya virus	>6.4	≥7.6
Influenza A H5N1 virus (Avian Influenza)	>5.9	>5.7
Non-Enveloped Viruses		
Bluetongue Virus, type 11	>5.0	5.1
Calicivirus	1.7 to 2.4	-
Human Adenovirus-5	>5.9	≥6.9
Parvo (Parvovirus B19)	-	1.8

* “>” refers to inactivation below the limit of detection of the assay. In some cases assays have a very small dynamic range due to limits on attainable virus titers.

** inherent low-level background in non-infected indicator cells precludes “>” of HTLV

*** intracellular inoculum

“-” means not tested

Bacteria

The INTERCEPT Blood System for platelets has been shown to inactivate a variety of bacteria in platelet components. Inactivation studies using a range of gram positive and gram negative pathogenic bacteria demonstrated inactivation of approximately 6 logs of organisms, with the exception of *P. aeruginosa* and *B. cereus* (including spores), which showed reductions of 4.5 and 3.6 logs, respectively. Bacterial spores are resistant to inactivation; however, spore-forming bacteria in the vegetative state are sensitive to inactivation. The results of these studies are summarized in Table 2.

Table 2: Inactivation Claims – Bacteria

Bacterial Species Tested Using the INTERCEPT Blood System	Extent of Inactivation* (log ₁₀ reduction)	
	Platelets in plasma/ Additive Solution	Platelets in plasma
Gram-Negative Bacteria		
<i>Escherichia coli</i>	>6.4	≥7.3
<i>Serratia marcescens</i>	>6.7	-
<i>Klebsiella pneumoniae</i>	>5.6	≥6.7
<i>Pseudomonas aeruginosa</i>	4.5	-
<i>Salmonella choleraesuis</i>	>6.2	-
<i>Yersinia enterocolitica</i>	>5.9	>7.3
<i>Enterobacter cloacae</i>	5.9	-
<i>Anaplasma phagocytophilum</i> (HGE agent)**	-	>4.2
Gram-Positive Bacteria		
<i>Staphylococcus epidermidis</i>	>6.6	>7.4
<i>Staphylococcus aureus</i>	6.6	>7.6
<i>Streptococcus pyogenes</i>	>6.8	-
<i>Listeria monocytogenes</i>	>6.3	-
<i>Corynebacterium minutissimum</i>	>6.3	-
<i>Bacillus cereus</i> (includes spores)	3.6	-
<i>Bacillus cereus</i> (vegetative)	>6.0	-
<i>Bifidobacterium adolescentis</i>	>6.5	-
<i>Propionibacterium acnes</i>	>6.7	-
<i>Lactobacillus species</i>	>6.9	-
<i>Clostridium perfringens</i> (vegetative form)	>7.0	-
Spirochete Bacteria		
<i>Treponema pallidum</i> (syphilis)	≥6.8 to ≤7.0	>5.9
<i>Borrelia burgdorferi</i> (Lyme disease)	>6.8	>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

“-” means not tested

Parasites

The INTERCEPT Blood System for platelets has been shown to inactivate contaminating parasites in platelet products. Various *in vitro* studies have demonstrated inhibition of parasite replication following photochemical treatment. The results of these studies are summarized in Table 3.

Table 3: Inactivation Claims – Parasites

Parasites Tested Using the INTERCEPT Blood System	Extent of Inactivation* (log ₁₀ reduction)	
	Platelets in plasma/ Additive Solution	Platelets in plasma
<i>Plasmodium falciparum</i> ** (malaria)	≥6.0	≥6.9
<i>Trypanosoma cruzi</i> (Chagas' disease)	>5.3	>5.0
<i>Leishmania mexicana</i> (metacyclic promastigote stage)	>5.0	-
<i>Leishmania major Jish</i> (amastigote stage)	>4.3	-
<i>Babesia microti</i> (babesiosis)	>5.3	>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

"-" means not tested

Leukocytes

The INTERCEPT Blood System for platelets has been shown to inactivate contaminating donor leukocytes including T-cells in platelet products. Various *in vitro* studies have demonstrated inhibition of leukocyte replication as well as inhibition of cytokine synthesis by leukocytes following photochemical treatment. The results of these studies are summarized in Table 4.

Table 4: Inactivation Claims – Leukocytes

Assay System		Extent of Inactivation*	
		Platelets in plasma/ Additive Solution	Platelets in plasma
<i>In vitro</i>	Limiting dilution assay	>5.4 log ₁₀ reduction of viable T-cells	≥6.1 log ₁₀ reduction of viable T-cells
	DNA modification	Approximately one amotosalen adduct per 83 base pairs	Approximately one amotosalen adduct per 89 base pairs
	Polymerase chain reaction	Amplification inhibited by amotosalen – DNA adducts	-
	Cytokine synthesis	Elimination of IL-8, IL-1b synthesis during storage	-
<i>In vivo</i>	Murine transfusion model	Prevention of TA-GVHD in a murine parent to F ₁ transfusion model	-

“-” means not tested

Clinical Evaluation of INTERCEPT Platelet Components

Whole Blood Derived Buffy Coat Platelets

A randomized, controlled, double-blinded clinical trial was performed to evaluate the efficacy and safety of platelets prepared by the buffy coat method suspended in 35% plasma/65% InterSol and treated with the INTERCEPT Blood System. The results of this 103 patient clinical trial demonstrated that INTERCEPT buffy coat platelets can be used in the same manner as untreated platelets for the support of thrombocytopenic patients. Equal doses of INTERCEPT buffy coat platelets provided similar one and 24-hour post-transfusion count increments, and patients treated with INTERCEPT buffy coat platelets exhibited adverse event profiles similar to those who received reference platelets.

Apheresis Platelets

A randomized, controlled, double-blinded clinical trial was performed to evaluate the efficacy and safety of apheresis platelets, collected on the Amicus Cell Separator, suspended in 35% plasma/65% InterSol, and treated with the INTERCEPT Blood System. The results of this 43 patient clinical trial confirmed the results of the larger trial performed with buffy coat platelets.

A second randomized, controlled, double-blinded clinical trial was performed evaluating the hemostatic efficacy and safety of transfusion of apheresis platelet concentrates collected on the Amicus Cell Separator, suspended in 35% plasma/65% InterSol treated with the INTERCEPT Blood System in thrombocytopenic patients (n=645). The results from this large trial demonstrated equivalence of INTERCEPT apheresis platelets to conventional apheresis platelets in prevention and treatment of Grade 2 and higher grade bleeding, according to WHO criteria. An increase in 3 specific pulmonary events: acute respiratory distress syndrome, pneumonitis not otherwise specified (nos), and pleuritic chest pain was noted in the INTERCEPT group. Subsequent analyses and expert consultation indicated that the observed differences in these adverse events were related to inconsistencies of verbatim terms used for MedDRA coding dictionary and inconsistent reporting of events of acute respiratory distress syndrome by study personnel, and that there were no differences between the INTERCEPT platelets and conventional platelets with respect to serious pulmonary events.

INTERCEPT Platelet Components Stored for Seven-Days

A randomized, double-blind, single-center, two-treatment, two-period cross-over clinical study was conducted to determine whether buffy coat platelets treated with the INTERCEPT Blood System and stored for 7 days in 35% Plasma/65% InterSol provided safety and acceptable therapeutic efficacy when compared to 7-day old Reference platelet concentrates in the treatment of thrombocytopenic patients.

Transfusion of INTERCEPT Platelets stored for 7 days resulted in acceptable clinical outcomes; although, non-inferiority to 7-day old Reference platelets in terms of 1-hour CCI could not be demonstrated with the pre-specified non-inferiority margin of 2.2×10^3 .

The results of the study demonstrated that both INTERCEPT and Reference Platelets stored for 7 days were capable of preventing bleeding. Platelet transfusions with 7-day old platelets prepared with the INTERCEPT Blood System were shown to be safe and well-tolerated in thrombocytopenic patients and had a similar profile to transfusions with conventionally produced 7-day old platelets.

Post-Marketing Experience with INTERCEPT Platelet Components

Following CE Mark approval, a hemovigilance (HV) program to document and characterize the safety profile of INTERCEPT Platelets in routine use was initiated; this program is ongoing. The objective of the observational, non-randomized, non-controlled hemovigilance program is to gain additional safety experience with INTERCEPT Platelets as they are prepared and transfused under routine blood bank and clinical conditions, respectively, and to gain additional experience in broad patient populations. To date more than 250,000 transfusions of INTERCEPT Platelets have been administered to thrombocytopenic patients in routine clinical use. Safety data for 16,631 transfusions of INTERCEPT Platelet components, administered to 3,274 patients, has been collected in three separate HV studies (HV1, HV2, and HV3). These non-interventional studies have been performed at multiple sites in Europe. INTERCEPT treatment was used in place of gamma irradiation for prevention of TA-GVHD in most of these centers. Related adverse events following INTERCEPT platelet transfusions were infrequent and most were of mild severity (Grade 1). The most frequently reported signs/symptoms were fever, chills, urticaria and other dermatological reactions. These types of reactions have previously been described in association with transfusion of conventional platelet components. No unexpected adverse events were observed during the conduct of these studies. In HV1, there were 3 adverse events Grade 2 or higher (one of which was possibly related). In HV2, there were 5 adverse events Grade 2 or higher (all of which were unrelated or probably unrelated). No reports of TA-GVHD events related to the transfusion were noted in either study. This is especially important since >95% of platelet components were not gamma irradiated and many were given to at-risk immune compromised patients.

Contraindications

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

Notes to Physicians

Neonatal patients who require platelet 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 psoralen, which may result in erythema.

While laboratory studies of photochemical treatment processing with the INTERCEPT Blood System for platelets have shown a reduction in the levels of certain viruses, bacteria and parasites, no pathogen inactivation process has been shown to eliminate 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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