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INTERCEPT™ Blood System for Platelets

Technical Data Sheet

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The INTERCEPT Blood System for Platelets consists of the INTERCEPT Processing Set for Platelets (Class III) and the INTERCEPT Illuminator-INT200 (Class IIb) medical devices and 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. The device uses amotosalen (a photoactive compound) and low energy ultraviolet (UVA) illumination to photochemically treat platelet components.

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 or DS processing sets. When using platelet additive solutions, either the SV, LV, or DS processing sets can be used and the plasma to platelet additive solution ratio in the suspension medium needs to be approximately 35%/65%.

Platelet additive solutions approved for use with INTERCEPT: InterSol, SSP+, T-PAS+, Grifols PAS III M.

INTERCEPT Processing Sets for Platelets

The INTERCEPT Processing Set for Platelets is a sterile and 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, an EVA blend plastic Compound Adsorption Device (CAD) container and one (SV, LV), two (DS), or three (TS) EVA blend plastic platelet storage containers.

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.

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

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 Platelets is used with an INTERCEPT Illuminator to inactivate a broad spectrum of viruses, bacteria, and parasites as well as contaminating donor leukocytes in platelet components. This process for treatment of platelet 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

Platelets prepared and stored using the INTERCEPT Blood System for Platelets (INTERCEPT Platelets) are intended for transfusion in all patients of all ages requiring platelet transfusions according to local, national or regional clinical practice guidelines.

Indications for Use

INTERCEPT Platelets are indicated for transfusion support of patients requiring platelet transfusions according to clinical practice guidelines. Any type of thrombocytopenia or qualitative disorder 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 for prevention of transfusion transmitted CMV infection. INTERCEPT treatment may be used in place of CMV testing and leukoreduction for prevention of transfusion transmitted CMV infection. INTERCEPT treatment may be used in place of bacterial culture or testing for the prevention of transfusion transmitted sepsis.

INTERCEPT Platelets are not clinically different from untreated platelets and are infused according to standard platelet infusion methods.

INTERCEPT Platelets suspended in additive solution or in 100% plasma may be stored up to 7 days from time of collection. Treated platelets must be stored at 20-24°C with continuous agitation. INTERCEPT Platelets stored up to 7 days have been shown to adequately prevent and control bleeding. Any extension of platelet storage time should be evaluated according to applicable local policies and regulations.

Contraindications

Use of INTERCEPT Platelets 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 many viruses, bacteria and parasites; there is no pathogen inactivation process that has been shown to eliminate all pathogens.

INTERCEPT Platelet 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.

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

- Allergic reactions and anaphylaxis
- Febrile non-haemolytic transfusion reactions
- Alloimmunisation against platelet and HLA antigens
- Haemolytic transfusion reaction
- Transfusion associated graft versus host disease (TA-GVHD)
- Transfusion-related acute lung injury (TRALI)
- Post-transfusion purpura
- Citrate toxicity in neonates and in patients with impaired liver function
- Transfusion-associated circulatory overload (TACO)
- Bacterial sepsis
- Viral transmission (hepatitis, HIV, Zika, Dengue, etc.)
- Syphilis transmission
- Protozoal transmission (e.g., malaria)
- Transmission of other pathogens that are not tested for or recognized

Clinical Benefits

INTERCEPT Platelets benefit patients by:

- Reducing the risk of transfusion-transmitted infections (TTI) and of TA- GVHD
- Maintaining the platelet-mediated haemostatic capacity of the patient's blood.
- 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 Platelets has been tested against a broad spectrum of pathogens and demonstrated inactivation of viruses, bacteria, parasites, and donor leukocytes.

Pathogen inactivation data is 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, FCV and Parvo 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) but is effective against this organism in the vegetative state (Table 2).

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.
- Where " – " is shown, the pathogen was not evaluated in the indicated component.

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 Platelets 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) Platelets in plasma/additive solution	Platelets in 100% plasma
Enveloped Viruses		
BVDV (bovine viral diarrhea virus, model virus for human HCV)	>4.7	>4.6
CHIKV (chikungunya virus)	>5.6	>5.3
CMV (cell-associated cytomegalovirus)[a]	>5.0	>4.2
DENV (dengue virus)	>6.3	>5.8
DHBV (duck hepatitis B virus, model virus for human HBV)	>4.1	>4.8
FLUAV (avian influenza virus A, H5N1)[f]	>5.9	>5.7
HBV (hepatitis B virus, strain MS-2)[f]	>5.5	>4.5
HCV (hepatitis C virus, strain Hutchinson)	>4.5	>4.5
HIV-1 (human immunodeficiency virus type 1, cell-associated)[a]	>4.6	>5.2
HIV-1 (human immunodeficiency virus type 1, cell-free)	>4.6	≥4.7[f]
HIV-1 (human immunodeficiency virus type 1, clinical isolate)[f]	>3.4[c]	-
HIV-1 (human immunodeficiency virus type 1, latent proviral)[f]	Inactivated to the limit of detection	-
HIV-2 (human immunodeficiency virus type 2, clinical isolate)[f]	>2.5[c]	-
HTLV-I (human T-cell lymphotropic virus)[a,f]	4.7	3.8[c]
HTLV-II (human T-cell lymphotropic virus)[b,f]	5.1	4.7
PRV (pseudorabies virus, model for CMV)[f]	>5.1	>4.2
SARS-CoV (severe acute respiratory syndrome, coronavirus)[f]	-	≥4.0
SARS-CoV-2 (severe acute respiratory syndrome, coronavirus-2)[f]	>3.2[c]	>3.5[c]
WNV (West Nile virus)	>6.3	>6.9
YFV (yellow fever virus)[f]	>5.5	>5.3
ZIKV (Zika virus)	>5.5	>5.7
Non-Enveloped Viruses		
Ad5 (human adenovirus 5)	>6.5	≥5.4
BTV (bluetongue virus, type 11)	≥4.4	5.0
EMCV[e]	0.0	-
FCV (feline calicivirus)[f]	2.1[d]	0.9[d]
PPV[c]	0.2	-
Parvovirus B19[f]	-	1.8[d]

[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 input titer.

[d] inactivation < 4 log_{10} suggests reduced inactivation efficacy against these pathogens.

[e] viruses not inactivated.

[f] performed with INT100 Illuminator.

Bacteria

The INTERCEPT Blood System for Platelets has been shown to inactivate a variety of bacteria. The results of these studies are summarized in Table 2.

Table 2. Inactivation Claims - Bacteria

Bacteria Tested	Extent of Inactivation (log_{10} reduction)	
	Platelets in plasma/additive Solution	Platelets in 100% plasma
Gram-Negative Bacteria		
Acinetobacter baumannii[d]	>7.3	-
Anaplasma phagocytophilum (HGE agent)[a,d]	-	>3.6[b]
Enterobacter cloacae[c]	>6.7	≥6.6
Escherichia coli[c]	>7.2	>7.3
Klebsiella pneumoniae[c]	≥5.7	3.6
Pseudomonas aeruginosa[d]	>6.7	≥6.7
Pseudomonas fluorescens[c]	≥7.6	4.1
Salmonella choleraesuis	>7.1	≥6.7
Serratia marcescens	≥6.4	6.9
Serratia liquefaciens[d]	>5.6	>6.4
Yersinia enterocolitica[d]	≥5.9	>6.3
Gram-Positive Bacteria		
Bacillus cereus (vegetative)[d]	>5.5	≥5.6
Bacillus thuringiensis[c]	>5.5	≥5.6
Bifidobacterium adolescentis[d]	>6.1	-
Clostridium perfringens (vegetative form)	>6.7	>6.7
Corynebacterium minutissimum[d]	>5.3	>6.4
Cutibacterium acnes[d]	≥6.5	>6.7
Lactobacillus species[d]	-	>6.1
Listeria monocytogenes[d]	>3.8[b]	>6.6
Staphylococcus aureus[c,d]	>7.6	≥7.7
Staphylococcus aureus (MRSA)	-	>6.1
Staphylococcus aureus (MSSA)[d]	-	>6.2
Staphylococcus epidermidis[c]	>7.8	>7.6
Streptococcus agalactiae[d]	≥6.3	≥5.8
Streptococcus mitis[d]	>6.1	≥6.1
Streptococcus pneumoniae[d]	≥6.6	>6.6
Streptococcus pyogenes[c]	>6.3	>6.1
Spirochete Bacteria		
Borrelia burgdorferi (Lyme disease)	>5.4	>5.5
Treponema pallidum (syphilis)[d]	≥6.4	>6.3

[a] intracellular inoculum.

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

[c] WHO approved bacterial reference strain used.

[d] performed with INT100 Illuminator.

Parasites

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

Table 3. Inactivation Claims - Parasites

Parasites Tested	Extent of Inactivation (log_{10} reduction)	
	Platelets in plasma/additive Solution	Platelets in 100% plasma
Babesia microti (babesiosis)[a,b]	>4.9	>4.5
Leishmania major Jish (amastigote stage)[b]	>5.6	-
Leishmania mexicana (metacyclic promastigote stage)[b]	>6.3	-
Plasmodium falciparum (malaria)[a]	>6.8	>7.0
Trypanosoma cruzi (Chagas disease)	>5.1	>5.6

[a] intracellular inoculum

[b] performed with INT100 Illuminator

Leukocytes

The INTERCEPT Blood System for platelets has been shown to inactivate 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 Platelets

Treatment of platelet components with the INTERCEPT Blood System does not cause substantial differences in pH, lactate concentration, platelet count, morphology score, swirling, glucose concentration, aggregation, secretory and total adenosine triphosphate concentration, extent of shape change, or platelet hypotonic shock response compared to untreated platelet components.

Clinical Use of INTERCEPT Platelets

Whole Blood Derived Platelets (euroSPRITE)

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 Platelets produced from pooled buffy coat platelets can be used in the same manner as untreated platelets for the support of thrombocytopenic patients. Equal doses of INTERCEPT Platelets provided similar one and 24-hour post-transfusion count increments, and patients treated with INTERCEPT Platelets exhibited adverse event profiles similar to those who received reference platelets.

Apheresis Platelets (SPRINT)

A 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 non-inferiority of INTERCEPT Platelets to conventional apheresis platelets in prevention and treatment of Grade 2 and higher bleeding, according to WHO grading 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.

Therapeutic Efficacy and Safety of Stored INTERCEPT Platelets (TESSI)

A randomized, controlled, double-blinded, non-inferiority study designed to compare the safety and efficacy of INTERCEPT Platelets stored for 6-7 days with conventional platelets of a similar age. The primary endpoint was the 1-hour CCI. 211 patients were randomized and received one study platelet transfusion (105 Test, 106 Reference) of platelets stored > 5 days (80% of PCs were stored for 7 days). The 1- hour CCI for INTERCEPT Platelets was not inferior to that of conventional platelets. Multiple secondary endpoints, including bleeding and time to the next platelet transfusion demonstrated hemostatic efficacy for INTERCEPT Platelets stored more than 5 days. The safety profile of INTERCEPT and reference platelet components were nearly identical in this study; no differences were detected in the overall rate of adverse events, hemorrhagic adverse events, or serious adverse events. The study demonstrates that INTERCEPT Platelet stored 6 or 7 days are safe and effective.

Post-Marketing Clinical Follow-up (PMCF) experience with INTERCEPT Platelets

Following CE Mark approval, Cerus developed a post-market clinical follow-up (PMCF) strategy for INTERCEPT Platelets as part of the company's broader quality and post-market surveillance (PMS) systems. PMCF activities include the proactive collection of hemovigilance (HV) data through company-sponsored Phase IV observational, non-randomized, non-controlled studies to characterize the safety profile of INTERCEPT Platelets and document the safety and efficacy of INTERCEPT Platelets and the INTERCEPT Blood System for Platelets in routine use in broad patient populations.

Since 2003, safety data have been obtained through four cycles of Cerus-sponsored HV studies. These four studies captured data on 19,175 INTERCEPT Platelet components transfused in 4,067 patients. Within this population, 59 patients were under the age of 1 year and 185 patients were 1-18 years of age. More than half (51%) of the patients enrolled in these studies were hematology-oncology patients, of which 12% were HSCT patients. Adverse events within 24 hours and serious adverse events within 7 days of platelet transfusions were reported. The frequencies of adverse events attributed to INTERCEPT Platelets were not increased compared to rates for conventional platelet transfusions reported by national HV programs implemented by European regulatory authorities. Additional Cerus HV studies are ongoing.

National HV programs are also monitored for relevant clinical data as part of the PMS for INTERCEPT Platelets. To date, France and Switzerland have produced the most consistent and high quality HV data. Limitations associated with the analysis of national HV program data include variable reporting by site and region and differences in individual clinicians' clinical assessments. These limitations may be partially mitigated in countries like France and Switzerland by the consistent publication of data allowing for year-on-year trend analyses.

Agence Nationale de Sécurité Medicament (ANSM) et des Produits de Sante Hemovigilance Program (France)[1]

Since the introduction of INTERCEPT Platelets in France on a regional basis in 2009, Cerus has monitored safety and efficacy data for INTERCEPT and conventional platelets via the ANSM HV program, which collects data from all transfusing hospitals in France and its overseas territories.

Cumulative analysis of data from the ANSM reports from 2009 through 2021 show progressive improvements in overall platelet safety as France transitioned from partial INTERCEPT use between 2010 and 2017 (10% of the national platelet supply on average [range 7.9%-21.4%]) to 100% INTERCEPT starting in November 2017. No cases of transfusion-transmitted bacterial infections (TTBI) were reported for INTERCEPT Platelets between 2010-2017, a period in which conventional platelets were associated with 2 to 3 TTBI per year on average (range 0-6). A total of 23 high-imputability TTBIs associated with conventional platelets were reported to ANSM between 2010-2019. No TTBI were associated with INTERCEPT Platelets between 2010 and 2021. A single case involving a spore-forming bacteria for which Cerus does not have a claim of inactivation *(Bacillus cereus)* was reported to ANSM in 2022. During this period overall TR rates declined from 526 (2010) to 342.9 (2021). Allergic TRs, alloimmunization, febrile non-haemolytic TRs (FNHTR), immunologic incompatibility and PC refractoriness were (in decreasing frequency) the most common TRs (93% of TRs on average) for all platelet types during this period.

Swissmedic Hemovigilance Program (Switzerland)

In Switzerland, INTERCEPT Platelets were phased into routine use during 2011, accounting for approximately 80% of all platelet concentrates transfused that year, and 100% of platelets produced thereafter. Since 2011[2], no TTBI have been reported to the Swissmedic HV system.

In 2014, Swissmedic reported that the introduction of the INTERCEPT Blood System for Platelets not only reliably prevented TTBI, but also led to a significant reduction in the number and severity of non-transfusion-transmitted infection (TTI)-related TRs after platelet transfusion (per platelet component TR risk ~1/270 with conventional platelets vs. ~1/375 for INTERCEPT Platelets; per platelet component risk of severe TR ~1/2,800 for conventional platelets vs. ~1/8,700 for INTERCEPT Platelets). Swissmedic considered the likely explanation for this to be the generally lower plasma content of pathogen inactivated platelet components, which reduces allergic and febrile TRs to plasma constituents[3]. Since the 2014 analysis, overall TR rates for platelets have increased from approximately 285 (2015) to 452 (2022) per 100,000 platelet components issued; however, Swissmedic attributes these changes to improved hemovigilance reporting.

Clinical Experience from the Literature

Large-scale retrospective studies from Belgium[4], France[5], Austria[6] and Switzerland[7] have confirmed that conversion to INTERCEPT Platelets does not lead to an increased need for platelets or red blood cells to satisfy patient transfusion needs. Four observational studies conducted among diverse patient populations, including children, demonstrated no difference in the hemostatic efficacy of 51,519 INTERCEPT Platelets transfused to 7,367 patients compared to comparable numbers of conventional platelet concentrates transfused in an equivalent population.

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INTERCEPT Blood System
www.interceptbloodsystem.com

Global Headquarters
Cerus Corporation
1220 Concord Avenue
Concord, CA 94520, USA
+1 925 288 6000

European Headquarters
Cerus Europe B.V.
Stationsstraat 79-D
3811 MH Amersfoort
The Netherlands
+31 33 496 0600

Email: customercare@cerus.com
www.cerus.com

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