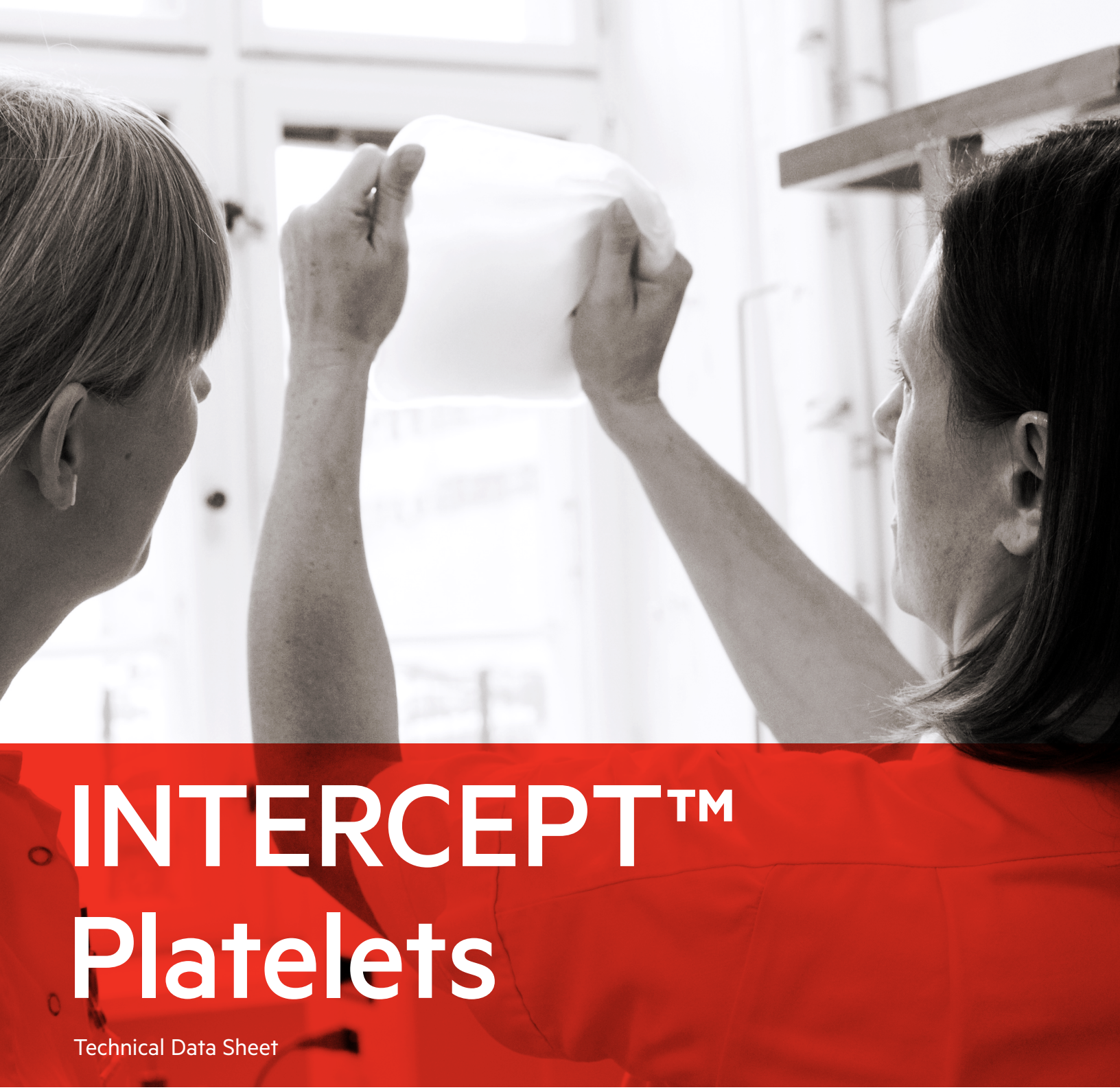

INTERCEPT™ Platelets

Technical Data Sheet

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Intercept Blood System

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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 (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, DS or TS processing sets can be used and the plasma to platelet additive solution ratio in the suspension medium needs to be approximately 35%/65%.

INTERCEPT Platelet Processing Sets

The INTERCEPT Processing Set 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) dual storage containers (DS) and triple storage containers

(TS) 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. The INTERCEPT platelet processing set with triple storage containers is provided as six integral containers in a sealed over-wrap.

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 IIa 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

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 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 pharmacological effect of residual amotosalen is intended.

Platelet Additive Solutions

Platelet additive solutions approved for use with INTERCEPT: InterSol, SSP+, PASIIIM (e.g.T-PAS+, Grifols PAS IIIM). Platelet additive solutions 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 24ºC 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 7 days from time of collection at 20°C to 24ºC 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, morphology score, glucose concentration, aggregation, secretory and total adenosine triphosphate concentration, extent of shape change, or platelet hypotonic shock response compared to untreated platelet components.

Intended Use

The set 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.

Indications

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 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.

INTERCEPT Platelets may be stored up to 7 days from time of collection, 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.

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

Contraindications

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

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 100% 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 Hutchinson)	>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. "≥" refers to inactivation at or below the limit of detection of the assay.

** 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 good overall inactivation. 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

Bacteria Tested Using the INTERCEPT Blood System	Extent of Inactivation* (log_{10} reduction)	
	Platelets in plasma/additive Solution	Platelets in 100% plasma
Gram-Negative Bacteria		
Escherichia coli	>6.4	≥7.3
Serratia marcescens	>6.7	-
Klebsiella pneumoniae	>5.6	≥6.7
Pseudomonas aeruginosa	4.5	-
Salmonella choleraesuis	>6.2	-
Yersinia enterocolitica	>5.9	≥7.3
Enterobacter cloacae	5.9	-
Anaplasma phagocytophilum (HGE agent)**	-	>4.2
Gram-Positive Bacteria		
Staphylococcus epidermis	>6.6	>7.4
Staphylococcus aureus	6.6	>7.6
Streptococcus pyogenes	>6.8	-
Listeria monocytogenes	>6.3	-
Corynebacterium minutissimum	>6.3	-
Bacillus cereus (includes spores)	3.6	-
Bacillus cereus (vegetative)	>6.0	
Bifidobacterium adolescentis	>6.5	-
Propionibacterium acnes	>6.7	
Lactobacillus species	>6.9	-
Clostridium perfringens (vegetative form)	>7.0	-
Spirochete Bacteria		
Treponema pallidum (syphilis)	≥6.8 to ≤7.0	>5.9
Borrelia burgdorferi (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.

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

*** 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 100% plasma
*Plasmodium falciparum*** (malaria)	≥6.0	≥6.9
Trypanosoma cruzi (Chagas' disease)	>5.3	>5.0
Leishmania mexicana (metacyclic promastigote stage)	>5.0	-
Leishmania major Jish (amastigote stage)	>4.3	-
Babesia microti (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 100% plasma
In vitro		
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 89 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	-
In vivo		
Murine transfusion model	Prevention of TA-GVHD in a murine parent to F_1 transfusion model	-

"-" means not tested

Clinical Use of INTERCEPT Platelets Components

Whole Blood Derived Buffy Coat 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 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 (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 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.

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 components stored 6 or 7 days are safe and effective.

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. The objective of the observational, non-randomized, non-controlled hemovigilance program was 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.

Safety data were obtained from three HV programs in routine use without patient selection. The populations monitored included 4,067 patients, where 59 patients were under the age of 1 year and 185 patients were 1-18 years of age. 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 processed platelet transfusions were not increased compared to conventional platelet transfusions reported in European regulatory HV programs.

ANSM Active Hemovigilance Program (France)

Since 2009, INTERCEPT Platelets have been monitored in comparison to other types of platelet concentrates transfused in France through an active hemovigilance program in that country. During the period from 2009-2011, the reported frequencies of acute transfusion reaction (ATR) for exposure to INTERCEPT Platelets were comparable to the frequencies of ATRs for exposure to conventional platelet components, with approximately 1-2 events per 1,000 platelet components. In some years, the ATR frequency for exposure to INTERCEPT Platelets was below the rate for conventional platelets. The vast majority of the reported events were of low to moderate intensity and of the type expected with transfusion with conventional platelet components.

In addition to the information related to ATR frequency per patient and per transfusion, data for the frequency of transfusion related acute lung injury (TRALI) are reported in the ANSM Annual Hemovigilance Reports for 2008-2012. Data for conventional platelets and INTERCEPT Platelets indicate a similar low frequency of TRALI, and demonstrated that the ANSM HV system is sensitive to diagnosis of severe respiratory adverse events.

Cumulative analysis of data from the ANSM reports from 2009 through 2014 supplemented with data provided by French national transfusion service (Établissement Français du Sang-EFS) in Alsace for the years 2006-2008 and 2012 provides information on the frequency of transfusion related sepsis in regions using INTERCEPT Platelets compared to regions using conventional platelets. Of note, as of 2006 all whole blood and platelet collections utilized optimal skin disinfection, leukocyte reduction, and initial blood draw diversion, but bacterial detection tests were not used. These data demonstrate the efficacy of the INTERCEPT Blood System for the prevention of transfusion related sepsis without use of bacterial detection.

Swissmedic Hemovigilance Program (Switzerland)

In Switzerland, INTERCEPT Platelets were phased into routine use during in 2011, accounting for approximately 80% of all platelet concentrates transfused that year, and 100% of platelets produced thereafter. No septic transfusion reactions due to bacterial contamination of platelets were observed after the introduction of INTERCEPT. Using hemovigilance surveillance data from 2009 through 2012, Swissmedic compared the frequencies of transfusion reactions for INTERCEPT Platelets reported in 2011 and 2012 compared to reports of transfusion reactions for conventional platelet components reported in 2009 and 2010. These data demonstrated that use of INTERCEPT Platelets prevented septic transfusion reactions, and was associated with a reduction in the number and the severity of non-infection-related transfusion reactions.

In 2014, Swissmedic reported that the introduction of the INTERCEPT Blood System pathogen inactivation process not only reliably prevented septic transfusion reactions, but also led to a significant reduction in the number and severity of non-infection-related transfusion reactions after platelet transfusion (risk per platelet component of transfusion reaction ~1/270 with conventional platelets and ~1/375 for INTERCEPT Platelets; risk per platelet component of severe transfusion reaction ~1/2800 for conventional platelets and ~1/8700 for INTERCEPT Platelets). They consider the likely explanation for this to be the generally lower plasma content of pathogen inactivated platelet component, which reduces allergic and febrile transfusion reaction to plasma constituent (Amsler and Jutzi, Swissmedic Haemovigilance Annual Report 2014). Limitations of the hemovigilance system include data collection that was limited to only transfusion associated adverse events (TRALI, TACO, TAD, etc.), as assessed by the reporter.

Notes to Physicians

While laboratory studies of amotosalen processing withUVA 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 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.

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