



INTERCEPT Platelets

9/7/2016



September 7, 2016

The Blood Center is pleased to introduce INTERCEPT® Platelets (psoralen-treated; pathogen-reduced apheresis platelets) to our service area. INTERCEPT Platelets are an important advantage to reduce the risk of transfusion for your patients.

The anticipated “go-live” date is December 1, 2016. While INTERCEPT® Platelets are an important addition to our product line, there may be instances where this product is not available. Therefore, the acceptance of non psoralen-treated products will be necessary.

INTERCEPT Platelets are pathogen reduced Trima apheresis platelet components suspended in 100% plasma in which a broad spectrum of clinically relevant pathogens as well as leukocytes have been inactivated, thus reducing the risk of transfusion-transmitted infections (TTI) and potentially reducing the risk of transfusion-associated graft versus host disease (TA-GVHD). INTERCEPT Platelets offer the following advantages when compared to conventional platelet products:

- **Improved blood product safety**

INTERCEPT Blood System for Platelets demonstrates inactivation of CMV model virus in platelets in plasma as noted in the FDA-approved package insert, with a ≥ 4.2 pfu/mL log reduction.¹ Pathogen Reduction meets AABB standard⁴ which, revised in March 2016, allows for Irradiation or Pathogen Reduction⁴. Furthermore, INTERCEPT Platelets help address residual risks related to sepsis, established pathogens such as HIV, HBV, HCV, and emerging pathogens for which tests do not exist, such as chikungunya and dengue.⁴

- **Improved clinical outcomes**

Reduction in TTI risk, including sepsis, has been demonstrated in routine use with INTERCEPT Platelets.³ Improved clinical outcomes may reduce hospital costs associated with treatment, re-calls and follow-up investigations.^{3,5}

- **Avoidance of cost and complexity of bacterial testing**

FDA has recently issued a revised draft guidance recommending the hospital to mitigate the risk of bacterial contamination by utilizing pathogen-reduced platelets or by conducting secondary bacterial testing on platelet products, beginning at day 4, prior to transfusion.² The use of pathogen reduced platelet products offers the ability to avoid or replace bacterial testing,¹ which may enable hospitals to avoid costs associated with bacterial testing, associated labor, and platelet waste due to potential false positive results.^{2,4}

The Blood Center has served the community for over 55 years as a full-service blood product provider. Through the years we have maintained an excellent record of consistently achieving our primary mission to ensure a safe, reliable blood supply for patients in the communities we serve. Offering pathogen-reduced platelets is a major milestone of our ongoing focus on innovation that supports patient well-being.

The implementation process, hospital staff education, and training for these new products will be supported by The Blood Center as well as Cerus' Medical Science Liaison (MSL) and Hospital Implementation teams.

We will have information sessions beginning in September 2016 in addition to meeting with your team on-site to facilitate the implementation of INTERCEPT® Platelets.

Sincerely,

Billy Weales
President & CEO

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THE CRITICAL NEED FOR PSORALEN-TREATED PLATELETS (INTERCEPT, PATHOGEN REDUCED)

Current blood testing measures have greatly improved blood safety, particularly with regard to established transfusion-transmitted infections (TTIs) such as HIV, HBV, and HCV. Yet, residual risks exist such as those due to emerging pathogens and bacterial contamination. Examples of recent emerging pathogens are chikungunya, dengue, and Zika, pathogens for which there are no commercially available tests.

Bacterial contamination of platelet products represents the greatest risk to patients receiving platelets. Healthy donors carry bacteria on the surface of the skin and in subcutaneous layers but also have bacteria in their bloodstreams after activities like dental hygiene. These bacteria are commonly present in donated blood but are usually in small amounts and may not survive the processing steps. However, some bacteria survive and grow, especially in platelet products which must be stored at room temperature for several days, thus presenting a good growth media. Bacterial culture testing helps remove contaminated platelets from inventory, but detection is limited and failures are not uncommon.⁶⁻⁸ It is estimated that ~ 1 in 1,500 platelet units contain bacteria and that ~1 in 10,000 patients who receive contaminated platelets develop signs and symptoms consistent with septic transfusion reactions.^{7,9} When extrapolated to the nation as a whole, these findings suggest that 100 patients each year suffer significant harm with over 25 fatalities due to contaminated platelets.^{9,10} The data also show that the medical teams treating these patients often times do not recognize platelets as the cause of sepsis.⁹ Psoralen-treated platelet products help address such risks.³

BACKGROUND AND CLINICAL ATTRIBUTES OF PSORALEN-TREATED PLATELETS

Recognized as a safe and effective choice of European and other global blood centers for over a decade, the INTERCEPT Blood System for Platelets is FDA approved, bringing the proven benefits of psoralen-treated platelets to the United States.

The INTERCEPT Blood System for Platelets provides broad-spectrum inactivation, reducing the risks of TTI, including sepsis. In addition, the number of T-cells is reduced to a level that potentially lowers the risk of transfusion-associated graft-versus-host disease (TA-GVHD)³. ≥ 4 log of inactivation are attained for most clinically relevant pathogens (Figure 1), including:³

- A broad spectrum of bacteria frequently implicated in TTI and sepsis.
- Emerging pathogens, including those that cause malaria, dengue, and chikungunya, for which there are no commercially available tests. A recent FDA Guidance¹¹ identifies pathogen reduction as an appropriate blood safety measure to reduce transfusion risks due to Zika.
- T-cells, which have been associated with TA-GVHD.
- High levels of CMV inactivation are achieved with INTERCEPT⁴.
- Established threats such as HIV-1, HBV, and HCV.

Figure 1: Pathogens Inactivated



GRAM-NEGATIVE BACTERIA

- Klebsiella pneumoniae*^{†‡}
- Yersinia enterocolitica*^{†‡}
- Escherichia coli*^{†‡}
- Pseudomonas aeruginosa*^{†‡}
- Salmonella choleraesuis*^{†‡}
- Enterobacter cloacae*^{†‡}
- Serratia marcescens*^{†‡}



GRAM-POSITIVE BACTERIA

- Staphylococcus epidermidis*^{†‡}
- Staphylococcus aureus*^{†‡}
- Streptococcus pyogenes*^{†‡}
- Listeria monocytogenes*^{†‡}
- Corynebacterium minutissimum*^{†‡}
- Bacillus cereus (vegetative)*^{†‡}
- Lactobacillus species*^{†‡}
- Bifidobacterium adolescentis*[†]
- Propionibacterium acnes*^{†‡}
- Clostridium perfringens (vegetative)*^{†‡}



VIRUSES

- HIV-1^{†‡}
- HTLV-I[†]
- HTLV-II[†]
- CMV[†]
- WNV^{†‡}
- DHBV (model for HBV)^{†‡}
- BVDV (model for HCV)^{†‡}
- Pseudorabies (model for CMV)[‡]
- Chikungunya^{†‡}
- Dengue^{†‡}
- Influenza A[†]



SPIROCHETES

- Treponema pallidum*[†]
- Borrelia burgdorferi*[†]



PROTOZOA

- Trypanosoma cruzi*^{†‡}
- Plasmodium falciparum*[†]
- Babesia microti*[†]



LEUKOCYTES

- T-cells^{†‡}

† pathogen reduced Amicus apheresis platelets in PAS-3, ‡ pathogen reduced Trima apheresis platelets in 100% plasma

How it Works

The INTERCEPT Blood System for Platelets uses amotosalen - a well characterized photoactive compound (psoralen-derivative) that targets DNA and RNA - and uses UVA illumination to irreversibly cross-link nucleic acids. In doing so, the INTERCEPT treatment blocks replication of viruses, bacteria, and parasites, rendering them inactive (Figure 2). After INTERCEPT processing, remaining additive levels are negligible and the platelet product has normal functional and storage characteristics.³

Figure 2: Mechanism of action



Psoralen-Treated Platelets in Routine Use

Hemovigilance (HV) programs provide a comprehensive view of transfusions and potential adverse events via the surveillance of blood donations in routine use settings. Over 300,000 psoralen-treated platelet units have been transfused in French and Swiss national HV programs, with no reported bacterial transfusion-transmitted infections nor sepsis-related fatalities to-date.¹²⁻¹⁴ In the comparable control groups of over 2,300,000 units, in whom conventional platelet products were transfused, 50 TTIs were noted, including 8 fatalities (Table 1).¹²⁻¹⁴

Table 1: Prevention of transfusion transmitted infections (TTIs) with psoralen-treated platelets

HV Program	Conventional Platelets		Psoralen-Treated Platelets	
	Platelet Units Transfused (n)	TTIs (Fatalities)	Platelet Units Transfused (n)	TTIs
France 2006–2014 ^{12,13}	2,299,334	49 (8)	180,762	0
Switzerland 2010–2014 ¹⁴	36,500	1 (0)	130,843	0
Total	2,335,834	50 (8)	311,605	0

In addition to the data assembled in the mandated national hemovigilance programs in France and Switzerland, the use of psoralen-treated platelets was evaluated in routine settings involving 21 centers over 7 years, largely consisting of hematology/oncology patients. This study population included neonatal patients through adults. Approximately 97% of platelet components transfused were not treated with gamma irradiation. As outlined in Table 2 below, there were no reports of TA-GVHD even when the majority of platelets were not treated with irradiation (Table 2).¹⁵

Table 2: Routine use of psoralen-treated platelets¹⁵

Intervention: Psoralen-Treated Platelet Components			
Outcome: Safety			
Study	PCs	Patients	Timing
HV1	5,106	651	2003-2005
HV2	7,437	1,400	2005-2007
HV3	6,632	2,016	2006-2010
Total	19,175	4,067	2003-2010

Clinical Development Program for Psoralen-Treated Platelets

Psoralen-treated platelets have been evaluated in several clinical trials comprised of over 800 subjects. Primary endpoints were met in the controlled, randomized clinical trials, including corrected count increments (CCI) and bleeding criteria, both of which are measures of hemostatic efficacy.¹⁶⁻²⁰



ICCBBA PRODUCT CODES AND BILLING P-CODES

ICCBBA Product Codes

The ICCBBA (International Council for Commonality in Blood Banking Automation) has assigned unique product codes (E-Codes) to psoralen treated platelets. The Blood Center will be using the following subset of the approved ICCBBA codes when producing psoralen treated products. If you plan on further processing or manipulating products, speak with The Blood Center, ICCBBA or your Laboratory Management Software provider for additional code information. If a code does not exist for your intended further manipulation step, please contact The Blood Center which may be able to request a new code from ICCBBA (Table 3).

Table 3: ICCBBA Codes

E8331V00	Apheresis PLATELETS ACD-A /XX/20-24C ResLeu:<5E6 Psoralen-treated
E8332V00	Apheresis PLATELETS ACD-A /XX/20-24C ResLeu:<5E6 1st container Psoralen-treated
E8333V00	Apheresis PLATELETS ACD-A /XX/20-24C ResLeu:<5E6 2nd container Psoralen-treated
E8334V00	Apheresis PLATELETS ACD-A /XX/20-24C ResLeu:<5E6 3rd container Psoralen-treated
E8335V00	Apheresis PLATELETS ACD-A /XX/20-24C ResLeu:<5E6 <3E11 plts Psoralen-treated
E8336V00	Apheresis PLATELETS ACD-A/XX/20-24C ResLeu:<5E6 Pediatric dose Psoralen-treated
E8337V00	Apheresis PLATELETS ACD-A/XX/20-24C ResLeu:<5E6 1st container Pediatric dose Psoralen-treated
E8338V00	Apheresis PLATELETS ACD-A/XX/20-24C ResLeu:<5E6 2nd container Pediatric dose Psoralen-treated
E8339V00	Apheresis PLATELETS ACD-A/XX/20-24C ResLeu:<5E6 3rd container Pediatric dose Psoralen-treated

A complete listing of E-Codes can be found at the following ICCBBA webpage:

<http://www.iccbba.org/tech-library/iccbba-documents/databases-and-reference-tables/product-description-codes-database2>

Outpatient Billing P-Codes

The Centers for Medicare and Medicaid Services (CMS) has established a permanent Healthcare Common Procedure Coding System (HCPCS) Level II billing code (P-code) designated specifically for billing of psoralen-treated (pathogen reduced) apheresis platelets when transfused in the hospital outpatient setting. When billing for outpatient administration of conventional apheresis platelet products and psoralen-treated (pathogen-reduced) apheresis platelet products, The Blood Center advises hospital customers to bill using the appropriate P-code (Table 4).



Table 4: HCPCS Level II Billing Codes for Apheresis Platelet Products

HCPCS Level II Code	Product Description	CMS CY16 Payment Rate
P9072	Platelets, pheresis, pathogen reduced, each unit	\$641.85
P9034	Platelets, pheresis, each unit	\$425.15
P9035	Platelets, pheresis, leukocytes reduced, each unit	\$488.29
P9036	Platelets, pheresis, irradiated, each unit	\$528.11
P9037	Platelets, pheresis, leukocytes reduced, irradiated, each unit	\$641.85
P9052	Platelets, hla-matched leukocytes reduced, apheresis/pheresis, each unit	\$704.98
P9053	Platelets, pheresis, leukocytes reduced, cmv-negative, irradiated, each unit	\$590.97
P9055	Platelets, leukocytes reduced, cmv-negative, apheresis/pheresis, each unit	\$462.48

<https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/HospitalOutpatientPPS/Hospital-Outpatient-Regulations-and-Notices-Items/CMS-1633-FC.html>

BAG CHARACTERISTICS, STORAGE, AND LABELING

Shape and Size

Psoralen-treated platelets are distributed in a 1.3 liter bag. They are handled, stored, ‘spiked’ and transfused as any conventional platelet product.

Storage

Psoralen-treated platelets may be stored at 20-24°C with continuous agitation for up to 5 days from the day of collection.

Psoralen-treated platelet bags are slightly larger than conventional bags. Depending on the storage rotator in use, storage configurations may need to be adjusted. The greatest difference in bag measurements is in the length. As such, you may find it most advantageous to store INTERCEPT bags with the ports and tails inward on the shelf. Figure 3 below shows one such shelf arrangement.

Figure 3: Possible shelf arrangement of Psoralen-Treated Platelets

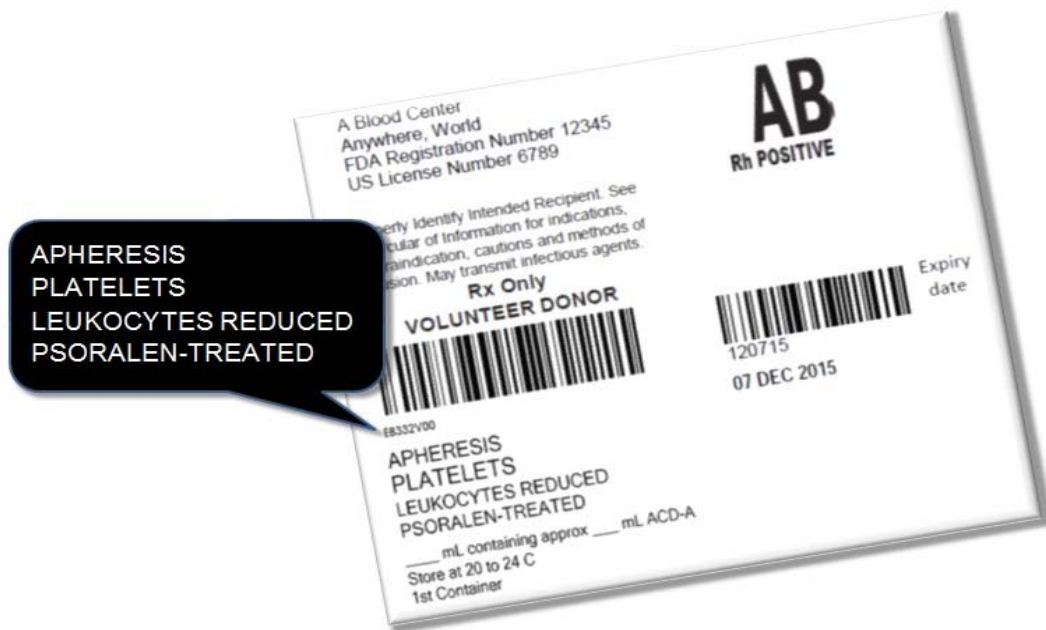


Labeling

Labels on psoralen-treated platelets will differ from conventional platelets as follows (Figure 4):

- A “Rad-sure®” label will not generally be seen on psoralen-treated platelet units.
- ‘CMV-Negative’ will not generally appear on the label.

Figure 4: Psoralen-Treated Platelet Label






OPERATIONAL CONSIDERATIONS



Operational Considerations

Industry Guidelines

 CMV	 Irradiation	 Bacterial Testing
<p>AABB Std 5.19.2 BB or TS Policy to reduce risk of CMV.¹</p>	<p>AABB Std 5.19.3.1 Methods known to prevent transfusion-associated graft-vs-host disease shall be used, and include either irradiation or the use of a pathogen reduction technology¹</p>	<p>AABB Std 5.1.5.2 Requires methods detect or use pathogen reduction technology in all PLT components.¹</p> <p>FDA Draft Guidance² - Bacterial Safety Pathogen Reduction or Bacterial Testing</p>
<p>INTERCEPT demonstrates inactivation of CMV in platelets in PAS-3 as noted in the FDA-approved package insert, with a ≥ 4.9 pfu/mL log reduction.³</p>	<p>Pathogen Reduction meets AABB standard¹. Revised in March 2016 allows for Irradiation or Pathogen Reduction¹</p>	<p>PR meets AABB Standard,¹ and per FDA draft guidance,² can eliminate the need for POI testing</p>

1. "Standards for Blood Banks and Transfusion Services," AABB, 30th edition, 2015.
2. FDA Draft Guidance, March 2016: "Bacterial Risk Control Strategies for Blood Collection Establishments and Transfusion Services to Enhance the Safety and Availability of Platelets for Transfusion."
3. INTERCEPT Blood System Platelets Package Insert, March 2016.



COMPUTER SYSTEMS

Laboratory Computer System

When updating your laboratory computer system and the hospital billing system, it is advisable to ensure the pathogen-reduced apheresis platelet P-code is entered into the computer system

Billing System

When updating your billing system, it is advisable to ensure that each of the ICCBBA E-codes associated with psoralen-treated apheresis platelets are appropriately linked to the HCPCS P-code for pathogen-reduced apheresis platelets to use for billing.

Ordering System

Each hospital transfusion service will need to determine how to structure blood component ordering practices relative to psoralen-treated platelets. You may choose to update your hospital computerized



physician order entry (CPOE). Changes may include product selection and safety-check rules. Options may include amending ordering screens to indicate psoralen-treated or pathogen reduced blood components as a new product, platelet product attribute, or replacement for all platelet products.

It may not be possible or you may choose not to change the clinical ordering screens for platelets. In this case you may choose to implement a policy or a signed letter from a Chief Medical Officer or department chair which allows the blood bank to administer psoralen treated products according to local policy. When updating the laboratory computer system, verify that any 'clinical rules' checking system recognizes that psoralen-treated platelets are appropriate for all patients. The Cerus team can help with examples of how this process has been implemented in hospitals that are using these products today.

TRAINING

Transfusion Service Staff

Hospital transfusion service staff may need to be trained on how platelet product orders will be received from physicians

Clinician Training

Clinicians should be trained on the ordering processes and the differences in the physical appearance of psoralen-treated platelets when compared to conventional platelets. The intended use, contraindications, warnings and precautions, and the benefits of the product may be explained to them or managed by the blood bank clinicians, as deemed appropriate by the blood bank, Transfusion Practice committee, Patient Safety Committee, Medical Executive Committee or other appropriate hospital groups. Neonatal clinician training may include the following note about phototherapy lights. None of the currently marketed neonatal phototherapy devices ("bili lights") in the US fall within the contraindicated range²¹ described above. Hospitals can easily characterize their own neonatal phototherapy units to determine this.

Nursing Professionals

Advise nursing and floor staff of psoralen-treated platelets. Nurses should be informed that products will come in a slightly larger bag. Nursing should be made aware of the attributes of psoralen treated components. Nursing staff might be accustomed to seeing CMV-negative printed below the blood type or a "Rad-sure[®]" label on irradiated products. These labels will not generally be seen on psoralen-treated platelet products. Platelets that have been pathogen reduced will have a label that states "psoralen treated."



INTENDED USE, CONTRAINDICATIONS, AND WARNINGS

Rx Only

Intended Use

The INTERCEPT Blood System for platelets is intended to be used for ex vivo preparation of pathogen-reduced Amicus apheresis platelet components suspended in 65% PAS-3/35% plasma, and Trima apheresis platelet components suspended in 100% plasma, in order to reduce the risk of transfusion-transmitted infection (TTI), including sepsis, and to potentially reduce the risk of transfusion-associated graft versus host disease (TA-GVHD).⁴

Contraindications

Contraindicated for preparation of platelet components intended for patients with a history of hypersensitivity reaction to amotosalen or other psoralens.

Contraindicated for preparation of platelet components intended for neonatal patients treated with phototherapy devices that emit a peak energy wavelength less than 425nm or have a lower bound of the emission bandwidth of <375nm due to the potential for erythema resulting from interaction between ultraviolet light and amotosalen.⁴

Warnings and Precautions

Only INTERCEPT Processing Sets for platelets are approved for use with the INTERCEPT Blood System. Use only the INTERCEPT INT100 Illuminator for UVA illumination of amotosalen-treated platelet components. No other source of UVA light may be used. Please refer to the Operator's Manual for the INT100 Illuminator. Discard any platelet components not exposed to the complete INT100 illumination process

Tubing components and container ports of the INTERCEPT Blood System for Platelets contain polyvinyl chloride (PVC). Di(2-ethylhexyl)phthalate (DEHP) is known to be released from PVC medical devices, and increased leaching can occur with extended storage or increased surface area contact. Blood components will be in contact with PVC for a brief period of time (approx. 15 minutes) during processing. The risks associated with DEHP released into the blood components must be weighed against the benefits of therapeutic transfusion.

Psoralen-treated platelets may cause the following adverse reaction: Acute Respiratory Distress Syndrome (ARDS). An increased incidence of ARDS was reported in a randomized trial for recipients of psoralen-treated platelets, 5/318 (1.6%), compared to recipients of conventional platelet components (0/327). Monitor patients for signs and symptoms of ARDS.

Additional warnings apply to the manufacturing process; refer to package insert for further information.⁴

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