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INTERCEPT® Blood System for Platelets Pathogen Reduction System

(psoralen-treated; pathogen-reduced)

Frequently Asked Questions (FAQ)

1. What are the advantages of INTERCEPT® Blood System treated (psoralen treated) platelets compared to conventional platelets?

INTERCEPT® Blood System treated (psoralen treated) platelets are a transfusion-ready product that delivers significant clinical benefits to patients to reduce risk of sepsis, transfusion-transmitted infection (TTI), and prevent transfusion-associated graft-versus-host disease (TA-GVHD) [1]

Benefits of INTERCEPT treated (psoralen treated) platelets:

- Broad spectrum inactivation of established and emerging pathogens (bacteria, viruses, protozoans) reducing the risk of transfusion-transmitted infection (TTI) and sepsis/bacteremia, as well as leukocytes (T-cells).[1]
- Proactively mitigates risk from emerging arboviral and parasitic threats (Zika, chikungunya, dengue, and babesia.)
    - FDA Guidance for Zika virus states that pathogen reduction (e.g. INTERCEPT Blood System) can be used in place of Zika testing or importing from non-endemic areas.[2]
    - Pathogen reduction (e.g. INTERCEPT Blood System) is an FDA recommended option to mitigate Babesia transfusion transmission risk for the states required to implement a strategy.[3]
    - The INTERCEPT Blood System reduces the risk of *T. Cruzi* and *Plasmodium* parasite TTI.[1]
- Meets FDA Guidance "Bacterial Risk Control Strategies for Blood Collection Establishments and Transfusion Services to Enhance the Safety and Availability of Platelets for Transfusion" without reducing shelf life, or adding the cost and complexity of implementing and managing secondary bacterial testing or secondary bacterial cultures in the hospital setting.[4] See question 11 of this document for further detail regarding Pathogen Reduction and secondary bacterial testing.
- Alternative to gamma irradiation: FDA[1] has approved and AABB Standard 5.19.3.1[5] recommends pathogen reduction (e.g. INTERCEPT treatment) as an alternative to gamma irradiation for the prevention of TA-GVHD. Use of pathogen reduction reduces labor, material, and regulatory costs associated with the irradiation of platelet units, and the maintenance of irradiation equipment.
- Receive fresher platelets: due to eliminating the need for primary bacterial culture, hospitals may receive units sooner, allowing for longer overall shelf life.[6]
- Outpatient reimbursement. HCPCS codes have been created by CMS to allow for outpatient billing/payment for pathogen reduced (INTERCEPT treated) platelets.

2. Can INTERCEPT treated (psoralen treated) platelets be used for any indication

- Yes. INTERCEPT treated (psoralen treated) platelets can be used according to US standards of care in all patient populations except patient populations with contraindications listed on question #3 and in the package insert.[1] There are no patient medical need requirements for the use of these platelets.
- INTERCEPT treated (psoralen treated) platelets may be used in conjunction with conventional platelets as needed.

3. Are there any contraindications for INTERCEPT treated (psoralen treated) platelets?

- Patients with a history of a hypersensitivity reaction to amotosalen or other psoralens should not use INTERCEPT treated (psoralen treated) platelets.
  - NOTE: No cases of psoralen or amotosalen hypersensitivity have been reported to Cerus.
- INTERCEPT treated (psoralen treated) platelets should not be used in neonatal patients treated with phototherapy devices that emit a peak energy wavelength less than 425 nm or have a lower bound of the emission bandwidth <375 nm.
  - NOTE: American Academy of Pediatrics-Clinical Practice Guidelines recommend a spectrum between 430-490 nm (visible light) for intensive phototherapy; which is outside the bounds of the INTERCEPT Blood System contraindication language.[7] All neonatal phototherapy devices currently marketed in the US are compliant with the recommendation and therefore do not emit radiation overlapping with the INTERCEPT contraindicated range.[8] No photosensitivity reactions have been reported to Cerus in neonates undergoing phototherapy.[9]

4. Can you comment on ethical/logistical issues around dual inventories (i.e., pathogen reduced, conventional)?

- The movement to a 100% supply of INTERCEPT treated (psoralen treated) platelets in the hospital blood bank can require a transition period as hospital adoption and supply increases. Blood banks have experience managing multiple platelet inventories in the form of irradiated and/or CMV-tested products. INTERCEPT treated (psoralen treated) platelets can be stocked and made available using similar storage and release strategies.
- Hospitals that have recently implemented have employed a variety of strategies, from providing pathogen reduced products to specific patient populations (i.e., hematology/oncology, pediatrics) or on a first in, first out basis.[10,11]

5. Can you comment on the safety of the psoralen used to produce INTERCEPT treated (psoralen treated) platelets?

- Psoralens are common in a wide variety of foods, including citrus fruits, vegetables such as celery and carrots, figs, and many traditional food seasonings.
- The safety of the INTERCEPT treatment (psoralen treatment) pathogen reduction process has been demonstrated in several animal models, in vitro and in vivo studies.[12-15]
- No increased toxicological risk was associated with the psoralen (known as amotosalen) exposure in animal toxicity studies using at least 10,000-fold the anticipated clinical exposure from 300 mL of INTERCEPT treated (psoralen treated) platelets.[13,16,17]
- No adverse reproductive or developmental effects were observed in neonatal rats treated with amotosalen relative to the anticipated dose exposure.[18]
- No evidence of carcinogenicity was observed in clinical studies after repeated dosing with amotosalen at doses ~1,200 times the routine exposure from a single 300mL INTERCEPT treated (psoralen treated) platelet transfusion.[19]

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6. Who is currently using INTERCEPT treated (psoralen treated) Blood System?

In the US:

- > 65 blood centers currently produce INTERCEPT treated (psoralen treated) pathogen reduced platelets, for a partial list go to: https://intercept-usa.com/implement-intercept/us-customer-list
- > 250 hospitals, including several large academic medical centers, cancer centers, children's hospitals, military/VA hospitals, and critical care centers, are routinely transfusing INTERCEPT treated (psoralen treated) platelets.

- Over the last 15 years, INTERCEPT Blood System platelet and plasma kits have been sold to produce approximately 6.5 million pathogen reduced (psoralen treated) blood components globally.

7. Are data available about routine use of INTERCEPT treated platelets in hospitals and countries that have already implemented?

- Results from ten years of active hemovigilance study involving 4,765 patients, 21,548 INTERCEPT treated (psoralen treated) platelet transfusions, and 26 centers in 15 European countries was described in 2015 by Knutson et al[20] and Cerus 2017.[21]

- National hemovigilance programs have been in place in Belgium, France and Switzerland since 2006. These systems track tens of thousands of units and patients each year. To date, no transfusion-transmitted infections (TTIs) or sepsis-related fatalities, acute respiratory distress syndrome (ARDS), or TA-GVHD have been reported in association with more than 875,000 INTERCEPT treated (psoralen treated) platelet units transfused in these countries.[22-25]

8. Is there any experience/data related to INTERCEPT treated (psoralen treated) platelet use in pediatric populations?

- A US academic tertiary care medical center reported findings from a quality assurance review study of platelet utilization, associated red blood cell transfusion trends, and short-term safety of conventional vs. INTERCEPT treated (psoralen treated) platelets over a 21-month period while transitioning from conventional to INTERCEPT treated platelets. Over 1000 transfusions were transfused to NICU patients (age 0-12 months), infants (patients age 0-12 months not admitted to the NICU) and pediatric patients (age 1-18 years). No difference in adverse events were seen in any of these patient groups between conventional and INTERCEPT platelets.[9]

- A seven-year, multi-center active hemovigilance program in 21 hospitals tracked >19,000 transfusions in 4,067 patients. Two hundred and forty-two (242) pediatric patients were included in this study. Of these, 46 were neonates. Similar rates of adverse events were observed in pediatric and neonate patients receiving INTERCEPT treated (psoralen treated) and conventional platelets. There were no reports of any adverse events in the NICU population.[20]

- An analysis of pediatric data from the French national hemovigilance program found no cases of transfusion-associated sepsis or TA-GVHD in >1,000 pediatric and neonatal patients transfused with >7,250 INTERCEPT treated (psoralen treated) platelets without gamma irradiation and CMV serology.[26]

- Analysis of 51 pediatric (>1 to <18) patients and 41 infants (<1) transfused with INTERCEPT treated (psoralen treated) platelets during the chikungunya virus epidemic on Ile de La Réunion, France, where more than 30% of 750,000 inhabitants were infected. Local blood donation was suspended to prevent transfusion transmitted infection. To sustain the availability of platelet components, the Établissement Français du Sang implemented universal INTERCEPT treated (psoralen treated) treatment. No unexpected adverse events were reported in pediatric or neonate patients.[27]

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9. How effective is INTERCEPT treatment (psoralen treatment) on CMV?

- AABB Standard 5.19.25 states that "the blood bank or transfusion service shall have a policy regarding transfusion of cellular components selected or processed to reduce the risk of cytomegalovirus (CMV) transmission".
- INTERCEPT treated (psoralen treated) demonstrates inactivation of CMV in platelets in PAS-3 at ≥ 4.9 $\log_{10}$ reduction, for platelets in 100% plasma, pseudorabies virus was used as a CMV model and showed ≥ 4.2 $\log_{10}$ reduction, respectively.[1]
- Many current US hospitals use INTERCEPT treatment as their risk reduction technique for mitigating transfusion transmission of CMV.
- In a mouse model study, conventional platelets spiked with CMV led to CMV infection in transfusion recipients, similarly spiked platelets then treated with the INTERCEPT® Blood System did not result in infection.[28]
- In an in vitro study, no cell-free or cell-associated CMV was detected by viral cell culture following INTERCEPT treatment of platelets, while CMV was detected in untreated leukoreduced components.[29]

10. Can you provide information on the difference in corrected count increment (CCI) with INTERCEPT treated (psoralen treated) platelets? Do lower CCIs affect hemostatic efficacy or increase the need for blood components?

- Lower corrected count increment (CCI), a measure of post-transfusion circulating platelet levels, have been reported with pathogen-reduced platelets.[30]
- Multiple large-scale clinical trials have shown a lack of correlation between CCI response and bleeding outcome.[31-35]
- In the PLADO study no significant difference in ≥ Grade 2 bleeding was observed between patients receiving low, medium, and high conventional platelet doses despite different CCI. [34] The PLADO study also observed that the number of Red Blood Cells (RBC) transfusions did not differ between the three platelet dose groups.
- While a low CCI response may trigger the need for additional workup to determine etiology, including risk of refractoriness, it does not conclusively indicate a lack of platelet efficacy.
- CCI can be impacted by a variety of reasons, including: patient condition, platelet dose and processing, and transfusion history.[36]
- INTERCEPT® Blood System treated platelet key takeaways:
- Large clinical trials show no difference in Grade ≥2 or higher bleeding with INTERCEPT treated platelets, despite mildly reduced CCIs.3[2,33,37,38]
- Immunogenicity, a differentiating factor in a refractory diagnosis, was significantly lower in clinical trials for INTERCEPT treated platelets compared to conventional.[32]
- Hemovigilance studies of the large-scale, routine use of INTERCEPT treated platelets have shown no impact on clinical hemostasis, utilization of platelets and/or RBC, or instance of refractory response to platelet transfusion.[39-41]
- A retrospective review of platelet use in a large Austrian hospital found no difference in platelet or RBC use over two 21-month periods before and after the introduction of INTERCEPT treated (psoralen treated) platelets. Approximately 1,700 patients were evaluated in each study arm, including cardiac surgery (~40%), hematology-oncology (~27%) and pediatric/neonate (~9%) patients. Platelet, RBC and plasma utilization, and the occurrence of transfusion-related adverse events, were comparable between the control and test periods.[40]
- A Cochrane Review of nine clinical trials found no difference in clinically significant or severe bleeding, or in red cell transfusion requirements between conventional and pathogen-reduced platelets.[42]
- A meta-analysis of five randomized controlled trials found no difference in bleeding trends with INTERCEPT treated (psoralen treated) platelets vs. conventional platelets.[43]

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11. Can INTERCEPT treatment (psoralen treatment) replace bacterial detection for platelets (including primary culture and secondary testing)?

- Yes. The AABB Standards for Blood Banks and Transfusion Services, 31th Ed. requires blood centers to "have methods to detect bacteria or use pathogen reduction technology in all platelet components."[5]
- In the September 2019 FDA guidance: "Bacterial Risk Control Strategies for Blood Collection Establishments and Transfusion Services to Enhance the Safety and Availability of Platelets for Transfusion: Guidance for Industry" pathogen reduction (e.g. INTERCEPT Blood System for Platelets Pathogen Reduction system) is listed as an option to mitigate the bacterial risk of platelets without the need of primary culture or secondary culture or testing.[4]

12. Can you speak to the Acute Respiratory Distress Syndrome (ARDS) listed in the Warnings and Precautions section of the INTERCEPT treated (psoralen treated) platelet package insert?

- An increased incidence of ARDs was reported in patients receiving INTERCEPT treated (psoralen treated) platelets (n=5/318) vs. conventional platelets (n=0/318) in the SPRINT study.[44]
- A subsequent reanalysis of the SPRINT data conducted by an independent blinded expert panel observed no difference in the incidence of acute lung injury (ALI) or ARDs. The expert panel determined that the original discrepancy was likely due to differences in ALI diagnosis criteria across study sites.[44,45]
- National hemovigilance programs as described above, have not identified increased risk of ARDS associated with INTERCEPT treated (psoralen treated) platelets.[22-25]
- It is important to note that incidence of grade 3 or 4 respiratory adverse events were comparable between INTERCEPT treated (psoralen treated) and conventional platelets in the SPRINT trial. Additionally, mortality was lower for recipients of INTERCEPT treated (psoralen treated) platelets vs. conventional platelets.[1]

13. How effective is INTERCEPT treatment (psoralen treatment) on inactivating leukocytes (T-Cells) that may cause transfusion-associated graft-versus-host disease (TA-GVHD)?

- FDA[1] has approved and AABB Standard 5.19.3.1[5] recommends pathogen reduction (e.g. INTERCEPT treatment) of platelets as an alternative to gamma irradiation for the prevention of TA-GVHD.
- The 31st edition of the AABB standard 5.19.3.1 reads: "Methods known to prevent transfusion-associated graft-vs-host disease shall be used, and include either irradiation or the use of a pathogen reduction technology that is known to inactivate residual leukocytes and is cleared or approved by the FDA or Competent Authority".[5]
- The use of INTERCEPT treatment (psoralen treatment) as an alternative to irradiation is supported by extensive data, including[46]:
  - Ability to achieve a 4 log reduction of T-Cells with INTERCEPT treated (psoralen treated) pathogen reduction.[1]
  - A high density of DNA modification (~1 adduct per 83 base pairs) in T-cells treated with psoralen is sufficient to ensure inactivation of most genes; the frequency of DNA modification with gamma irradiation is much lower (~1 strand-break per 37,000 base pairs).[47,48]
  - In vitro cytokine production by leukocytes was substantially reduced in INTERCEPT Blood System treated platelets in comparison to both conventional platelets and gamma irradiated platelets, indicating inactivation of leukocytes (T-cells) cells.[49]
  - Results from ten years of active hemovigilance study involving 4,765 patients, 21,548 INTERCEPT treated (psoralen treated) platelet transfusions, and 26 centers in 15 European countries was described in 2015 by Knutson et al[20] and Cerus Corp 2017[21] with no cases of TA-GVHD.

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14. How does INTERCEPT treatment (psoralen treatment) relate to the FDA Guidance on bacterial risk control strategies for platelets?

FDA released Guidance in September 2019[4]: "Bacterial Risk Control Strategies for Blood Collection Establishments and Transfusion Services to Enhance the Safety and Availability of Platelets for Transfusion." This Guidance recommends several platelet bacterial contamination mitigation options for blood centers and hospitals to implement to reduce risk including:

- Transfusion-Ready for Hospitals (Performed at the Blood Center)
- Pathogen Reduction: Day 5 expiry; no further measures necessary
- Large Volume Delayed Sampling (LVDS)*
  - 36 hrs w/12 hr hold, to Day 5 OR
  - 48 hrs w/12 hr hold to Day 7 (pending approval**)
- Two-Step Strategies: must pick one of each for processing
- Step One Options (performed at the Blood Center)
  - Primary bacterial culture* sample taken ≥ 24 hr after collection with a 12 hr hold
  - LVDS culture* sample taken ≥ 36 hr after collection with a 12 hr hold
- Step Two Options (likely performed by the Hospital)
  - Secondary aerobic only culture on Day ≥3 to have Day 5 expiration
  - Secondary culture* on Day ≥4 to have Day 7 expiration (pending approval**)
  - Secondary bacterial testing every 24 hrs prior to transfusion starting on Day 4 to have Day 7 expiration

*aerobic and anaerobic; **At the time of the finalization of this guidance, the instructions for use of the culture-based device currently labeled as a "safety measure" require a primary culture and secondary test to extend dating of platelets. Therefore, the LVDS no sooner than 48 hours strategy for a 7-day dating period cannot be implemented until appropriately labeled devices are available

15. What are the advantages of INTERCEPT treatment (psoralen treatment) vs. culture and/or secondary bacterial testing?

- **INTERCEPT treated (psoralen treated) platelets are a transfusion-ready product.**
  Hospitals do not need to implement new technology (i.e., secondary bacterial testing). The INTERCEPT treatment (psoralen treatment) process is performed at the blood center; no further measures are necessary prior to release for up to five days. Conversely, secondary bacterial testing introduces a new test and process to hospitals, which may require additional training, new SOPs, personnel, inventory logistics, FDA registration, etc.
- **INTERCEPT treatment is effective against a broad spectrum of pathogens.**
  In addition to a host of clinically relevant bacteria, the INTERCEPT Blood System also inactivates viruses and protozoans, including certain emerging pathogens (Zika virus, babesia), and T-cells. Bacterial culture and testing only screen for bacterial contamination.
- INTERCEPT treatment is an alternative to gamma irradiation for the prevention of TA-GVHD.
- INTERCEPT treatment meets the requirement of a CMV mitigation strategy.
- Treatment with the INTERCEPT Blood System inactivates pathogens in the entire platelet unit, avoiding sensitivity and specificity issues related to sampling.
- Depending on viral marker testing turnaround times, hospitals may obtain fresher platelets with INTERCEPT treated (psoralen treated) platelets.[6]

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16. What is the shelf-life for INTERCEPT treated (psoralen treated) platelets and how can they help reduce waste?

- INTERCEPT treated (psoralen treated) platelets are approved for a 5-day shelf life.[1]
- Since INTERCEPT treated (psoralen treated) platelets do not require primary bacterial culture, hospitals may receive platelet units sooner, with a potential effective shelf-life of ~4 days vs. ~3 days for conventional platelets. Hospitals introducing INTERCEPT treated (psoralen treated) platelets have reported substantial improvements in the availability of fresher platelets.[6]
- Platelet outdate rate and associated waste may also be reduced with the gain in effective shelf-life.

Rx only. See package insert for full prescribing information at hcp.intercept-usa.com/resources.

There is no pathogen inactivation process that has been shown to eliminate all pathogens. Certain non-enveloped viruses (e.g. HAV, HEV, B19, and poliovirus) and *Bacillus cereus* spores have demonstrated resistance to the INTERCEPT process.

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 peak wavelengths less than 425 nm, or have a lower bound of the emission bandwidth <375 nm, due to the potential for erythema resulting from interaction between ultraviolet light and amotosalen.

WARNINGS AND PRECAUTIONS
Only INTERCEPT Processing Sets for platelet components are approved for use in the INTERCEPT Blood System. Use only the 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.

PLATELETS
INTERCEPT processed 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 INTERCEPT processed platelets, 5/318 (1.6%), compared to recipients of conventional platelet components (0/327). Monitor patients for signs and symptoms of ARDS.

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