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Thank you for your request for more information about transfusing neonatal patients with pathogen-reduced platelets treated with the INTERCEPT® Blood System. The INTERCEPT® Blood System for platelets is intended for *ex vivo* preparation of pathogen-reduced platelet components in order to reduce the risk of transfusion-transmitted infections, including sepsis, and as an alternative to gamma irradiation for the prevention of transfusion associated graft-versus-host disease.[1] The INTERCEPT Blood System utilizes a psoralen (amotosalen) and UVA light for inactivation of a broad spectrum of pathogens and donor T-cells.[1]

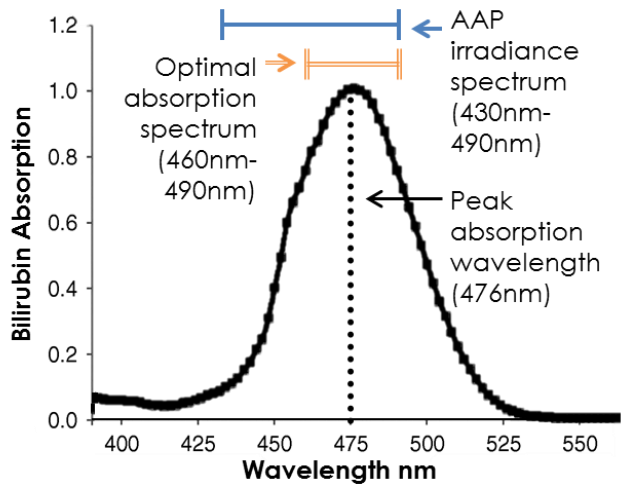
Executive Summary

- The FDA-approved package insert for the INTERCEPT Blood System for platelets includes a precautionary contraindication on the transfusion of neonatal patients being treated with phototherapy devices:
    - *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.*[2,3]
- This precautionary contraindication is based on the theoretical safety concerns associated with the generation of reactive oxygen species (ROS) by psoralens when they are exposed to ultraviolet light, not clinical experience.
    - The absorbance spectrum of amotosalen is primarily in the ultraviolet range, dropping off significantly at 375nm, and to zero at 400nm.
- The 2004 American Association of Pediatrics (AAP) guidelines dictate that phototherapy devices should not emit significant UV light <400nm.[4]
    - Currently marketed phototherapy devices adhere to this, and do not emit wavelengths in the range indicated in the contraindication.
- No adverse events related to this contraindication have been reported to date.
- Thus, INTERCEPT treated platelets can be safely transfused to neonatal patients who are treated with AAP compliant phototherapy devices.

General Considerations:

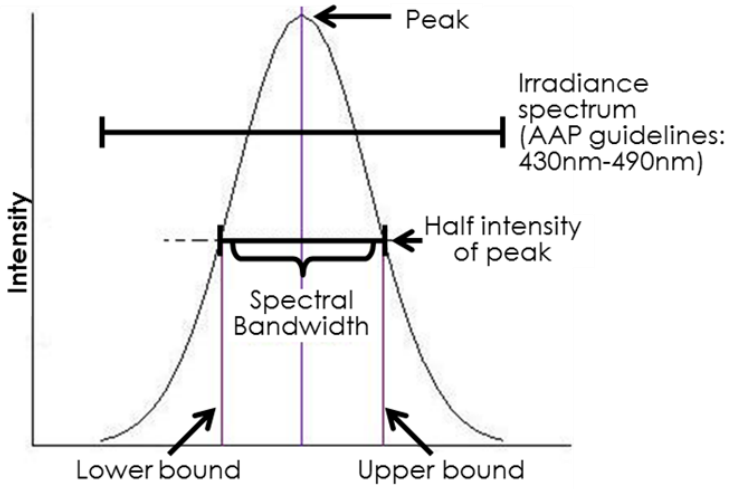
- **Treatment of Neonatal Hyperbilirubinemia**
  - Phototherapy is a highly efficacious, low side-effect, treatment for neonatal hyperbilirubinemia utilizing photoconversion of bilirubin to soluble photoisomers, allowing for excretion through kidneys or bile.
  - The 2004 AAP guidelines recommend phototherapy devices that emit within 430-490nm wavelengths, and that do not emit significant ultraviolet radiation [<400nm], for hyperbilirubinemia treatment.[4]
    - The optimal emission spectra for bilirubin phototherapy is based on the bilirubin absorption spectra and peaks in the blue-green region of visible light (460-490nm) at 476nm (figure 1).[4-8]

Figure 1: Bilirubin absorption spectrum



- **Understanding the 2004 AAP Hyperbilirubinemia Device Guidelines**
  - Phototherapy devices are mainly evaluated on emission spectra and the peak wavelength (wavelength with the highest total energy) produced.
  - Other key metrics include spectral bandwidth, and the upper and lower bound of the device's emission spectrum (figure 2).
  - While these metrics can vary between devices, in the US, all are above the INTERCEPT contraindicated minimums of >425nm for peak wavelength and >375nm for lower bound of the bandwidth.[6]

Figure 2: Phototherapy Device Irradiance Measurement



- **Peak wavelength:** the portion of the irradiance spectrum where the greatest energy is emitted.
- **Bandwidth:** distance between the two wavelengths on either side of the peak that are at half the intensity of the peak.
- **Lower bound:** the side of the bandwidth that has the shorter wavelength .

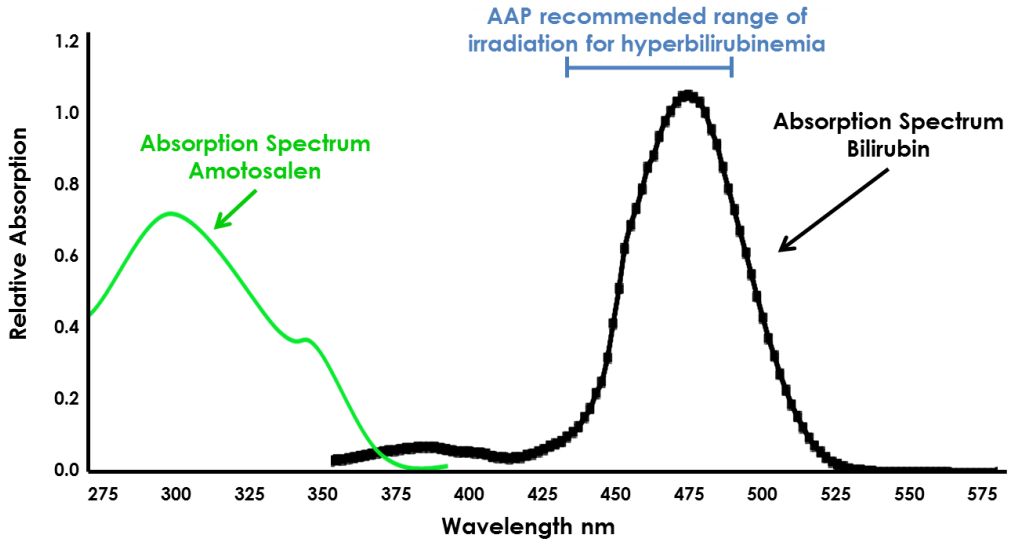
In this white paper, we discuss the theoretical basis for the precautionary contraindication and explain why INTERCEPT treated platelets do not pose a significant risk for neonatal patients being treated with AAP compliant phototherapy devices.

Interaction of Psoralen with Ultraviolet Light

When exposed to UV light, some psoralens have been shown to generate reactive oxygen species (ROS), which can contribute to localized inflammatory responses, erythema, and/or dermal/ocular phototoxicity.[9,10]

The active compound used in the INTERCEPT Blood System for pathogen reduction is the synthetic psoralen amotosalen. Amotosalen was selected from a group of over 100 psoralens due, in part, to it's enhanced nucleic acid binding and reduced ROS generation, when exposed to UV light, in comparison to other psorarlens.[11,12] The amotosalen absorbance spectrum drops off at 375nm, and to zero at 400nm. This does not overlap with the target range for phototherapy devices used for hyperbilirubinemia treatment, as set by the AAP guidelines and bilirubin absorption spectrum (figure 3).[4,5]

Figure 3: Absorption Spectrum of Amotosalen and Bilirubin



While the light emitted by phototherapy devices should not overlap with the activation/absorption spectrum of amotosalen, the contraindication of peak energy wavelength <425 nm, and/or having a lower bound of the emission bandwidth <375 nm, was described on the basis of theoretical safety concerns and historical phototherapy devices with broad spectrum illumination that may have overlapped with the amotosalen wavelength spectrum.[3]

Amotosalen Phototoxicity Studies

The potential phototoxic impact of residual amotosalen after INTERCEPT treatment was evaluated in two preclinical studies. These studies compared the dermal and ocular responses to irradiation from a Xenon Arc Lamp after transfusion with INTERCEPT plasma, vehicle, or positive control 8-methoxypsoralen (8-MOP, a psoralen used clinically for its high ROS generation) in rats. The Xenon Arc Lamp provides irradiation down to 300nm and, therefore, models the impact of wavelengths that fall below AAP standards,[4] and overlap with the amotosalen absorption spectrum. In both studies, no evidence of dermal or ocular photo-toxicity occurred in the vehicle or amotosalen-treated animals, whereas dermal phototoxicity was present, as expected, in the 8-MOP treated animals.[13]

Clinical Use of INTERCEPT Treated Platelets in the Neonate Population

It is not ethically feasible to perform the clinical trials necessary to conclusively prove that the residual amotosalen in INTERCEPT treated blood components does not increase the risk of

neonatal erythema from any of the phototherapy devices used in the US or Europe. However, in Europe, where hemovigilance reporting is mandatory, and >875,000 INTERCEPT-treated platelet units have been transfused without age restriction,[14-20] there have been no reports of adverse events relating to transfusion of INTERCEPT-treated platelets and neonates undergoingphototherapy.[17,21,22] In the US, where hemovigilance is optional, data showing no increase in adverse events relating to INTERCEPT-treated platelets and phototherapy has been recently published.[23]

Conclusion

In conclusion, the FDA-approved package insert for the INTERCEPT Blood System for platelets includes a precautionary contraindication related to transfusion of neonatal patients who are treated with phototherapy devices that emit a peak energy wavelength <425 nm, and/or have a lower bound of the emission bandwidth <375 nm. No related adverse events related to this contraindication have been reported to date. In addition, currently marketed phototherapy devices do not emit wavelengths in the range indicated in the contraindication. Thus, use of the INTERCEPT Blood System for platelets should not pose a significant risk for neonatal patients who are treated with AAP compliant phototherapy devices.

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