Date of Decision: May 7, 2024

# RISK ASSESSMENT SUMMARY

VMF 006-494

PrecisePRP™ Equine

(equine leucoreduced allogeneic pooled freeze-dried platelet-rich plasma)

Powder for injectable suspension

Horses

PrecisePRP™ Equine is indicated to provide a species-specific source of concentrated platelets in plasma in horses.

Developed by:

VetStem, Inc.

## Executive Summary

PrecisePRP™ Equine is equine leucoreduced allogeneic pooled freeze-dried platelet-rich plasma (PRP) intended to provide a species-specific source of concentrated platelets in plasma for horses. PrecisePRP™ Equine is an allogeneic animal cell, tissue, and cell- and tissue-based product (ACTP) that is administered as an intra-articular injection. ACTPs are articles containing, consisting of, or derived from cells or tissues that are intended for implantation, transplantation, infusion, transfer, or other means of administration to an animal recipient. (The term “allogeneic” refers to cells or tissues derived from a donor that is unrelated to, but the same species as, the recipient.)

### Product Characterization

FDA evaluated the product characteristics of PrecisePRP™ Equine and determined that:

- The protein markers selected for platelet identification are well established and appropriate to identify platelets in the product.
- The methods and controls used to reduce and count leukocytes in the product are appropriate to support the labeling statement that the leukocyte count of the product is less than 1,500 white blood cells per microliter.
- The potency markers selected for characterization are well known to be secreted by platelets and current scientific literature supports that the potency markers are relevant to platelet function.
- The manufacturing process is adequately controlled, and the risk of product contamination is appropriately mitigated.
- The other components of PrecisePRP™ Equine, in addition to platelets and plasma, are well understood and do not raise new safety concerns about the product.

The donor eligibility procedures for PrecisePRP™ Equine require that each donor horse meet specific selection and screening criteria and be tested for relevant disease agents before each donation. The donor horses are from a managed donor colony and the horses are periodically tested for relevant disease agents as part of herd maintenance. Platelets and plasma from donor horses are pooled, and the pooled plasma sample is also required to be tested for relevant disease agents. FDA determined that these procedures appropriately mitigate the risk of disease transmission from the donor horses to the animal recipient, other animals, and people who are in contact with PrecisePRP™ Equine or the animal recipient.

### Target Animal Safety

FDA reviewed the scientific literature on the historical use of platelets in human and veterinary medicine. The most common adverse events seen with intra-articular use of allogeneic and autologous PRP were transient joint pain and inflammation which were not serious. (The term “autologous” means the donor and recipient are the same individual.) The adverse events and their outcomes were similar despite injection of PRP into different joints and with varying compositions (for example, different platelet counts and concentrations). FDA determined that, based on the historical use of platelets in both people and animals, there is a low likelihood of harm to animal recipients of PrecisePRP™ Equine.

The developer conducted one safety study in adult research horses. Following sedation, the horses were administered either PrecisePRP™ Equine or sterile saline by intra-articular injection into the tarsocrural joint (the most proximal joint in the hock and also called the

tibiotarsal joint) on Day 0 and then the radiocarpal joint (the most proximal joint in the carpus, or "knee" in a horse) on Day 14. Each horse received the same treatment on both days.

Both the treated and control groups experienced transient lameness post-injection (one horse in the PrecisePRP™ Equine group and four horses in the control group). Transient joint pain and inflammation are documented in the literature as being associated with intra-articular injection of PRP. FDA did not identify any other safety signals associated with animal recipients receiving two injections of PrecisePRP™ Equine 14 days apart.

**User Safety**
FDA determined that the labeling for PrecisePRP™ Equine adequately mitigates the risks to people who handle, administer, or are exposed to the product. In addition, safe handling of animal blood is standard veterinary practice.

**Environmental Risk**
Platelets are found in most animals, and the relevant characteristics of the platelets are unchanged in PrecisePRP™ Equine. The product is also unlikely to be used in a large number of animals at one time in one geographic location and is for non-food producing animals only. Therefore, FDA determined that the potential environmental risk of PrecisePRP™ Equine is low.

**Conclusions**
Based on the data and information reviewed, FDA concluded that the developer of PrecisePRP™ Equine properly identified and appropriately mitigated the potential risks associated with the product, and FDA has no additional safety concerns. At this time, the Agency does not intend to object to the developer's marketing of the product.

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# I. GENERAL INFORMATION

## A. File Number

VMF 006-494

## B. Developer

VetStem, Inc.
14261 Danielson St.
Poway, CA 92064

Drug Labeler Code: 086198

## C. Proprietary Name

PrecisePRP™ Equine

## D. Product Category

ACTP

## E. Donor-Recipient Relationship

Allogeneic

## F. Dosage Form

Powder for injectable suspension

## G. How Supplied

PrecisePRP™ Equine is supplied as a single-use vial equal to 500,000 ± 100,0000 platelets per microliter when reconstituted with 8 mL sterile water for injection.

## H. Dispensing Status

Prescription (Rx)

## I. Route of Administration

Intra-articular

## J. Species

Horses

## K. Indication

To provide a species-specific source of concentrated platelets in plasma.

## II. INTRODUCTION

FDA assessed the potential hazards and likelihood of harm associated with the use of PrecisePRP™ Equine. PrecisePRP™ Equine is an allogeneic ACTP. As with any allogeneic ACTP, there are potential risks for immunogenic reactions and transmission of relevant disease agents with its use. There is also the potential for contamination or other product quality deviations to occur during manufacturing that could pose a risk to animals. FDA evaluated the PrecisePRP™ Equine product characteristics, manufacturing, donor eligibility, the available current scientific literature on PRP, and a safety study conducted in horses using PrecisePRP™ Equine to determine if these risks are appropriately mitigated.

## III. PRODUCT CHARACTERIZATION

### A. Characterization

PrecisePRP™ Equine is equine leucoreduced allogeneic pooled freeze-dried PRP intended to provide a species-specific source of concentrated platelets in plasma in horses.

FDA evaluated data, information, and controls supporting product identity including selected protein markers for platelet identification. FDA evaluated the developer's rationale and justification, as well as current scientific literature to assess the use of these markers. The markers selected are well-established platelet markers appropriate to identify platelets in this product and support the product’s intended use as a platelet concentrate.

FDA assessed the methods and controls used to reduce and count leukocytes in the product. A panleukocyte marker was used to characterize residual leukocytes in the product. Leukocyte quantification is performed on pre-lyophilized samples for product release. The methods are appropriate to support the leukocyte count label statement of less than 1,500 white blood cells per microliter.

In addition, FDA assessed the developer’s evaluation of product potency, including the potency markers selected and the methods used to detect and quantify the markers. FDA assessed current scientific literature to evaluate the appropriateness of the potency markers selected. FDA also reviewed available information on the assay specifications, including analytical sensitivity and assay time, range, and format. The potency markers selected for characterization are well known to be secreted by platelets, and FDA determined that current scientific literature supports the relevance of the potency markers to platelet function.

FDA evaluated information pertaining to the manufacture of PrecisePRP™ Equine. Part of the manufacturing process includes collecting platelets via apheresis using an FDA-cleared device that results in a leukocyte count of less than 1,500 leukocytes per microliter. FDA assessed batch records and other documents used to perform pooling, filling, and lyophilization, and based on these documents, determined that proper handling and storage of raw materials, filling specifications, and lyophilization parameters are utilized in the manufacture of PrecisePRP™ Equine. FDA also evaluated the methods used for reducing risk of releasing contaminated product, including the methods and acceptance criteria for sterility, mycoplasma, and

endotoxin testing. FDA concluded that the manufacturing process is adequately controlled and supports consistent manufacturing. FDA also determined that an appropriate quality program is utilized supporting that the product is consistently manufactured and evaluated for adequate quality.

In addition to platelets and plasma, manufacture of PrecisePRP™ Equine also involves the use of the following components:

- an anti-coagulant used in blood collection;
- a bidirectional clave supplied with the PRP for administration; and
- sterile water supplied by the end user to reconstitute the lyophilized end product.

Use of these components is well understood, and these components do not raise new safety concerns with respect to the product.

**Conclusions:** FDA concluded that the relevant product characteristics for PrecisePRP™ Equine are maintained, any identified risks are mitigated, and the components that are in addition to platelets and plasma do not raise new safety concerns in regard to the product. In addition, FDA concluded that PrecisePRP™ Equine manufacture is consistent with the recommendations in GFI #253: Current Manufacturing Practice for Animal Cells, Tissues, and Cell-, and Tissue-Based Products, including that the process is adequately controlled, and risk of product contamination is appropriately mitigated.

## B. Donor Eligibility

FDA evaluated the donor eligibility procedures for PrecisePRP™ Equine. Allogeneic ACTPs, including PRP, have the potential to transmit diseases from the donor to the animal recipient, to other animals, or humans who are in contact with the product or animal recipient. Platelets and plasma from up to 18 individual, donor horses from a managed donor colony are pooled. Pooling has the potential to increase risk associated with relevant disease agent transmission because one contaminated donation can affect multiple recipients. FDA considered the use of pooling when evaluating the donor eligibility procedures for PrecisePRP™ Equine. The donor eligibility procedures for PrecisePRP™ Equine include use of donor selection criteria, including historical criteria (e.g., source criteria, vaccination criteria) donor herd management criteria (e.g., physical examination criteria, health observation criteria), screening criteria (e.g., clinical pathology criteria) and criteria for relevant disease agent testing performed ahead of each donation and periodically as part of herd maintenance. Donor screening and testing is performed in accordance with Guidance for Industry #254: Donor Eligibility for Animal Cells, Tissues, and Cell- and Tissue-Based Products and includes screening and/or testing for the equine agents listed in the guidance's Appendix A as well as other disease agents relevant for the specific product. In addition to donor testing, disease agent testing is performed on a sample of the pooled plasma to further mitigate relevant disease agent transmission risk.

**Conclusions:** Based on the donor eligibility procedures and product testing, FDA determined the risk associated with the potential for relevant disease agent transmission is appropriately mitigated.

## IV. TARGET ANIMAL SAFETY

### A. Scientific Literature

FDA considered the history of use of platelets in human and veterinary medicine to inform the risk profile of PrecisePRP™ Equine. To assess this, FDA evaluated the current scientific literature available on the use of:

- intra-articular PRP in animals (autologous and allogeneic),
- intra-articular PRP in humans (autologous and allogeneic), and
- allogeneic platelets for transfusion in humans.

Hazards associated with allogeneic platelet administration are well reported given decades of human medical community experience with platelet transfusions. Allogeneic PRP for intra-articular use poses some of the same hazards as allogeneic platelets for transfusion, such as risks for immunogenic reactions and infection due to disease agents introduced from the donor or through product processing and administration. The following adverse events have been reported with use of allogeneic, intra-articular PRP: transient intra-articular burning post-injection,[1] joint pain in the days following injection,[2,3] transitory joint inflammation,[3,4] self-limited local edema,[3] and self-limited difficulty walking.[3] Similar reactions have been identified with autologous intra-articular PRP use, such as ipsilateral knee pain with ankle treatment,[5] lower leg muscle soreness,[5] periarticular heat and/or swelling,[6] immediate and/or prolonged joint pain, swelling, or stiffness,[6,7] immediate injection site bruising or pain,[7] immediate post-injection nausea or faintness,[7] or other musculoskeletal symptoms at other locations in the body (upper body, non-treated limb).[7]

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[1] Bottegoni, C., Dei Giudici, L., Salvemini, S., Chiurazzi, E., Bencivenga, R., & Gigante, A. (2016). Homologous platelet-rich plasma for the treatment of knee osteoarthritis in selected elderly patients: an open-label, uncontrolled, pilot study. *Therapeutic advances in musculoskeletal disease*, *8*(2), 35–41. https://doi.org/10.1177/1759720X16631188

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[3] Caiaffa, Ippolito, F., Abate, A., Nappi, V., Santodirocco, M., & Visceglie, D. (2021). Allogenic platelet concentrates from umbilical cord blood for knee osteoarthritis: preliminary results. *Medicinski Glasnik : Official Publication of the Medical Association of Zenica-Doboj Canton, Bosnia and Herzegovina*, *18*(1), 260–.

[4] Garbin, L. C., Contino, E. K., Olver, C. S., & Frisbie, D. D. (2022). A safety evaluation of allogeneic freeze-dried platelet-rich plasma or conditioned serum compared to autologous frozen products equivalents in equine healthy joints. *BMC Veterinary Research*, *18*(1), 141–141. https://doi.org/10.1186/s12917-022-03225-4

[5] Paget, L. D. A., Reurink, G., de Vos, R.-J., Weir, A., Moen, M. H., Bierma-Zeinstra, S. M. A., Stufkens, S. A. S., Kerkhoffs, G. M. M. J., & Tol, J. L. (2021). Effect of Platelet-Rich Plasma Injections vs Placebo on Ankle Symptoms and Function in Patients With Ankle Osteoarthritis: A Randomized Clinical Trial. JAMA : The Journal of the American Medical Association, 326(16), 1595–1605.

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[7] Bennell KL, Paterson KL, Metcalf BR, et al. Effect of Intra-articular Platelet-Rich Plasma vs Placebo Injection on Pain and Medial Tibial Cartilage Volume in Patients With Knee Osteoarthritis: The RESTORE Randomized Clinical Trial. *JAMA.* 2021;326(20):2021–2030. doi:10.1001/jama.2021.19415

FDA considered the risk profile elucidated from the scientific literature on allogeneic platelets for transfusion and allogeneic and autologous PRP when conducting the risk evaluation for PrecisePRP™ Equine.

**Conclusions:** Adverse events were identified with the use of autologous and allogeneic PRP manufactured using a variety of processes. The adverse events that occurred were non-serious and clinical signs and outcomes were similar despite treating different joints and administering PRP with varying compositions (e.g., different platelet counts, different platelet concentrations, the presence or absence of leukoreduction). FDA concluded that the scientific literature on historical use of platelet concentrates in human and veterinary medicine supports a low likelihood of harm to animal recipients of PrecisePRP™ Equine.

## B. Safety Study Conducted in Research Horses

**Title:** Safety Study of Leucoreduced Allogeneic Freeze-Dried Pooled Platelet-Rich Plasma (PrecisePRP™ Equine) in Normal Equine Subjects (VS-2023-001)

**Study Dates:** April 2023 – August 2023

**Study Location:** Auburn, Alabama

**Study Design:**

Objective: This study was intended to evaluate safety of PrecisePRP™ Equine for intra-articular injection in adult horses when administered twice, 14 days apart.

Study Animals: Twelve adult horses (11 geldings and 1 mare; greater than 1 year of age), free from previous inclusion in experimental study.

Experimental Design: Horses were randomized to either the treatment group or the control group in a 1:1 ratio. Horses were administered either 4 mL of PrecisePRP™ Equine or sterile saline in the left or right tarsocrural joint (randomly selected) on day 0 and 4 mL of PrecisePRP™ Equine or sterile saline in the left or right radiocarpal joint on day 14.

Administration: Horses were given standing sedation with xylazine hydrochloride (0.02-0.8 mg/kg by intravenous injection). The joint to be injected was prepared with a chlorhexidine and alcohol scrub. It was not clipped.

Following sedation, PrecisePRP™ Equine or saline (4 mL) was administered by intra-articular injection on day 0 and day 14 using a 21-gauge, 1.5 inch needle.

**Table IV.1 Treatment Groups**

| Treatment group | Number of horses | Dose volume (mL) | Route of administration | Treatment days |
|---|---|---|---|---|
| Control (0.9% sodium chloride) | 6 | 4 | Intra-articular injection | Days 0 and 14 |
| PrecisePRP™ Equine | 6 | 4 | Intra-articular injection | Days 0 and 14 |

Measurements and Observations: Physical examinations were conducted on study days -7, 0, 7, 14, and 21. Injection site observations (heat, swelling, joint circumference, and passive flexion pain) and temperature, pulse rate, respiratory rate, attitude appetite, and observations for general health were conducted on days 0-7 and 14-21. On injection days, the injection site observations were measured three times (1, 6, and 12 hours post-injection). Complete blood cell counts and serum biochemistry panels were performed on study days -7, 0 or -3, 7, 14, and 21. A lameness examination using the American Association of Equine Practitioners scoring system was conducted on study days -7, 0-7, and 14-21.

**Results:**

All horses survived to study conclusion. No clinically relevant abnormalities were noted on the veterinary physical examinations, serum biochemistry panels, and complete blood cell counts performed. Similarly, there was no significant difference between joint heat, swelling, circumference, or passive joint flexion pain between the control group and the PrecisePRP™ Equine treatment group.

In the daily health observations performed, one horse in the control group that experienced a colic event had an elevated pulse rate observed for a one-day period. One horse in the PrecisePRP™ Equine treatment group was observed to have a high normal heart rate after each injection, which was not clinically significant.

Five horses experienced post-injection lameness in the treated limb during the study; four in the control group and one in the PrecisePRP™ Equine treatment group. The lameness observed in all horses was transient and did not require treatment. The horse in the PrecisePRP™ Equine treatment group developed lameness four days after the second injection. The lameness resolved within 24 hours without treatment.

**Conclusions:** Based on the study findings, FDA identified transient lameness associated with administration of PrecisePRP™ Equine that was similar to the intra-articular administration of saline. FDA did not identify any other safety signals associated with administration of PrecisePRP™ Equine based on the results of this study.

## V. HUMAN FOOD SAFETY

PrecisePRP™ Equine is intended for use in horses. Because it is not intended for use in food-producing animals, FDA did not evaluate data pertaining to residues in food (i.e., human food safety) in this risk evaluation.

**Conclusions:** FDA concluded there is no human food safety risk associated with PrecisePRP™ Equine as the product is intended for use in horses only.

## VI. USER SAFETY

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to PrecisePRP™ Equine:

"For use in horses only. Not for use in humans. Keep out of reach of children."

This product is labeled for use by or on the order of a licensed veterinarian. Safe handling of animal blood is standard veterinary practice.

**Conclusions:** FDA concluded that product labeling adequately mitigates risks to PrecisePRP™ Equine user safety.

## VII. ENVIRONMENTAL RISK

FDA evaluated the potential risk to the environment from marketing PrecisePRP™ Equine. Hazards to the environment were not identified. The product is derived from tissues endogenous to most animals. The relevant characteristics of the platelets are unaltered. The product is not expected to be used in a large number of animals at one time in one geographic location, and the product is intended for use in non-food producing animals only.

**Conclusions:** FDA concluded the potential risk to the environment is low from the marketing of PrecisePRP™ Equine.

## VIII. AGENCY CONCLUSIONS

FDA concluded that the developer of PrecisePRP™ Equine properly identified and appropriately mitigated the potential risks associated with the product, and FDA has no additional safety concerns. Although PrecisePRP™ Equine is not approved, conditionally approved, or index listed,[8] because FDA has determined the risks associated with PrecisePRP™ Equine are appropriately mitigated, at this time the Agency does not intend to object to marketing of the product.

### A. Marketing Status

This product may be dispensed only by or on the lawful order of a licensed veterinarian (Rx marketing status). Adequate directions for lay use cannot be written because professional expertise is required to properly administer the injection, provide adequate instructions for post treatment care, and monitor the safe use of the product, including treatment of any adverse reactions.

## IX. REFERENCES

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[8] See sections 512, 571, and 572 of the Federal Food, Drug, and Cosmetic Act [21 U.S.C. §§ 360b, 360ccc, and 360ccc-1]

Treatment of Hip Osteoarthritis. *Journal of clinical medicine*, *11*(15), 4505. https://doi.org/10.3390/jcm11154505

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Textor, J. A., & Tablin, F. (2013). Intra-Articular Use of a Platelet-Rich Product in Normal Horses: Clinical Signs and Cytologic Responses. *Veterinary Surgery*, *42*(5), 499–510. https://doi.org/10.1111/j.1532-950X.2013.12015.x