Date of Decision: April 24, 2024

RISK ASSESSMENT SUMMARY

VMF 006-550

PrecisePRP™ Canine

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

Powder for injectable suspension

Dogs

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

Developed by:

VetStem, Inc.

Executive Summary

PrecisePRP™ Canine is canine leucoreduced allogeneic pooled freeze-dried platelet-rich plasma (PRP) intended to provide a species-specific source of concentrated platelets in plasma in dogs. PrecisePRP™ Canine 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™ Canine 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™ Canine, 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™ Canine require that each donor dog meet specific selection and screening criteria and be tested for relevant disease agents before each donation. Platelets and plasma from donor dogs 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 dogs to the animal recipient, other animals, and people who are in contact with PrecisePRP™ Canine 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™ Canine.

The developer conducted one laboratory safety study in healthy, intact male beagles. Following sedation, the beagles were administered either PrecisePRP™ Canine or sterile saline by intra-articular injection into the stifle on Day 0 and the hip on Day 16. Each dog received the same treatment on both days. No adverse events associated with PrecisePRP™ Canine were

observed. Based on these results, FDA did not identify any safety signals to animal recipients receiving two injections of PrecisePRP™ Canine 16 days apart.

The developer conducted a clinical field study in 12 client-owned dogs that received multiple injections of PrecisePRP™ Canine on the same day. The dogs were a range of ages and had from two to eight joints treated. No adverse events were reported. Based on these results, FDA did not identify any safety signals to animal recipients receiving injections of PrecisePRP™ Canine in multiple joints on the same day.

User Safety
FDA determined that the labeling for PrecisePRP™ Canine 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™ Canine. The product is also unlikely to be used in a large number of animals at one time in one geographic location and is for dogs only. Therefore, FDA determined that the potential environmental risk of PrecisePRP™ Canine is low.

Conclusions
Based on the data and information reviewed, FDA concluded that the developer of PrecisePRP™ Canine 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.

Table of Contents

I. GENERAL INFORMATION

A. File Number

VMF 006-550

B. Developer

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

Drug Labeler Code: 086198

C. Proprietary Name

PrecisePRP™ Canine

D. Product Category

ACTP

E. Donor-Recipient Relationship

Allogeneic

F. Dosage Form

Powder for injectable suspension

G. How Supplied

PrecisePRP™ Canine 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

Dogs

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™ Canine. PrecisePRP™ Canine 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™ Canine product characteristics, manufacturing, donor eligibility, the available current scientific literature on PRP, and the studies conducted using PrecisePRP™ Canine to determine if these risks are appropriately mitigated.

III. PRODUCT CHARACTERIZATION

A. Characterization

PrecisePRP™ Canine is canine leucoreduced allogeneic pooled freeze-dried PRP intended to provide a species-specific source of concentrated platelets in plasma in dogs.

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™ Canine. 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™ Canine. 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™ Canine 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™ Canine 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™ Canine 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™ Canine. 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 36 individual, community-based donor dogs are pooled. Pooling has the potential to increase risk associated with relevant disease agent transmission because one contaminated donation can affect multiple recipients. In addition, community donors are at risk for exposure to relevant disease agents in their environment and from contact with other animals. FDA considered these risk factors when evaluating the donor eligibility procedures for PrecisePRP™ Canine. The donor eligibility procedures for PrecisePRP™ Canine include use of donor selection criteria, including historical criteria collected from dog owners and referring veterinarians (e.g., travel history criteria, medical history criteria), screening criteria (e.g., physical examination criteria, clinical pathology criteria), and criteria for relevant disease agent testing performed ahead of each donation. 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 canine 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™ Canine. 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]

---

[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

[2] Mazzotta, A., Pennello, E., Stagni, C., Del Piccolo, N., Boffa, A., Cenacchi, A., Buzzi, M., Filardo, G., & Dallari, D. (2022). Umbilical Cord PRP vs. Autologous PRP for the Treatment of Hip

[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.

[6] 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

[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™ Canine.

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™ Canine.

B. Laboratory Safety Study

Title: Pilot Safety Study of Intraarticular Leucoreduced Allogeneic Freeze-Dried Pooled Platelet-Rich Plasma (PrecisePRP™ Canine) in Normal Canine Subjects (VS-2023-02)

Study Dates: May 2, 2023 – August 14, 2023

Study Location: Fort Collins, CO

Study Design:

Objective: This study was intended to evaluate safety of PrecisePRP™ Canine for intra-articular injection in adult dogs when administered twice, 16 days apart.

Study Animals: Twelve healthy, intact male beagle dogs 1.5 years of age or older at day 0, weighing 8.2 to 13.2 kg.

Experimental Design: Dogs were randomized to either the treatment group or the control group in a 1:1 ratio. Dogs were administered either 2 mL of PrecisePRP™ Canine or sterile saline in the left or right stifle (randomly selected) on day 0 and 2 mL of PrecisePRP™ Canine or sterile saline in the opposite side hip joint on day 16.

Administration: Dogs were premedicated with acepromazine (0.01 mg/kg) 20 minutes ahead of the procedure. Dogs were administered propofol (2 mg/kg) to induce anesthesia and isoflurane for maintenance. The joint to be injected was clipped, cleaned, and disinfected.

Following sedation and joint preparation, PrecisePRP™ Canine or saline (2 mL) was administered by intra-articular injection on day 0 (stifle) and day 16 (hip) using a 21-gauge needle. The needle length used was 1.5 inches for the stifle. Needle length varied for the hip between 2.5 and 3.5 inches depending on dog size and amount of subcutaneous fat present.

Table IV.1 Treatment Groups

Treatment group	Number of dogs	Dose volume (mL)	Route of administration	Treatment days
Control (0.9% sodium chloride)	6	2	Intra-articular injection	Days 0 and 16
PrecisePRP™ Canine	6	2	Intra-articular injection	Days 0 and 16

Measurements and Observations: Veterinary physical examinations, lameness examinations, and body weight measurements were conducted on study days -1, 0, 7, 16, and 23. Injection site observations (heat, swelling, and passive flexion pain) and temperature, pulse rate, and respiratory rate were measured on days -1 (stifle and hip), 0 through 7 (stifle), and 16 through 23 (hip). 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 -6, 0, 7, 16, and 23. Daily observations were performed once a day on study days -1 through 23 to assess general health, appetite, and attitude and collect dog temperature, pulse rate, and respiratory rate.

Results:

All dogs survived to study conclusion. All dogs at all timepoints had a lameness grade of 0. No heat, swelling, or pain was detected on injection site observations. No clinically significant abnormalities were noted on the physical examinations, daily health observations, complete blood cell counts, or serum biochemistry panels performed. Body weight changes were small and considered not clinically significant.

Conclusions: FDA did not identify any safety signals to animal recipients receiving two injections of PrecisePRP™ Canine 16 days apart based on the results of this study.

C. Clinical Field Study

FDA evaluated information provided on 12 client-owned dogs that received multiple doses of PrecisePRP™ Canine on the same day in a clinical field study (VS-2023-05). The purpose of this study was to collect data on dogs injected with 2 mL of PrecisePRP™ Canine per joint under field conditions. Dogs treated ranged from 1.6 to 12.7 years of age. Five dogs had two joints treated, one dog had three joints treated, four dogs had four joints treated, one dog had six joints treated, and one dog had eight joints treated. No adverse events were reported.

Conclusions: FDA did not identify any safety signals to animal recipients receiving injections of PrecisePRP™ Canine in multiple joints on the same day based on this information.

V. HUMAN FOOD SAFETY

PrecisePRP™ Canine is intended for use in dogs. 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™ Canine as the product is intended for use in dogs only.

VI. USER SAFETY

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

"For use in dogs 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™ Canine user safety.

VII. ENVIRONMENTAL RISK

FDA evaluated the potential risk to the environment from marketing PrecisePRP™ Canine. 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™ Canine.

VIII. AGENCY CONCLUSIONS

FDA concluded that the developer of PrecisePRP™ Canine properly identified and appropriately mitigated the potential risks associated with the product, and FDA has no additional safety concerns. Although PrecisePRP™ Canine is not approved, conditionally approved, or index listed,[8] because FDA has determined the risks associated with PrecisePRP™ Canine 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

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

instructions for post treatment care, and monitor the safe use of the product, including treatment of any adverse reactions.

IX. REFERENCES

Mazzotta, A., Pennello, E., Stagni, C., Del Piccolo, N., Boffa, A., Cenacchi, A., Buzzi, M., Filardo, G., & Dallari, D. (2022). Umbilical Cord PRP vs. Autologous PRP for the Treatment of Hip Osteoarthritis. *Journal of clinical medicine*, *11*(15), 4505. https://doi.org/10.3390/jcm11154505

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

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–.

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

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. https://doi.org/10.1001/jama.2021.16602

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

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