



TANOVEA™-CA1

(rabacfosadine for injection)

16.4 mg rabacfosadine per vial

Antineoplastic

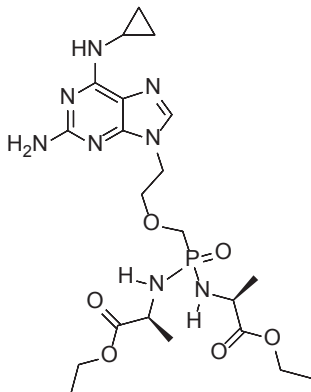
For intravenous use in dogs only

Conditionally approved by FDA pending a full demonstration of effectiveness under application number 141-475.

CAUTION: Federal (US) law restricts this drug to use by or on the order of a licensed veterinarian. Use only as directed. **It is a violation of Federal Law to use this product other than as directed in the labeling.**

DESCRIPTION:

Rabacfosadine is an acyclic nucleotide phosphonate. The molecular weight of rabacfosadine is 526.5 g/mole. The empirical formula is $C_{21}H_{35}N_8O_6P$. The structural formula is:



TANOVEA-CA1 is supplied as a sterile, white to off-white lyophilized powder in the form of a cake contained in a 3 mL amber glass vial. Each single-use vial contains 16.4 mg of rabacfosadine, present as the succinate salt, along with 20 mg of mannitol and 1.6 mg of citrate as excipients.

INDICATIONS:

TANOVEA-CA1 is indicated for the treatment of lymphoma in dogs.

DOSAGE AND ADMINISTRATION:

Always provide the Client Information Sheet to the dog owner with each dose administration.

Administer TANOVEA-CA1 at 1 mg/kg body weight as a 30-minute intravenous infusion, once every three weeks, for up to five doses.

Stepwise dose reductions to 0.8 mg/kg and 0.66 mg/kg or dose delays may be used to manage adverse reactions.

TANOVEA-CA1 is supplied as a sterile lyophilized powder for reconstitution before use. After reconstitution with 2 mL 0.9% Sodium Chloride Injection, USP, the reconstituted solution contains 8.2 mg/mL of rabacfosadine.

Reconstitution and administration of TANOVEA-CA1

Wear chemotherapy resistant gloves, goggles, and protective clothing in the preparation and administration of TANOVEA-CA1. Use aseptic technique in the preparation and administration of TANOVEA-CA1.

Reconstitution instructions

1. Obtain the desired number of vials from the refrigerator.
2. Add 2 mL of 0.9% Sodium Chloride Injection, USP to the single-use vial.
3. Gently invert the vial several times until the drug has completely dissolved and the solution is particle free.
4. The solution should be clear without visible particulates. If particulates are observed, the solution should be discarded.

Dilution for infusion and administration instructions

1. TANOVEA-CA1 should be diluted for infusion within 4 hours of reconstitution.
2. Add the calculated volume of reconstituted TANOVEA-CA1 (8.2 mg/mL) to 0.9% Sodium Chloride Injection, USP in a polyvinyl chloride (PVC) infusion bag or polypropylene infusion syringe to yield a total infusion volume of 2 mL per kg body weight.
3. **The volume to add should be calculated based on the exact weight of the dog.** (See Table 1. for example doses and administration volumes).
4. The infusion solution should be used within 24 hours of being added to the infusion bag or syringe and within 4 hours of being added to an intravenous transfer set. Protection from light is not needed.
5. Administer TANOVEA-CA1 as a 30-minute intravenous infusion.

Table 1. Example doses and volumes.

The dose to be administered should be calculated based on the exact weight of the dog. The table shows example doses and administration volumes at 1 mg/kg over 30 minutes.

Dog weight (kg)	Dog weight (lb)	Dose (mg)	Volume of reconstituted TANOVEA™ solution (mL)	Volume 0.9% NaCl (mL)	Total infusion volume (mL)	Rate of infusion (mL/minute)
5	11	5	0.6	9.4	10	0.3
10	22	10	1.2	18.8	20	0.7
15	33	15	1.8	28.2	30	1.0
20	44	20	2.4	37.6	40	1.3
25	55	25	3.0	47.0	50	1.7
30	66	30	3.7	56.3	60	2.0
35	77	35	4.3	65.7	70	2.3
40	88	40	4.9	75.1	80	2.7

Compatibility of administration sets containing ethyl vinyl acetate (EVA) has not been evaluated.

CONTRAINDICATIONS:

Do not use in dogs with pulmonary fibrosis or a history of chronic pulmonary disease that could lead to fibrosis, such as chronic bronchitis (see WARNINGS). Do not use in West Highland White Terriers due to a genetic predisposition for development of pulmonary fibrosis. Use with caution in other terrier breeds due to potential genetic predisposition for development of pulmonary fibrosis.

Do not use in dogs that are pregnant, lactating, or intended for breeding. Rabacfosadine is cytotoxic and can cause birth defects and affect female and male fertility. TANOVEA-CA1 has not been evaluated in pregnant, lactating, or breeding dogs.

WARNINGS:

Rabacfosadine was associated with life-threatening or fatal pulmonary fibrosis in the field studies. The pulmonary fibrosis may be an idiosyncratic toxicity. Monitoring for signs of pulmonary dysfunction and/or radiographic changes consistent with pulmonary fibrosis is recommended (see ADVERSE REACTIONS).

HUMAN WARNINGS:

NOT FOR USE IN HUMANS. KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

Wear chemotherapy resistant gloves to prevent contact with feces, urine, vomit, and saliva of treated dogs for 5 days following treatment. Place all waste materials in a plastic bag and seal before general disposal. Rabacfosadine is cytotoxic and can cause birth defects and affect female and male fertility. Pregnant and breast feeding women should not prepare or administer the product.

Special instructions for preparing and administering the product:

TANOVEA-CA1 should be administered under the supervision of a veterinarian experienced in the use of cancer chemotherapeutic agents.

Use standard measures for the safe handling of cytotoxic drugs

- Wear chemotherapy resistant gloves, goggles, and protective clothing
- Do not eat, drink, or smoke while handling the product
- Do not store food in or near the preparation area

Accidental skin contact

- In case of accidental contact with the skin, wash the affected area immediately and thoroughly with soap and water

Accidental eye exposure

- Remove contact lenses
- Rinse the eyes with large amounts of tap water (use eyewash station if present) for at least 10 minutes while holding back the eyelid
- Seek medical advice immediately and show the package insert or label to the physician

Accidental self-injection

- Remove glove
 - Let the wound bleed a few drops of blood
 - Rinse the wound thoroughly with plenty of tap water
 - Seek medical advice immediately and show the package insert or label to the physician
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PRECAUTIONS:

The safety and effectiveness of TANOVEA-CA1 has not been evaluated in conjunction with other chemotherapeutic agents or other treatment modalities.

The effect of concomitant medications on the metabolism of TANOVEA-CA1 has not been evaluated.

ADVERSE REACTIONS:

In two multi-institutional field studies, 22 dogs with untreated, relapsed, or refractory lymphoma received single-agent rabacfosadine (not commercial formulation) as an intravenous infusion at doses of 0.66 to 1.2 mg/kg administered once every three weeks for one to six doses.

All dogs experienced at least one adverse reaction, however not all adverse reactions were seen in each dog. Adverse reactions associated with rabacfosadine treatment when administered once every three weeks include:

General: lethargy, dehydration, fever

Gastrointestinal: anorexia/hyporexia, vomiting, diarrhea

Renal: increased creatinine, increased blood urea nitrogen, proteinuria, pyuria, bacteruria

Hepatic: elevated liver enzymes, elevated bilirubin

Cardiorespiratory: pulmonary fibrosis, aspiration pneumonia, tachypnea, dyspnea, tachycardia

Metabolic: weight loss

Hematologic: neutropenia, thrombocytopenia, anemia, hypertriglyceridemia, hypoproteinemia, hypoglobulinemia, hypoalbuminemia, increased creatine kinase, hypokalemia, hypophosphatemia

Ocular: injected sclera

Dermatologic: otitis externa, alopecia, dermatitis, pyoderma, ulcerations, excoriations

Most adverse reactions were Veterinary Cooperative Oncology Group (VCOG)¹ Grade 1-2. Grade 3 reactions included anorexia/hyporexia, weight loss, vomiting, diarrhea, otitis externa, dehydration, aspiration pneumonia, neutropenia, thrombocytopenia, anemia, bilirubinemia, and hypertriglyceridemia. Grade 4 reactions included tachypnea and neutropenia. Grade 5 reactions included dyspnea (secondary to pulmonary fibrosis). With the exception of pulmonary fibrosis, adverse reactions resolved either spontaneously, with supportive treatment, dose modifications, or dose delays.

Additional adverse reactions seen in dogs administered rabacfosadine at more frequent dosing schedules include:

- Dermatopathy including pruritic and erythemic lesions on the dorsum, and exudation, crusting, erythema, and necrosis with epidermal sloughing on the ears, face, ventral neck, and/or forelimbs.
- Glucosuria
- Type II pneumocyte hyperplasia (based on necropsy)

To report suspected adverse events, for technical assistance, or to obtain a copy of the Safety Data Sheet, contact VetDC, Inc at 1-877-468-3832.

For additional information about adverse drug experience reporting for animal drugs, contact FDA by telephone at 1-888-FDA-VETS or online at <http://www.fda.gov/AnimalVeterinary/SafetyHealth>.

INFORMATION FOR DOG OWNERS:

Always provide the Client Information Sheet and review it with the dog owner or person responsible for care of the dog. Advise dog owners about possible adverse reactions, when to contact a veterinarian, and how to clean up any saliva, urine, or feces from dogs treated with TANOVEA-CA1. The Client Information Sheet also contains warnings for humans and what to do in case of accidental human exposure to TANOVEA-CA1.

CLINICAL PHARMACOLOGY:

Rabacfosadine is a prodrug of 9-(2-phosphonylmethoxyethyl)-N6-cyclopropyl-2, 6-diaminopurine (cPrPMEDAP) and 9-(2-phosphonylmethoxyethyl) guanine (PMEG). Rabacfosadine is hydrolyzed intracellularly to cPrPMEDAP and subsequently deaminated

to PMEG. PMEG is then converted to its active phosphorylated form, PMEG diphosphate (PMEGpp), which is a potent, chain-terminating inhibitor of the major nuclear, replicative deoxyribonucleic acid (DNA) polymerases. The two prodrug moieties present in rabacfosadine increase the permeability and accumulation of metabolites in various cell types including peripheral blood mononuclear cells (PBMCs).

In vitro rabacfosadine has been demonstrated to inhibit DNA synthesis, resulting in S phase arrest and induction of apoptosis. Also *in vitro* rabacfosadine inhibits the proliferation of mitogen-stimulated lymphocytes and lymphoma/leukemia cell lines.

The *in vivo* data from studies in healthy dogs and dogs with lymphoma illustrated rapid clearance of rabacfosadine following a 30-minute intravenous infusion resulting in plasma exposure to the metabolite cPrPMEDAP and undetectable levels of the generally more cytotoxic agent PMEG. The exposure of rabacfosadine and cPrPMEDAP was linear with no gender differences. The mean peak plasma concentrations (C_{max}) for rabacfosadine and cPrPMEDAP occurred at approximately 30 minutes (T_{max}) and 1-2 hours, respectively. In dogs with lymphoma, rabacfosadine and cPrPMEDAP had a plasma half-life of <0.5 hour and 6 hours, respectively. In contrast to plasma, high concentrations of PMEG were readily detectable in PBMCs. Following rabacfosadine administration at 1 mg/kg over 30 minutes by intravenous infusion (once every 2 or 3 weeks), cPrPMEDAP and PMEGpp concentrations in lymphoid cells and tissues (represented by PBMCs) were 131 and 1,420 nM, respectively. In lymphoid cells, high concentrations of the active metabolite PMEGpp accumulated and persisted for greater than 24 hours. In PBMCs, the metabolites cPrPMEDAP and PMEGpp showed a terminal half-life of 25 hours and 68.7 hours, respectively. The observed PMEGpp concentrations in lymphoid cells and tissues are sufficient to allow for the desired antiproliferative effect following a single intravenous infusion administered once every three weeks.

Following intravenous administration of [^{14}C]-rabacfosadine to dogs, the excretion of radiolabeled material was similar in both feces and urine accounting for 42.4% and 32.5% of the dose, respectively, at 120 hours. By 24 hours, radioactivity was widely distributed throughout the body. Some of the highest concentrations in tissues observed, with the exception of excretory organs, were found in lymphoid tissues. The mean overall elimination of radioactivity after intravenous dosing was 79.7% over 120 hours.

Approximately 10% of the administered dose was retained in tissues. The overall mass balance including radioactivity retained in the tissues would be estimated to be a mean of 88.8%. No central nervous system penetration was observed.

While the cytotoxic agent PMEG has been observed in PBMCs, PMEG was not observed in the liver, kidney, bile, or urine following administration of [^{14}C]-rabacfosadine to dogs. Because the effective clinical plasma concentration is anticipated to be <2 μ M and rabacfosadine is a prodrug that has a short half-life in dogs, rabacfosadine is unlikely to be a clinically relevant inhibitor or inducer of the major CYP450 pathways.

REASONABLE EXPECTATION OF EFFECTIVENESS:

This drug is conditionally approved pending a full demonstration of effectiveness. In two pilot field studies evaluating different dosing regimens of rabacfosadine for the treatment of lymphoma in 65 dogs, 22 dogs received rabacfosadine (not commercial formulation) in a manner similar to the dosing schedule described in DOSAGE AND ADMINISTRATION. The data from these 22 dogs support a reasonable expectation of effectiveness. Of these 22 dogs, 8 dogs were treatment-naïve and 14 dogs had failed previous therapy. Response to treatment was evaluated using Response Evaluation Criteria in Solid Tumors (RECIST).²

In the first study, 17 of 50 dogs with treatment-naïve, relapsed, or refractory, T- or B-cell lymphoma received rabacfosadine as an intravenous infusion of 0.66 mg/kg to 1.2 mg/kg, once every three weeks, for one to five doses as described below:

- Three dogs were administered rabacfosadine by intravenous infusion at a dose of 1.2 mg/kg once every three weeks for one to four doses. One dog experienced a best response of complete response (CR) with progression free survival (PFS) of 370 days. One dog experienced a partial response (PR), but was withdrawn by the owner after 8 days on drug, while still in remission. The remaining dog experienced a best response of PR with PFS of 8 days.
- Five dogs were administered rabacfosadine by intravenous infusion at a dose of 1.0 mg/kg, once every 3 weeks for one to five doses. Three dogs experienced a best response of CR and two dogs experienced a best response of PR. PFS in the three dogs experiencing CR was 23, 119, and 179 days; PFS in the two dogs experiencing PR was 22 and 35 days.
- Six dogs were administered rabacfosadine by intravenous infusion at a dose of 0.82 mg/kg once every three weeks for one to five doses. Two dogs experienced a best response of CR, two dogs experienced a best response of PR, and two dogs experienced a best response of progressive disease (PD). PFS in three of the dogs showing response ranged from 50 to 751 days. One dog experiencing PR was withdrawn by the owner after 30 days on drug, while still in remission.
- Three dogs were administered rabacfosadine by intravenous infusion at a dose of 0.66 mg/kg once every three weeks for two to five doses. Two dogs experienced a best response of CR with PFS of 134 and 170 days. One dog experienced a best response of PR and with PFS of 48 days.

Ten of the 50 dogs that received rabacfosadine at various dosing schedules that achieved response (9 dogs with CR and 1 dog with PR), but then experienced recurrence of lymphoma, were subsequently retreated with rabacfosadine at a dose of 0.82 mg/kg once every 3 weeks for 1 to 5 doses. Five dogs experienced a best response of CR, one dog experienced a best response of PR, two dogs experienced a best response of stable disease (SD), and two dogs had a best response of PD during the retreatment. PFS in the six dogs with CR or PR ranged from 43 to 99 days.

In the second study, 5 of 15 dogs with relapsed B-cell lymphoma were treated with rabacfosadine by intravenous infusion at a dose of 1.0 mg/kg once every three weeks for one to six doses. Two dogs experienced a best response of CR, with PFS of 365 and 449 days. Two dogs experienced a best response of SD and one dog experienced a best response of PD.

The overall response rate (ORR) in the 22 dogs that were treated with rabacfosadine once every 21 days across both studies was 77% (46% CR, 32% PR). The ORR was 100% (8 of 8 dogs) in naïve dogs and 64% (9 of 14 dogs) in pre-treated dogs. The overall median PFS in the 17 dogs experiencing response was 134 days.

ANIMAL SAFETY:

The margin of safety and toxicity of rabacfosadine (not commercial formulation) was evaluated in three laboratory safety studies and one laboratory cardiovascular study. For each laboratory safety study, there were six male and six female, 7 to 8 month old Beagle dogs per treatment group. Three dogs/sex/group were necropsied following the last dose and three dogs/sex/group were necropsied following a 21-day recovery period.

In the first study, a single dose of rabacfosadine was administered by a 30-minute intravenous infusion at doses of 0, 0.25, 0.82, 2.5, and 8.2 mg/kg. Doses up to 2.5 mg/kg were tolerated. There were no adverse signs in the dogs administered 0.25 mg/kg. One dog administered 0.82 mg/kg vomited once. Dogs administered 2.5 mg/kg had abnormal feces (black, green, liquid, red, soft, mucoid) beginning on Day 4 and resolving by Day 10, and vomiting. There was a dose dependent weight loss and decreased food consumption in dogs administered \geq 0.82 mg/kg. In all groups, including control, there were dermatologic changes (fur loss, thin fur, dry skin, red skin, skin lesions, scabs); there appeared to be a higher incidence in the dogs administered 2.5 mg/kg. Hematological changes included dose dependent leukopenia and VCOG Grade 1 to 4 neutropenia in dogs administered \geq 0.82 mg/kg, with the nadir occurring between Days 6 and 9 and recovery occurring by Day 12. The 8.2 mg/kg dose was not tolerated. Dogs administered 8.2 mg/kg had clinical signs of abnormal feces, dehydration, vomiting, salivation, fever, tremors, decreased activity, and weakness resulting in a moribund state, and were either preterminally found dead or euthanized by Day 7. On necropsy at Day 3, pathology changes included dose-dependent effects on the gastrointestinal tract, lymphoid tissue, bone marrow, prostate, adrenal cortex, and kidneys (see below for more details). Following a 21-day recovery period, the majority of the changes in the intestines and lymphoid tissues reversed. Dose-dependent effects on the kidney were still observed.

In the second study, rabacfosadine was administered by a 30-minute intravenous infusion at doses of 0.082, 0.25, and 0.82 mg/kg once daily for 5 consecutive days and was tolerated at all dose levels. Dogs administered 0.82 mg/kg/day had suspected dehydration, vomiting, abnormal feces (soft, liquid, green, red feces), anorexia/hyporexia, decreased activity, and fever. Dogs with suspected dehydration received Lactated Ringers Solution subcutaneously. Treatment-related body weight loss and decreased food consumption were observed in dogs administered \geq 0.25 mg/kg/day. In all groups, including control, there were dermatologic changes (fur loss, thin fur, dry skin, red skin, skin lesions, and scabs); there appeared to be a higher incidence in the groups administered drug. Hematological changes included dose-dependent leukopenia in all treated groups and dose-dependent VCOG Grade 1 to 4 neutropenia in dogs administered \geq 0.25 mg/kg/day with nadirs occurring between Days 6 and 9 with recovery by Day 12. On necropsy at Day 6, pathology changes included dose-dependent effects on the gastrointestinal tract, lymphoid tissue, bone marrow, and male reproductive system (see below for more details). Following a 21-day recovery period, dose-dependent changes were present in the gastrointestinal tract, salivary gland, kidney, and testes in all treated dogs, in the pancreas and thymus in dogs administered \geq 0.25 mg/kg/day, and in the bone marrow in dogs administered 0.82 mg/kg/day.

In the third study, rabacfosadine was administered by a 30-minute intravenous infusion at doses of 0, 0.25, 0.50, and 1.0 mg/kg once every 7 days for 3 doses was tolerated at all dose levels. Treatment-related body weight loss and decreased food consumption were observed in dogs administered 1.0 mg/kg. In all groups, including control, there were dermatologic changes (fur loss, thin fur, dry skin, red skin, skin lesions, scabs); there appeared to be a higher incidence in the groups administered drug. Hematological changes included VCOG Grade 1 neutropenia predominantly in dogs administered 1.0 mg/kg. On necropsy on Day 16, pathology changes included dose-dependent effects on the gastrointestinal tract and lymphoid tissue, and non-dose dependent effects on the salivary gland, male reproductive tract, and kidney (see below for more details). These changes had only partial reversibility after a 21-day recovery period.

The pathology changes observed in the three studies included, in the gastrointestinal tract, necrosis of the stomach and combinations of mucosal hemorrhage, dilatation of mucosal glands/crypts, necrosis of crypt epithelial cells, atrophy of the mucosa/villi, edema, and

inflammation of the intestinal wall. In the lymphoid tissue, observations included atrophy and necrosis of the thymus, spleen, lymph nodes, and gut associated lymphoid tissue (GALT). In the bone marrow, observations included hematopoietic hypocellularity. In the mandibular salivary gland, observations included glandular cell necrosis, atrophy, and inflammation. In the male reproductive tract, observations included small testes and epididymides, degeneration/atrophy of the seminiferous epithelium, and necrosis of the prostate. In the kidneys, observations included renal tubular vacuolation, dilatation, basophilia, degeneration, necrosis, and fibrosis. Tubular regeneration was observed following the recovery period. In the adrenal gland, observations included increased mitotic figures/necrosis in the adrenal cortex and adrenal fibrosis. In the pancreas, observations included acinar cell necrosis.

In the cardiovascular study, four telemeterized male, 7 to 8 month old Beagle dogs were administered 0, 0.25, and 2.5 mg/kg rabacfosadine intravenously in an escalating dose regimen with a washout between doses. Dogs were monitored for 24 hours following dosing. There were no treatment-related effects on arterial blood pressure (mean, systolic, diastolic), heart rate, or electrocardiographic parameters.

STORAGE CONDITIONS:

Unopened vials: Store the vials refrigerated at 2° to 8°C (36° to 46°F). Retain in the original package to protect from light.

After reconstitution: Store at 20° to 25°C (68° to 77°F). TANOVEA-CA1 should be diluted for infusion within 4 hours of reconstitution. The infusion solution should be used within 24 hours of being added to the infusion bag or syringe and within 4 hours of attachment to an intravenous administration set. Protection from light is not needed.

Disposal: Dispose of any unused product or waste materials in accordance with proper procedures for cytotoxic drugs.

HOW SUPPLIED:

TANOVEA-CA1 is supplied in a 3 mL amber Type I glass vial with rubber stopper, aluminum over-seal, and plastic flip-off cap, packaged in a carton. Each vial contains 16.4 mg of rabacfosadine, as succinate salt.

Pack size: 4 vials and 10 vials

REFERENCES:

1. Veterinary Cooperative Oncology Group – common terminology criteria for adverse events (VCOG-CTCAE) following chemotherapy or biologic antineoplastic therapy in dogs and cats v1.1. *Vet Comp Oncol.* 20 Jul 2011, DOI: 10.1111/j.1476-5829.2011.00283.x
2. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, Van Oosterom AT, Christian MC, Gwyther SG. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst.* 2000; 92:205-16.

Manufactured for:

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Product of USA