Paccal Vet®-CA1
(paclitaxel for injection)

60 mg paclitaxel per vial

Antineoplastic

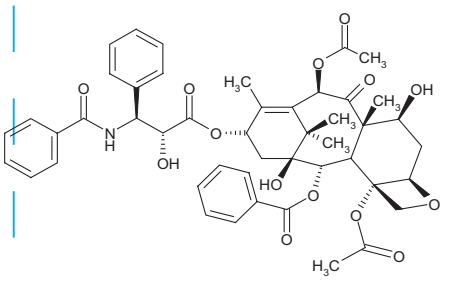
For intravenous use in dogs only

Conditionally approved by FDA pending a full demonstration of effectiveness under application number 141-422.

CAUTION: Federal (USA) 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:

Paccal Vet®-CA1 is an antimicrotubule agent. The empirical formula of paclitaxel is $C_{47}H_{51}NO_{14}$ and the molecular weight is 854. It is highly lipophilic and practically insoluble in water. The chemical name for paclitaxel is 5β,20-epoxy-1,7β-dihydroxy-9-oxotax-11-ene-2α,4,10β,13α-tetrayl 4,10-diacetate 2 benzoate 13-[(2R,3S)-3-(benzoylamino)-2-hydroxy-3-phenylpropanoate]. Paclitaxel has the following structural formula:



Paccal Vet-CA1 is supplied as a greenish-yellow to yellow sterile lyophilized powder in the form of a cake. Reconstitute the powder prior to intravenous infusion. Each single use vial contains 60 mg of paclitaxel, 40 mg of N-(*all-trans*-retinoyl)-L-cysteic acid methyl ester sodium salt and 40 mg of N-(13-*cis*-retinoyl)-L-cysteic acid methyl ester sodium salt. The reconstituted concentration is 1 mg/mL. In the aqueous solution for infusion these constituents are soluble and form micellar nanoparticles with a size of approximately 20-40 nm.

INDICATIONS: Paccal Vet-CA1 is indicated for the treatment of:

- Nonresectable stage III, IV or V mammary carcinoma in dogs that have not received previous chemotherapy or radiotherapy.
- Resectable and nonresectable squamous cell carcinoma in dogs that have not received previous chemotherapy or radiotherapy.

DOSAGE AND ADMINISTRATION:

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

Administer Paccal Vet-CA1 at 150 mg/m^2 body surface area (BSA) intravenously over 15-30 minutes, once every three weeks for up to four doses. Dose reductions of 10 mg/m^2 or dose delays may be used to manage adverse reactions.

Reconstitution and administration of Paccal Vet-CA1

Paccal Vet-CA1 is supplied as a sterile powder for reconstitution before use. After reconstitution the solution contains 1 mg of paclitaxel/mL. Paccal Vet-CA1 should be protected from light throughout the preparation process. Paccal Vet-CA1 preparation should be done with aseptic technique and the reconstituted product should be used immediately.

1. Obtain the desired number of vials from the refrigerator. The powder should be greenish-yellow to yellow. In case of discoloration, discard the vial. Let the vials stand protected from light at room temperature for approximately 20 to 30 minutes. The room temperature should not exceed 25°C (77°F).
2. Using a sterile syringe, inject 60 mL of Lactated Ringer's solution, USP, into a vial of Paccal Vet-CA1. Pressure must be equilibrated by a needle or vial spike before injection. The Lactated Ringer's solution should be injected slowly, directed onto the inside wall of the vial and not directly onto the powder as this will result in foaming.
3. Gently swirl the vial by hand for 20 to 30 seconds. Protect from light and allow the vial to stand for 3 to 5 minutes.
4. Gently and slowly swirl and/or invert the vial until the powder is completely dissolved. Do not shake, this will result in foaming. If foam develops, allow the solution to stand for several minutes. Reconstitution can continue even if all of the foam has not dissipated. If undissolved product is present, the vial should be placed on a shaker and rotated for up to 15 minutes, while protecting from light.
5. The solution should be clear and greenish-yellow without visible precipitates. If precipitates or discoloration (orange-reddish) are observed, the solution should be discarded.
6. Inject the appropriate amount of reconstituted Paccal Vet-CA1 into an empty, sterile, EVA (ethyl vinyl acetate) infusion bag. Protect the reconstituted product in the EVA infusion bag from light. The reconstituted product should be used immediately.
7. Administer Paccal Vet-CA1 intravenously over 15-30 minutes.

Compatibility of administration sets containing DEHP (di(2-ethylhexyl) phthalate) has not been demonstrated.

CONTRAINDICATIONS:

Do not use in dogs that have a neutropenia (< 2000 cells/µL) or that have a concurrent serious infection.

Do not use in dogs that are pregnant, lactating, or intended for breeding. Paclitaxel is a teratogen and can affect female and male fertility. Laboratory studies in the rat have shown reduced fertility, embryotoxicity, teratogenicity, and maternal toxicity.

WARNINGS:

Paclitaxel can cause severe, transient bone marrow suppression within four to seven days of administration (see **ADVERSE REACTIONS**).

Paclitaxel can cause gastrointestinal adverse reactions due to transient gastrointestinal mucosal cell toxicity. Monitor patients carefully for vomiting, diarrhea and dehydration. Provide supportive care as clinically indicated.

HUMAN WARNINGS:

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

Persons sensitive to retinoids should avoid contact with Paccal Vet-CA1.

Paclitaxel 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. Wear protective gloves to prevent contact with feces, urine, vomit and saliva for three days after the dog has received treatment. Place all waste material in a plastic bag and seal before disposal.

Special instructions for preparing and administering the product:

- Paccal Vet-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 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.

PRECAUTIONS:

Avoid extravasation during intravenous administration of paclitaxel as focal tissue necrosis can occur (see **ADVERSE REACTIONS**).

Drug interaction studies have not been performed. Paclitaxel is metabolized by cytochrome P450 isoenzymes and is a P-glycoprotein (P-gp) substrate. Exercise caution when administering paclitaxel with medications that inhibit or induce cytochrome P450 isoenzymes or with medications that are P-gp substrates.

ADVERSE REACTIONS:

Field Study:

In a field study, 168 dogs with cancer were treated with paclitaxel at 150 mg/m^2 IV administered over 30 minutes, for up to four cycles, three weeks apart.

All dogs experienced at least one adverse reaction. Eighty-five percent of dogs experienced a severe adverse reaction (VCOG[1] Grade 3, 4 or 5), and 11 dogs discontinued treatment due to adverse reactions. Five dogs died and three dogs were euthanized due to adverse reactions during the study. Paclitaxel has a low margin of safety, but adverse reactions were manageable with appropriate patient monitoring or supportive care. The most common adverse reactions are summarized in Table 1.

Table 1: Common Adverse Reactions in Paclitaxel Treated Dogs (n=168)

Adverse Reaction	Number affected	Percent affected
Neutropenia	137	82%
Vomiting	133	79%
Anorexia	127	76%
Diarrhea	118[a]	70%
Lethargy	116	69%
Alopecia	66	39%
Dehydration	43	26%
Dermatitis	40[b]	24%
Hepatopathy	32[c]	19%
Edema	24	14%
Pyrexia	22	13%
Lameness	20	12%
Urine abnormality	16	10%
Pruritis	16	10%
Erythema	14	8%
Anemia	13	8%
Loss of body condition	12	7%
Ulceration, cutaneous	12	7%
Thrombocytopenia	11	7%
Neoplasia	11	7%
Polydypsia	10	6%
Conjunctivitis	10	6%
Death	5[d]	3%
Euthanasia	3[d]	2%

[a] Nine dogs had hemorrhagic diarrhea

[b] Eight dogs had pyoderma and eleven had undefined skin lesions

[c] One dog had hepatomegaly

[d] Not related to disease progression

Adverse reactions that occurred in less than 6% of dogs during the study included leukopenia, lymphopenia, hypoproteinemia, hypoalbuminemia, hypotension, colitis, melena, hematochezia, septicemia, injection site reactions, focal necrosis associated with extravasation, transient aggression, behavioral changes, shivering, heart murmur, weakness, benign tumors, abdominal pain, dyspnea, decreased appetite, gastrointestinal ulceration, panting, tachycardia, mast cell tumor degranulation, acute tumor lysis syndromes, and possible cerebrovascular event.

In pilot studies conducted in dogs with mammary carcinoma and squamous cell carcinoma treated with Paccal Vet®-CA1, adverse reactions were generally consistent with those reported in Table 1 and the paragraph above.

To report suspected adverse events, for technical assistance, or to obtain a copy of the Material Safety Data Sheet (MSDS) contact Abbott Animal Health at 1-888-299-7416.

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, feces or vomit from dogs treated with Paccal Vet-CA1.

CLINICAL PHARMACOLOGY:

Mechanism of action

Paclitaxel is an antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization. Stabilization results in inhibition of the normal dynamic reorganization of the microtubular network that is essential for vital interphase and mitotic cellular functions. In addition, paclitaxel induces microtubule bundle formation throughout the cell cycle and induces microtubule aster formation during mitosis.

Pharmacokinetics

Similar to that observed in other animal species and in human patients, paclitaxel undergoes extensive tissue distribution in dogs. Consequently, paclitaxel follows a three-compartment model, with a rapid initial disappearance which ranges from 3 to 5 hours. However, a small proportion of the total exposure (e.g., 3 – 7% of the administered dose) may remain in the tissues from which it slowly depletes. The duration of this terminal phase may be as long as 12 hours. However, due to the very small proportion of the total dose associated with this deep compartment, no drug accumulation is observed when the drug is administered once every three weeks at an intravenous (IV) dose of 130 to 150 mg/m^2. Systemic drug exposure is directly proportional to dose within the dosing range of 130 to 150 mg/m^2.

REASONABLE EXPECTATION OF EFFECTIVENESS:

This drug is conditionally approved pending a full demonstration of effectiveness.
The following studies were used to demonstrate a reasonable expectation of effectiveness for Paccal Vet®-CA1 (paclitaxel for injection) for specific indications (see **INDICATIONS**).

Mammary carcinoma

Clinical data from 10 dogs with advanced-stage mammary carcinoma that were treated with paclitaxel in two separate pilot studies support a reasonable expectation of effectiveness.

A single group, single-center, open label, dose escalating, clinical study in 32 dogs with solid tumors was conducted to assess the safety and pharmacokinetics of Paccal Vet-CA1. Seven dogs had advanced stage mammary carcinoma. Dogs were treated once every 21 days for up to three cycles. Paccal Vet-CA1 was administered as an intravenous infusion over 15 to 30 minutes at an initial dose of 100 to 150 mg/m^2. Response to treatment was evaluated by tumor measurements (sum of the longest perpendicular diameters) prior to each treatment cycle. Complete response (CR) was defined as disappearance of all lesions, and partial response (PR) was defined as a minimum 50% decrease in the tumor measurement without the appearance of new lesions. At the study end (Day 84), one dog had CR, two had PR, and four had progressive disease (PD). Progression free survival (PFS) for the dog with a complete response was 1 year and survival was 498 days. Of the two dogs with PR, one had subsequent surgical excision of the tumor resulting in long term survival of 480 days. The other dog with PR had PFS and survival of 131 days. The dogs with PD had PFS of 20-56 days and survival of 40-56 days.

In a separate study in dogs with cancer, three dogs with metastatic mammary carcinoma were treated with paclitaxel. Treatment with paclitaxel resulted in PR in two of three dogs with metastatic mammary tumors and PFS of 84 and 258 days.

Collectively, six of the 10 dogs with mammary carcinoma that were treated with paclitaxel were assessed as responders (complete or partial response), including three responding cases with PFS greater than four months and one additional dog whose response to paclitaxel allowed subsequent surgical excision of the tumor resulting in long term control.

Squamous cell carcinoma

Clinical data from 17 dogs with resectable or nonresectable squamous cell carcinoma treated with paclitaxel in two separate pilot studies support a reasonable expectation of effectiveness.

A single group, multi-center, open label clinical study, was conducted in 14 dogs with resectable or nonresectable squamous cell carcinoma. Lesion locations included oral/tonsil, prepuce, nose/nares, and carpus. Four dogs had metastatic disease, one dog had previous chemotherapy, one dog had previous radiation therapy and one dog had previous surgery. Dogs were treated once every three weeks (one cycle) for up to four cycles. Paccal Vet-CA1 was administered as an intravenous infusion over 15 to 30 minutes at an initial dose of 150 mg/m^2. Dose reductions or dose delays were used to manage severe adverse reactions (VCOG-CTCAE grade 3-5). Response to treatment was evaluated by tumor measurements prior to each cycle. One dog died prior to the first tumor response measurement (Day 8), and three dogs were lost to follow up during the study. Two dogs had stable disease (SD) that was maintained through study end (Day 84), and were progression free on 91 and 144 days (time of last contact). Progression free survival (PFS) ranged from 21-63 days for dogs that developed progressive disease (n=8) during the study.

A single group, single-center, open label, dose escalating, clinical study in 32 dogs with solid tumors was conducted to assess the safety and pharmacokinetics of Paccal Vet-CA1. Three dogs had nonresectable oral squamous cell carcinoma, and two of these three dogs also had metastatic disease. Dogs were treated once every three weeks (one cycle) for up to four cycles. Paccal Vet-CA1 was administered as an intravenous infusion over 15 to 30 minutes at an initial dose of 150 mg/m^2. Response to treatment was evaluated by tumor measurements (sum of the longest perpendicular diameters) prior to each cycle. Complete response (CR) was defined as disappearance of all lesions, and partial response (PR) was defined as a minimum 50% decrease in the tumor measurements without the appearance of new lesions. At study end (Day 84), one dog had CR, one had PR, and one had progressive disease (PD, progressed at Day 64). The dog with PR was progression free until Day 260, and the dog with a CR was alive at the time of last contact (Day 388).

Collectively, two of the 17 dogs with squamous cell carcinoma that were treated with Paccal Vet-CA1 were assessed as responders (CR or PR), and two dogs had stable disease (SD) that was maintained through study end (Day 84). The dog with CR at study end had a PFS of 388 days and the dog with PR at study end had PFS of 260 days. The SD may represent a clinically relevant response, and dogs with SD had PFS of 91 and 144 days. PFS ranged from 21-64 days for dogs that developed PD (n=9) during the study.

ANIMAL SAFETY:

In the multidose target animal safety study, Paccal Vet-CA1 demonstrated a narrow margin of safety. All dogs that received Paccal Vet-CA1 experienced paclitaxel related toxicities. No dogs died, required euthanasia or discontinued treatment prior to the end of the study.

Twenty-four dogs (8 dogs per group, 4 males and 4 females) were administered either intravenous Lactated Ringer's Solution as a placebo, or paclitaxel at 130 mg/m^2 or 150 mg/m^2 once every three weeks (one cycle) for four cycles. Paclitaxel caused lethargy, depression, weight loss, decreased feed intake, anorexia, vomiting, diarrhea, hematochezia, melena, alopecia, whisker loss, focal dermatitis, focal ulcerative dermatitis, skin wounds of undetermined origin, focal inflammation after subcutaneous injection of antibiotics, conjunctivitis, oligospermia, decreases in hematology variables and injection site swelling.

Three dogs in the 130 mg/m^2 group and three dogs in the 150 mg/m^2 group became systemically ill after the first dose of Paccal Vet-CA1. Clinical signs included anorexia, depression, pale mucous membranes, vomiting, diarrhea, hematochezia, and fever. One dog had clinical signs of shock (pale and cyanotic mucous membranes, slow capillary refill time, hypothermia). Hematology changes included leukopenia (n=4), neutropenia (n=4) and lymphopenia (n=5). Two dogs in the 130 mg/m^2 group and three dogs in the 150 mg/m^2 group required supportive care with intravenous fluids and systemic antibiotics. These dogs recovered within four days after the onset of clinical signs.

Paclitaxel related hematology changes included leukopenia, neutropenia (Grades 1-3)[1], lymphopenia, monocytopenia, thrombocytopenia (Grade 1-2), anemia (Grade 1), and decreases in hemoglobin, mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), and mean corpuscular volume (MCV). The nadir for hematology variables occurred one to four days after paclitaxel administration and recovery was observed within three weeks. Prothrombin time (PT), partial thromboplastin time (PTT) and buccal mucosal bleeding time (BMBT) were not affected by paclitaxel.

During the study dogs in the paclitaxel groups had a higher frequency of vomiting, diarrhea, hematochezia and melena compared to the control group dogs. The increase in vomiting and diarrhea usually occurred within four days of paclitaxel administration. Feed consumption decreased or was absent up to 3 days after paclitaxel administration, and body weight decreased in the first week, followed by an increase during the second and third weeks.

Dogs in the paclitaxel groups had lower albumin, increased fibrinogen, and higher creatine kinase compared to the control group.

Injection site swelling occurred more frequently in the paclitaxel groups, was mild and resolved within one day after treatment. There were no occurrences of extravasation during the study. Whisker loss and facial alopecia were noted in seven 130 mg/m^2 paclitaxel group dogs and all 150 mg/m^2 paclitaxel group dogs. Coat thinning was noted in three 130 mg/m^2 paclitaxel group dogs and seven 150 mg/m^2 paclitaxel group dogs. Whisker loss, facial alopecia and coat thinning started three weeks after the second treatment.

Necropsy occurred seven days after the last administration of paclitaxel. Toxicologically relevant changes noted in the dogs in the paclitaxel groups included patchy facial alopecia, whisker loss, thinning of hair coat, dermal ulcerations, focal fat necrosis associated with subcutaneous injections, inflammation and thrombosis at catheter placement sites, oligospermia, mild mineralization and smooth muscle hypertrophy in the media of the aorta, hypercellular bone marrow, and extramedullary splenic hematopoiesis indicative of a normal regenerative response. On histopathology regenerative hair follicles were noted in dogs in the paclitaxel groups, indicating the alopecia may not be permanent. The hypercellular bone marrow may be a response to the daily blood collections for clinical pathology following the last treatment or a recovery response to the bone marrow suppressive effects of paclitaxel.

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 opening and reconstitution: Use the reconstituted product immediately because it does not contain a preservative. Protect from light during preparation and administration.

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

HOW SUPPLIED: Paccal Vet®-CA1 is supplied in a 75 mL clear glass vial with rubber stopper, aluminum over-seal and plastic flip-off cap, individually packaged in a carton. Each vial contains 60 mg of paclitaxel.

Pack size: One vial.

REFERENCES:

1. Veterinary cooperative oncology group – common terminology criteria for adverse events (VCOG-CTCAE) following chemotherapy or biologic antineoplastic therapy in dogs and cats v1.0. *Vet Compar Onco* 2004; 2(4):194–213.

Conditional Approval Application Number 141-422, conditionally approved by FDA pending a full demonstration of effectiveness.

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Oasmia Pharmaceutical AB
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Product inquiries should be directed to Abbott Laboratories, 1-888-299-7416

Product of Sweden

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