

Canalevia®-CA1

(crofelemer delayed-release tablets)



• First in Class
Anti-Diarrheal

Normalizes •
Fluid Flow
in the Gut

• Novel
Mechanism
of Action

Crofelemer, the active pharmaceutical ingredient in Canalevia-CA1, is sustainably derived from the sap of the Amazonian tree species *Croton lechleri*

Treating Diarrhea in Your Dog Undergoing Chemotherapy



A dog owner's guide to the treatment of chemotherapy-induced diarrhea (CID) with Canalevia-CA1 (crofelemer delayed-release tablets), a natural, plant-based prescription product.



IMPORTANT SAFETY INFORMATION

For oral use in dogs only. Not for use in humans. Keep Canalevia®-CA1 (crofelemer delayed-release tablets) in a secure location out of reach of children and other animals. Consult a physician in case of accidental ingestion by humans. Do not use in dogs that have a known hypersensitivity to crofelemer. Prior to using Canalevia-CA1, rule out infectious etiologies of diarrhea. Canalevia-CA1 is a conditionally approved drug indicated for the treatment of chemotherapy-induced diarrhea in dogs. The most common adverse reactions included decreased appetite, decreased activity, dehydration, abdominal pain, and vomiting.

Caution: Federal 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. Conditionally approved by FDA pending a full demonstration of effectiveness under application number 141-552.**

Support Your Dog's Comfort During Chemotherapy Treatment



An estimated 6 million new cancer diagnoses are made in dogs each year.¹ Approximately 30% of dogs treated with chemotherapy will experience CID.²



Canalevia®-CA1 eases the burden of illness by providing a well-tolerated treatment for CID in dogs, improving the dog's comfort and quality of life.



Naturally and sustainably harvested from the sap of a medicinal tropical plant, the *Croton lechleri* tree.



Can CID result in the need to decrease, pause, or stop my dog's chemotherapy treatment?

Approximately 37% of dogs undergoing cancer treatment may have their chemotherapy reduced, changed, or discontinued due to diarrhea²—which can compromise the full benefit of the chemotherapy agent. Managing CID can be important to help support the outcome of your dog's cancer treatment, and to help support your veterinarian's efforts to maintain your dog's chemotherapy treatment plan.

How can Canalevia-CA1 help my dog?

Treating CID can improve the quality of life for dogs undergoing an already traumatic experience, reduce the chance of extra visits to your vet, and support your dog's ability to maintain control, which is important for management of your home and general living environment. [Importantly, treating CID in dogs can help prevent interruption in their chemotherapy treatment plan.](#)

What is chemotherapy?

Chemotherapy is a drug treatment that uses powerful chemicals to kill fast-growing cells. Chemotherapy is most often used to treat cancer in people and dogs since cancer cells grow and multiply much more quickly than most other cells in the body. Due to the increasing number of chemotherapeutic agents being adopted by veterinarians and veterinary oncologists, chemotherapy is fast becoming the most widely used cancer treatment in veterinary medicine.

What is chemotherapy-induced diarrhea (CID)?

For the most part, dogs receive human chemotherapeutic agents during treatment and suffer the same side effects as humans. Most chemotherapeutic agents target rapidly dividing cells, and effects on these cells within the gastrointestinal tract can lead to a variety of symptoms. Diarrhea caused by chemotherapy, referred to as chemotherapy-induced diarrhea (CID), is a common problem in canine cancer patients. CID can induce distress and suffering in sensitive animals like dogs. Severe or prolonged diarrhea can result in significant dehydration and hospitalization due to water loss.



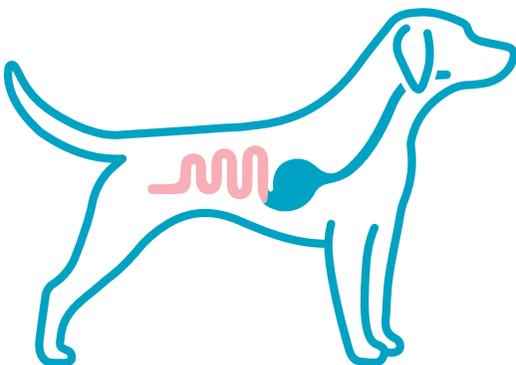
Extracting sap from a *Croton lechleri* tree in the Northwestern Amazon

What is the source of crofelemer, the natural active pharmaceutical ingredient in Canalevia-CA1?

Crofelemer is a natural product sustainably derived from the sap, or latex, of the Amazonian tree species *Croton lechleri*, which has a rich history of medicinal use by Indigenous peoples in the Western Amazon rainforests of South America. To learn more about the history of crofelemer, see [The Ethnobotanical Origins of Canalevia-CA1](#) section of this guide.

How does Canalevia-CA1 work?

CID occurs when excess fluids are secreted into your dog's gastrointestinal tract. Canalevia-CA1 treats CID by normalizing fluid influx into the dog's gastrointestinal tract.



How is Canalevia®-CA1 administered to dogs?

Administer one Canalevia-CA1 tablet orally twice daily for 3 days to dogs weighing up to 140 pounds. For dogs weighing more than 140 pounds, administer two tablets orally twice daily for 3 days. Tablets should be swallowed whole and should not be broken, crushed, or chewed. If the dose is chewed, one additional dose may be administered.

Can I administer Canalevia-CA1 to my dog at home?

Yes. Following consultation with your veterinarian, you may administer Canalevia-CA1 yourself to your dog at home.

Can I break or crush the Canalevia-CA1 tablet and put it in my dog's food?

No. Canalevia-CA1 tablets should be swallowed whole and should not be broken, crushed, or chewed. If the tablet is chewed, one additional dose may be administered. Give with or without food.

The most common side effects of Canalevia-CA1 are decreased appetite and activity, dehydration, stomach pain and vomiting.

If my dog vomits up the Canalevia-CA1 tablet, what do I do?

If your dog vomits up the Canalevia-CA1 tablet, one additional dose may be administered following consultation with your veterinarian.

How do I know if my dog is suffering from CID-related dehydration?

Diarrhea results from the secretion of excess fluids into your dog's intestines. Severe or prolonged diarrhea can result in significant dehydration and hospitalization due to water loss. After your dog has started chemotherapy, please contact your veterinarian if your dog develops watery diarrhea, becomes lethargic, quits eating, or has started vomiting.

Is Canalevia-CA1 available only by prescription?

Yes, Canalevia-CA1 is only available by prescription from licensed veterinarians in the U.S.

Have any other products received any type of approval from the FDA to treat CID in dogs?

Canalevia-CA1 is conditionally approved by the U.S. Food and Drug Administration (FDA) for the treatment of CID in dogs. **Canalevia-CA1 is the first and only treatment for CID in dogs to receive any type of approval from the FDA.**

Human products like Kaopectate or Pepto-Bismol are sometimes used to address CID in dogs, but using these over-the-counter treatments is discouraged because they contain aspirin products. Additionally, unlike Canalevia-CA1, human products like Imodium or Lomotil are opioids which can cause constipation.

What does "FDA conditional approval" mean?

Canalevia-CA1 is conditionally approved by the FDA under application number 141-552. Conditional approval status allows the product to be marketed and sold in the U.S. while Jaguar Animal Health continues to collect the substantial evidence of effectiveness required for a full approval from the FDA.

Where is Canalevia-CA1 available?

Any licensed veterinarian in the U.S. can prescribe Canalevia-CA1. If your dog is undergoing chemotherapy and suffering from diarrhea, please contact your veterinarian to find out if Canalevia-CA1 may be beneficial for your dog.

Where can I obtain information about Canalevia-CA1 to provide to my dog's veterinarian or veterinary oncologist?

Prescribing Information for veterinarians is available online at www.canalevia.com. Veterinarians and veterinary oncologists are also welcome to contact Jaguar Animal Health by phone at 877-787-3001 to speak with one of our staff veterinarians, or by email at info@canalevia.com.

Can I use Canalevia-CA1 for my cat suffering from CID?

No. Canalevia-CA1 is not approved by the FDA for use in cats nor has it been demonstrated to be safe or effective for treating CID in cats.

Contact Your Veterinarian About Canalevia-CA1



The Ethnobotanical Origins of Canalevia®-CA1



Crofelemer is the result of decades of research that began with the expertise of traditional healers of the Amazon Rainforest

The term ethnobotanical refers to the use of plants by Indigenous people in their everyday lives, including the use of plants for medicine. Crofelemer, the active pharmaceutical ingredient in Canalevia-CA1, is sustainably derived from the sap, or latex, of the Amazonian tree species *Croton lechleri*, which has a rich history of medicinal use by Indigenous peoples in the Western Amazon rainforests of South America. The tree produces a blood-red latex from which crofelemer is isolated and purified.

The latex of the *Croton lechleri* tree is commonly called “Sangre de drago” in Spanish, which translates to “Dragon’s blood” in English. Because the tree’s latex is one of the most widely used plant-derived medicines in the western hemisphere, extensive research has been conducted on the chemistry and pharmacology of *Croton lechleri* latex. The latex continues to be part of rural and urban traditional medicine in multiple countries, including Peru, Ecuador, and Bolivia. Traditional Indigenous healers have utilized the latex for centuries as an oral treatment for a variety of medical conditions, including diarrhea, stomach ulcers, coughs, and flu, and they apply the latex topically as a wound-healing agent for cuts, open sores, and for healing the gums after tooth extractions.

A Longstanding Commitment to Benefit Sharing & Sustainability

The *Croton lechleri* tree is rapidly growing and abundant in multiple countries in rainforest regions. We focus on the long-term sustainable management of the tree as part of our commitment to helping local communities conserve their natural resources while also earning income for the basic needs of their families, such as food, clothing, health care, and education. Our team members have practiced fair trade with our local and Indigenous partners for more than two decades, which has provided income-generating opportunities for individuals, communities, and families. Across Peru, large numbers of *Croton lechleri* trees have been planted following harvesting in collaboration with communities and small local businesses.

To learn more about Canalevia-CA1
for your dog suffering from
chemotherapy-induced diarrhea,
speak with your veterinarian or visit
www.canalevia.com



Since 2001, more than 800,000 *Croton lechleri* trees have been planted. For every 1 tree harvested at least 2 new trees are planted.

**Canalevia®-CA1**
(crofelemer delayed-release tablets)



IMPORTANT SAFETY INFORMATION

For oral use in dogs only. Not for use in humans. Keep Canalevia®-CA1 (crofelemer delayed-release tablets) in a secure location out of reach of children and other animals. Consult a physician in case of accidental ingestion by humans. Do not use in dogs that have a known hypersensitivity to crofelemer. Prior to using Canalevia-CA1, rule out infectious etiologies of diarrhea. Canalevia-CA1 is a conditionally approved drug indicated for the treatment of chemotherapy-induced diarrhea in dogs. The most common adverse reactions included decreased appetite, decreased activity, dehydration, abdominal pain, and vomiting.

Caution: Federal 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. Conditionally approved by FDA pending a full demonstration of effectiveness under application number 141-552.**

CANALEVIA®-CA1

(crofelemer delayed-release tablets)

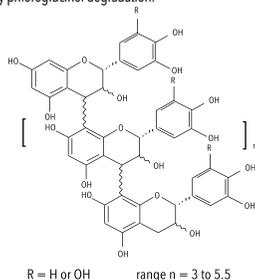
125 mg
antidiarrheal

For oral use in dogs only

CAUTION: Federal 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.**

Conditionally approved by FDA pending a full demonstration of effectiveness under application number 141-552

DESCRIPTION: CANALEVIA-CA1 (crofelemer delayed-release tablets) is an antidiarrheal, enteric-coated drug product for oral administration. CANALEVIA-CA1 contains 125 mg of crofelemer, a botanical drug substance that is derived from the red latex of *Croton lechleri* Müll. Arg. Crofelemer is an oligomeric proanthocyanidin mixture primarily composed of (+)-catechin, (-)-epicatechin, (+)-gallocatechin, and (-)-epigallocatechin monomer units linked in random sequence, as represented below. The average degree of polymerization for the oligomers ranges between 5 and 7.5, as determined by phloroglucinol degradation.



INDICATION: CANALEVIA-CA1 is indicated for the treatment of chemotherapy-induced diarrhea in dogs.

DOSE AND ADMINISTRATION: Administer 1 tablet orally twice daily for 3 days for dogs weighing \leq 140 pounds. Administer 2 tablets orally twice daily for 3 days for dogs weighing $>$ 140 pounds. Tablets should not be broken, crushed, or chewed. If the tablet is chewed, one additional dose may be administered. Give with or without food.

CONTRAINDICATIONS: Do not use in patients with a known hypersensitivity to crofelemer.

WARNINGS: Not for use in humans. Keep this and all medications out of reach of children. Consult a physician in case of accidental ingestion by humans.

Keep CANALEVIA-CA1 in a secure location out of reach of dogs, cats, and other animals to prevent accidental ingestion or overdose.

PRECAUTIONS: The safe use of CANALEVIA-CA1 has not been evaluated in dogs that are pregnant, lactating, or intended for breeding.

Prior to using CANALEVIA-CA1, rule out infectious etiologies of diarrhea. Prescribing CANALEVIA-CA1 to dogs with diarrhea secondary to infectious etiologies may delay appropriate treatment.

ADVERSE REACTIONS: In a masked, randomized study to support a reasonable expectation of effectiveness (CANA-001a) there was similar incidence of adverse events in dogs administered crofelemer (not commercial formulation) compared to control dogs administered a vehicle control. Crofelemer was administered orally twice a day for three days as enteric-coated beads containing 40 mg of the active ingredient. The vehicle control was enteric-coated beads without the active ingredient. The dogs had daily assessments for changes in attitude, hydration, appetite, and abdominal palpation. Table 1 shows the adverse reactions during CANA-001a study.

Table 1. Adverse Reactions in CANA-001a Study to Support Reasonable Expectation of Effectiveness

Adverse Reaction ¹	Crofelemer N = 29	Vehicle Control N = 32
Appetite decreased	7 (24%)	9 (28%)
Attitude decreased	5 (17%)	5 (16%)
Activity decreased	4 (14%)	4 (13%)
Dehydration ²	4 (14%)	5 (16%)
Abdominal palpation indicated pain ³	3 (10%)	5 (16%)
Vomiting	1 (3%)	2 (6%)

¹ Dogs may have experienced more than one occurrence and more than one type of abnormal assessment during the study

² Two crofelemer treated dogs and one vehicle control dog were administered fluid therapy

³ One of the vehicle control dogs was reported to not allow abdominal palpation at one timepoint on Day 2

In an open-label pilot study (CANA-001b), 48 dogs were administered crofelemer (not commercial formulation) orally twice a day for three days. The adverse reactions included decreased appetite in 16/48 (33%) dogs, vomiting in 3 (6%) dogs, decreased activity in 3 dogs (6%), abdominal pain in 1 (2%) dog, and 1 (2%) dog had blood in feces.

In a separate pilot clinical field study (CANA-003), dogs with acute diarrhea were randomized to receive crofelemer or placebo tablets. The study included 22 dogs administered crofelemer (not commercial formulation) tablets and 112 dogs administered 125 mg CANALEVIA-CA1 tablets. There were 66 dogs who received placebo tablets. Dogs were administered tablets orally twice a day for three days. Hematology and clinical chemistry were obtained prior to dosing and on Day 3 at the end of the study. Table 2 shows adverse reactions during the study.

Table 2. Adverse Reactions in Pilot Field Study CANA-003

Adverse Reaction	Crofelemer N = 134	Placebo N = 66
Vomiting	11 (8%)	1 (2%)
Decreased blood glucose ¹	10 (8%)	3 (5%)
Urinary system abnormality ²	10 (8%)	2 (3%)
Upper respiratory signs ³	7 (5%)	0 (0%)
Decreased blood calcium ⁴	5 (4%)	0 (0%)

¹ Dogs with decreased blood glucose at study end had normal blood glucose (reference range 74-145 mg/dL) prior to dosing. None of the dogs were reported to be clinically affected by the decreased blood glucose. The low blood glucose values ranged from 34 to 71 mg/dL.

² Urinary system abnormalities were documented as development of a urinary tract infection, cystitis, or a worsening pyuria in the urine.

³ Upper respiratory signs included coughing, nasal discharge, sneezing, and congestion.

⁴ Dogs with decreased serum calcium (reference range 8.7-12 mg/dL) at study end had normal calcium at screening. The decreased calcium values were not associated with decreased albumin values. None of the dogs were reported to be clinically affected by the decreased serum calcium. The lowest reported calcium was 5.8 mg/dL.

Five dogs administered crofelemer and one placebo group dog were removed from the study for no improvement in stools. One additional dog administered crofelemer was removed for hemorrhagic stool.

CONTACT INFORMATION: To report suspected adverse drug events and/or to obtain a

copy of the Safety Data Sheet (SDS) or for technical assistance, call Jaguar Animal Health at 1-877-787-3001.

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

CLINICAL PHARMACOLOGY: Mechanism of Action: In humans, crofelemer is an inhibitor of both the cyclic adenosine monophosphate (cAMP)-stimulated cystic fibrosis transmembrane conductance regulator (CFTR) chloride ion (Cl⁻) channel, and the calcium-activated Cl⁻ channels (CaCC) at the luminal membrane of enterocytes. The CFTR Cl⁻ channel and CaCC regulate Cl⁻ and the osmotic gradient which causes fluid influx into the lumen. Crofelemer inhibits the hypersecretion of Cl⁻ in diarrhea and normalizes the fluid influx into the GI tract. The mechanism of action in the dog has not been fully characterized.

REASONABLE EXPECTATION OF EFFECTIVENESS: A reasonable expectation of effectiveness may be demonstrated based on evidence such as, but not limited to, pilot data in the target species or studies from published literature.

CANALEVIA-CA1 is conditionally approved pending a full demonstration of effectiveness.

Additional information for Conditional Approvals can be found at www.fda.gov/animalca.

A reasonable expectation of effectiveness for CANALEVIA-CA1 is based on a pilot field study.

A multi-site, randomized, masked, vehicle-controlled field study in dogs with diarrhea of various etiologies was conducted to assess the effectiveness of crofelemer (not commercial formulation). The effectiveness dataset included 12 dogs administered crofelemer and 12 dogs administered vehicle control. Dogs were between the ages of four months and 12 years with a fecal score of 4 or 5 (watery or liquid stools with little or no particulate matter or severe watery diarrhea with no particulate matter visible). Crofelemer was administered at a dose of 1.9 to 12.9 mg/kg every 12 hours for three days. Fecal scores were obtained every four hours during the three day study. Fecal scores were based on a modified version of the Purina Fecal Scoring System and were defined as:

1. Well-formed stools with slightly moist surface which leaves marks when picked up
2. Soft or very soft, moist, amorphous
3. Viscous liquid with some particulate matter
4. Watery, liquid stools with little particulate matter visible
5. Severe watery diarrhea, no particulate matter visible
6. Hemorrhagic diarrhea

The resolution of diarrhea was considered treatment success and was defined as a fecal score of 1 or 2. After a dog achieved resolution of diarrhea, subsequent fecal scores had to be maintained as a 1 or 2 for the duration of the 3-day study in order to be considered a treatment success.

The resolution of diarrhea per day (24 hour treatment block) is described in Table 3.

Table 3. Number of Dogs Achieving Resolution of Diarrhea per 24 Hour Treatment Block

Treatment block	Crofelemer N = 12	Vehicle Control N = 12
\leq 24 hours	2 (17%)	0 (0%)
$>$ 24 hours and \leq 48 hours	2 (17%)	0 (0%)
$>$ 48 hours and \leq 72 hours	5 (42%)	3 (25%)

Daily Daily assessments included body temperature; fecal scores; and a scored assessments included body temperature; fecal scores; and a scored assessment of general attitude, hydration status, appetite, and reaction to abdominal palpation (see ADVERSE REACTIONS).

TARGET ANIMAL SAFETY:

The safety of CANALEVIA-CA1 and crofelemer was evaluated in four laboratory studies.

Target Animal Safety Study: In a 9 day laboratory safety study, healthy four month old Beagle dogs were orally administered crofelemer at 0, 27.2, 54.3, or 162.9 mg/kg twice daily (4 dogs per sex in each group) for 9 days. All dogs survived to study termination.

Clinical observations related to CANALEVIA-CA1 included discolored red feces, watery feces, and vomiting in a dose-dependent manner with increased incidence in the higher dose groups.

Hematology findings related to CANALEVIA-CA1 included 3 dogs that had a decreased hematocrit (reference range 37.2-52%) at study end compared to acclimation: 1 male administered 27.2 mg/kg with hematocrit of 39.6% prior to dosing and 35.8% on Day 9; 1 female administered 162.9 mg/kg with hematocrit of 40.7% prior to dosing and 36.4% on Day 9; and 1 female administered 162.9 mg/kg with hematocrit of 36.4% prior to dosing and 36.1% on Day 9.

There were no clinically relevant or significant findings for body weight, physical examination, food consumption, electrocardiogram, ophthalmoscopic, or necropsy examinations.

Target Animal Toxicity Studies: In two separate laboratory studies, healthy six to seven month old Beagle dogs were orally administered crofelemer (not commercial formulation) at 0, 50, 175, or 600 mg/kg once daily (four dogs per sex in each group) for 30 days and nine months duration, respectively. All dogs survived to study termination.

Clinical observations related to crofelemer included abnormal feces (mainly black and rust colored mucoid feces and diarrhea) observed as soon as 1 day after the first administration and occurred in a dose-dependent manner with increased incidence in the higher dose groups. Dogs in the 600 mg/kg/day group did not gain weight at the same rate, had decreased food consumption, and higher incidences of vomiting compared to the other groups.

Hematology findings related to crofelemer at the dose of 600 mg/kg/day were consistent with a microcytic, hypochromic anemia with mild regeneration, and thrombocytosis as characterized by decreases in hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration; and increases in platelets, percent reticulocytes, and absolute reticulocytes compared to the other groups. Females at 175 mg/kg/day and males and females at 600 mg/kg/day had increased neutrophils compared to the other groups. Crofelemer-related serum chemistry findings at 600 mg/kg/day, and to a lesser severity at 175 mg/kg/day, included decreased albumin, total protein, cholesterol, calcium, and sodium and increased potassium compared to the other groups.

On necropsy, gross lesions related to crofelemer included localized irritation of the gastrointestinal tract (reddened areas, erosion, and red streaks) and discoloration of the gastrointestinal tract (dark red areas and gray areas) and lymph nodes (red, gray, and green). Gross lesions were observed at all crofelemer doses in a dose-dependent manner where higher doses had higher incidences.

On histopathology, crofelemer-related lesions included congestion in the small and large intestines; inflammation and pigmentation of the gastrointestinal tract and pigmentation in the liver; congestion in the mesenteric and suprarenal lymph nodes; histiocytosis, erythrocytosis, basophilic bodies, and pigmentation of the lymph nodes; and splenic macrophage infiltration. Histopathologic lesions occurred in a dose-dependent manner where the higher doses had higher incidences.

Cardiovascular Study: The cardiovascular effects of crofelemer (not commercial formulation) were evaluated in a laboratory study in four healthy one to one and a half years old male Beagle dogs implanted with radiotelemetry devices. Dogs were orally administered crofelemer at 0, 60, 200, and 600 mg/kg one time. Each dog received all treatments with a seven day washout period between treatments. There were no crofelemer-related effects on the cardiovascular parameters (heart rate, blood pressure, electrocardiograms). Clinical observations related to crofelemer included soft, watery, mucoid, or discolored (brown or red) feces in the 200 and 600 mg/kg groups.

STORAGE INFORMATION: Store at 20°C-25°C (68°F-77°F) with excursions permitted between 15°C-30°C (59°F-86°F).

HOW SUPPLIED: CANALEVIA-CA1 (crofelemer delayed-release tablets) are available as white, uncoated enteric-coated tablets containing 125mg of crofelemer packaged in bottles containing 60 tablets.

Distributed by:

Jaguar Animal Health, San Francisco, CA 94104

JAH 111-060 Rev 03/22

