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clinician's forum™
Expert Views from a Roundtable on Canine Inappetence

Inappetence: Its Many Forms & Clinical Management

Inappetence may result in inadequate treatment and thus lack of therapeutic success. In other words, changes in appetite are challenges to effective treatment. Additionally, an important factor is the pet owner's interpretation of the pet's quality of life, which can lead to a decision to cease treatment or elect euthanasia.

Dr. Larson: Today we'll be discussing inappetence and some challenges specific to oncology, internal medicine, and clinical nutrition, particularly in dogs. Maybe we should begin by defining inappetence.

Dr. Freeman: There's a lot of different terminology when we talk about food intake. Many people think of anorexia, or no food intake, as all-encompassing, but anorexia is just one category of inappetence. The other areas are much more common: hyporexia, which is decreased food intake, and dysrexia, which refers to alterations in food intake patterns. Animals that are hyporexic are not taking in adequate calories but are not completely anorexic. A dysrexic animal won't eat the optimal diet for its disease. Some have cyclical appetites, where they'll eat one food for 5 days and then refuse it, then eat a different food for 2 days and then refuse that.

Dr. Burney: When I was a resident a common term then was "partial anorexia." However, you can't be partially pregnant, and you can't be partially anorexic. I think all of us participating in this discussion agree that we should use the terms outlined by nutritionists more recently for appetite because they are more descriptive.[1]

Dr. Johannes: Yes, when we are speaking with owners it is important to clarify the level of inappetence, because it is not black and white. It is important to train the nursing staff and ourselves to ask the appropriate nutritional questions and to reinforce the importance of monitoring eating behaviors.

Dr. Larson: Can you describe the incidence and some of the consequences of inappetence?

Dr. Johannes: The incidence is really not well defined, even in oncology. The

KEY POINTS

- Alterations in a patient's appetite range from anorexia (lack or loss of appetite[1]), to consuming less than adequate amounts (hyporexia), to changes in eating patterns (dysrexia).
- In addition to affecting case management, a pet's inappetence is distressing to the owner.
- During the diagnostic process and in addressing chronic conditions that affect appetite, veterinarians need a reliable tool to get the patient to eat—now.

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In the presence of disease, if patients are not eating, it is much harder for them to heal, and much harder for us to treat the disease process.

—Dr. Burney

Patients might have a very treatable disease but the medications make them feel bad, so the owners stop treatment because they lose faith that we can get a positive outcome.

—Dr. Cook

Veterinary Cooperative Oncology Group (VCOG) has published a grading system for appetite. But there are at least 3 other grading schemes that I have found. So pinpointing the incidence of inappetence is challenging. In the literature, it ranges from 20% to 80% in oncology, depending on the chemotherapy used, and 20% to 50% in general.[2] In cancer, when chemotherapy is quite effective, we are killing off a lot of tumor, which releases cytokines, further exacerbating the inappetence.

Dr. Burney: The ultimate consequence of continuous inappetence is death. However, the prevalence of inappetence is difficult to determine. In my practice probably about 30% of patients have some form of hyporexia or dysrexia, but the percentage is definitely not that high for anorexia. I can't tell you how many times a client tells me, "Oh, Dr. Burney, my dog is not eating anything at all." On questioning, I learn that just yesterday he ate a Vienna sausage, a pig's ear, and several cat treats––more than his caloric requirements, but low-quality or inappropriate foods. In such cases, the consequences can be severe nevertheless. Then, in the presence of disease, if patients are not eating, it is much harder for them to heal, and much harder for us to treat the disease process. If they need any medications or surgical procedure that might impact their appetite and they already are not eating, it just makes it that much harder to help a patient get better.

Dr. Freeman: In one study we did with dogs with heart failure, appetite changes were an important reason that owners ended up euthanizing their dogs. So not only is it bad in terms of the disease, but it may be the reason owners give up.

Dr. Larson: Can you tell us more about inappetence in heart disease and other common conditions?

Dr. Freeman: In heart failure, hyporexia and dysrexia are huge problems. I hear this all the time from owners who spend half their day trying to get their dog or cat with heart failure to eat.

Dr. Johannes: Many of my patients starting chemotherapy are suffering from hyporexia or dysrexia. Gastrointestinal lymphoma is probably the worst because I don't know if they're not eating because of the chemotherapy, because of the disease, or both. Depending on the type of chemotherapy, probably between 15% and 50% experience some level of inappetence. We expect to see it with doxorubicin, but depending on the patient, it's even seen with vincristine and cyclophosphamide. We need to emphasize to our clients what they may see and the importance of reporting what they're experiencing at home.

Dr. Cook: Dogs with chronic pancreatitis and diabetes frustrate me the most. You're dealing with not only inappetence but also with its complications and the stressor of giving insulin. Clients quit giving the insulin, and then the patient becomes ketotic. Or the patient will eat something inappropriate and the pancreatitis flares up. Other patients might have a very treatable disease but the medications make them feel bad, so the owners stop treatment because they lose faith that we can get a positive outcome.

Dr. Larson: Does your approach change if faced with an acute versus chronic condition associated with inappetence? And what's the impact when you do not yet have a diagnosis?

Dr. Burney: Nutritional support is incredibly important in all patients regardless of whether they have an acute

or chronic problem. It's appropriate to provide some form of nutrition as soon as possible. If a dog was hit by a car or is having surgery, it might be inappetent for a relatively short period, and chances are good that dog will recover without appetite stimulation. But patients that have chronic disease may be chronically hyporexic. Then it becomes a struggle for the rest of that pet's life to get it to ingest enough food to address the disease process. If we had better means to provide nutritional support in such cases, patients would do better.

Inappetence: Effect on Treatment

Dr. Larson: Do you think inappetence directly impacts your patient's response to treatment?

Dr. Johannes: A primary concern is that managing the disease, the pet's appetite, and client expectations is difficult. A lot of our clients are hesitant about starting chemotherapy in the first place, so they're probably going to stop therapy if we don't have a positive experience in those first 2 or 3 weeks.

Another issue is that inappetence may dictate how I dose chemotherapy. If I have to delay treatment or reduce the dose because of inappetence, I may be hurting the patient's ability to respond to that chemotherapy protocol. It puts us in a tough spot, especially if the condition is progressing and I can't begin treatment.

Or some clients say, "This isn't for me. It's not the quality of life I want for my pet," and they just stop treatment. If I have the ability to intervene to bring back the pet's appetitie, that changes the dynamic.

Dr. Freeman: To owners, appetite is so important in terms of their animal's quality of life. In chronic kidney disease (CKD), studies have shown that renal diets can slow progression of disease and improve survival, but they don't help if the animal won't eat them.

Dr. Larson: What is the impact of the weight loss that results from not eating very well?

Dr. Freeman: Weight loss is certainly a common issue, but more important is muscle. If we don't provide enough calories to a healthy animal, it's going to primarily lose fat. If we don't provide enough calories to an ill animal, it will primarily lose muscle—what we call cachexia.[3] This muscle loss associated with disease has deleterious effects on survival, quality of life, strength, and wound healing.

There is another type of muscle loss called *sarcopenia*, which occurs with aging in the absence of disease.[3] Since older animals are more likely to get diseases, we often see cachexia and sarcopenia concurrently.

Dr. Johannes: In human oncology the cachexia-anorexia syndrome is very well established and recognized. The impact that it plays on the cancer patient's quality of life and survival is also well recognized. Being able to intervene is becoming a growing focus in human oncology. Effective intervention may help with not just quality of life but with outcome.

Dr. Larson: Can you help us understand what's important in a basic nutritional assessment?

Dr. Freeman: A nutritional assessment can tell you a tremendous amount, and every patient should have one performed at every visit. The World Small Animal Veterinary Association guidelines (www.wsava.org/nutrition-toolkit) detail how this should be done. At every patient visit, we should get the body weight, body condition score, muscle condition score, and diet history. With that information, we can determine the animal's nutritional status and whether the diet is contributing to the underlying disease or if the diet needs to be modified to help manage the condition. We especially want to pay attention to aging animals and those with chronic disease.

Dr. Larson: Is muscle condition score an important component of the assessment of an inappetent patient?

Dr. Freeman: The body condition score primarily assesses fat, and the muscle condition score specifically looks at muscle. You can have a very obese animal with severe muscle loss, and conversely you can have a very thin animal that has normal muscle, so you have to do both assessments. We assess muscle condition score over the shoulders, the hindquarters, and the head, but primarily over the epaxial muscles of the back because that's where muscle loss starts and it's the easiest place to identify it.

Dr. Larson: What else should you be considering in a workup of an inappetent patient?

Dr. Cook: Trying to get a diagnosis is really important. Sometimes the physical exam will give us direction—we'll hear something abnormal in the chest or feel something abnormal in the abdomen. I can't emphasize enough that often there are tremendously important clues to be found in the very basic exam. Then I'll order routine lab work—complete blood count, biochemical profile, and urinalysis.

For example, underlying GI disease is one of the most common causes of inappetence, so I tend to lean toward that as the cause if the bloodwork doesn't give me anything useful. Ultrasound and thoracic radiographs are easy to do. Sometimes it's curable endocrine disease, but usually it's not. Then we're considering an occult neoplastic process in the abdominal cavity or inflammatory bowel disease. Sometimes those diagnoses are hard to make, so we look at things like cobalamin and folate levels, and then we rule out infectious diseases. All these things take time, and sometimes days go by without making a diagnosis. It would be extremely helpful to have something to achieve more effective nutrition while we're waiting for our test results to come back.

Dr. Larson: What are the most common drugs used to stimulate appetite?

Dr. Johannes: That's been the challenge. Everything we've been using as appetite stimulants has 2 characteristics: it's used off-label, and it's not designed to be an appetite stimulant. Whether it's mirtazapine, cyproheptadine, or diazepam, we're using it because a side effect is appetite stimulation. It's no wonder that we are frustrated, because it only works sometimes. A high percentage of our patients have some level of inappetence, but we didn't have any drug that directly affects the appetite pathway. Appetite regulation is complicated, but we do know that there is one hormone that has a direct positive

Appetite has a huge impact on quality of life—when that appetite is not there, it takes a toll on the clients as well.

—Dr. Johannes

I have a number of patients with some degree of chronic malnutrition in which I am using ENTYCE® (capromorelin oral solution).

—Dr. Burney

It's not just the animals with anorexia that can benefit. That's the smallest proportion. The much bigger populations are those with hyporexia and dysrexia.

—Dr. Freeman

impact on the appetite center to increase appetite, and that is ghrelin.

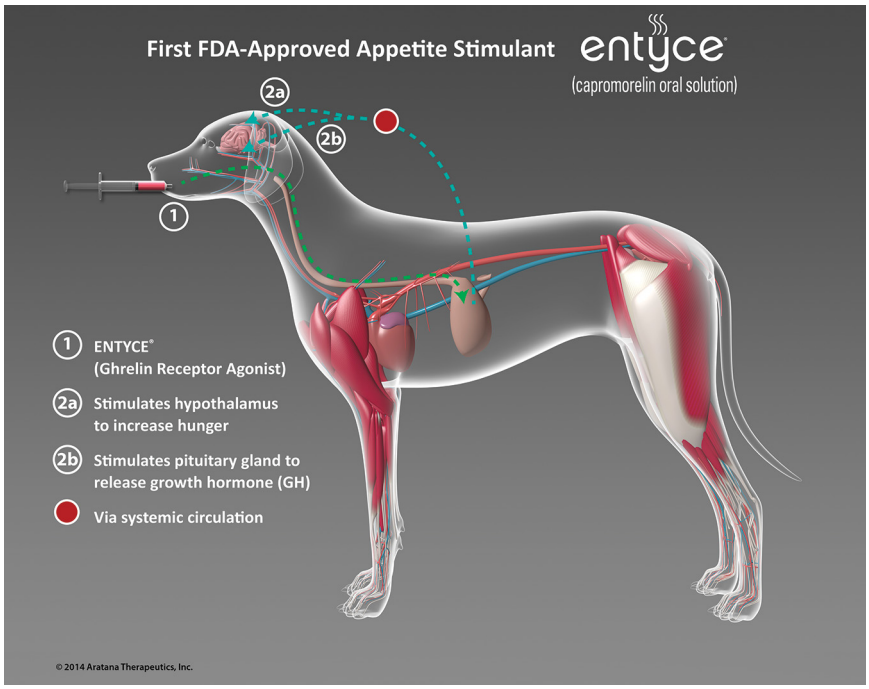
A New Option for Appetite Stimulation

Dr. Larson: ENTYCE® (capromorelin oral solution) is the first FDA-approved appetite stimulant for dogs. Can you tell us about its mechanism of action?

Dr. Johannes: Regulating appetite is not simple. There are a lot of signals coming from adipose tissue and acting on the hypothalamus to say "don't eat," but only the hormone ghrelin is saying "eat." As a ghrelin receptor agonist, capromorelin works at the hypothalamic appetite center to stimulate appetite. It also causes a release of growth hormone, which induces the production of insulin-like growth factor 1 in the liver. The spike in growth hormone seen with capromorelin becomes blunted because of negative feedback. Rather than an uncontrolled increase in growth hormone that might be deleterious, we get a subtle increase that may be advantageous—so capromorelin increases appetite while potentially helping to maintain lean muscle mass.

Dr. Larson: Can we discuss how ENTYCE may be helpful in both acute and chronic settings?

Dr. Cook: Sometimes the surgical team has patients recovering from traumatic



injury, and those dogs get thinner as the days go by because they're on multiple medicines and they're in pain. Maybe they're getting 60% of their caloric needs, but it's not nearly enough for what those dogs are facing. Something to improve food intake and potentially reverse muscle loss after acute injury could be tremendously helpful for getting those dogs up and home much more quickly.

Dr. Freeman: Changes in the gut mucosa and immune function also can occur very quickly. A healthy individual can go for long periods without eating. But because an ill or injured animal is using primarily lean body mass, negative effects, including malnutrition, immune function changes, and gastrointestinal atrophy, can start to occur within 3 to 5 days.[4] So we want to intervene before that.

Dr. Johannes: I talk to our critical care specialists and our cardiologists, and it becomes quite clear that there are a lot of other areas of veterinary medicine in which we struggle with appetite and could start utilizing capromorelin. The easy ones are acute conditions. The more challenging ones are chronic cases, where we have to add this on to the drugs they're already getting. I have a list of patients that are now receiving ENTYCE® (capromorelin oral solution), and I encourage you to start thinking how you can use this therapeutic.

Dr. Burney: When we address the primary cause but still have to fight the patient's appetite problems—that's where ENTYCE will be so useful. It's already a real boon to our patients' quality of life and enhancing their recovery.

Dr. Cook: CKD is an endemic disorder. If that dog's weight is moving down, its days are numbered even if the bloodwork is barely changed from the last visit. Half-eaten cans of food are going straight in the trash and the owner is getting more and more desperate.

Dr. Freeman: If you identify muscle loss in a chronic case, there are probably some challenges with nutritional status that need intervention. If they're not on an optimized diet for cancer or kidney disease or pancreatitis, capromorelin may get them to eat the more optimal diet and help them long term.

Dr. Johannes: Hopefully with the availability of capromorelin, we have the opportunity to really make a clinical impact in a disease category that we've struggled with. That for me is exciting. We still have a lot to learn. We don't know exactly how this is going to be incorporated in clinics. It's potentially going to change some treatment dynamics. That's the fun part.

Dr. Cook: I have tremendous difficulty getting good treatment outcomes when patients are dysrexic or hyporexic. It's extremely distressing to owners whose pet is not eating well—particularly us dog owners. We communicate love and affection for our dog with food. If our dog looks at our food and pulls a sad face, it's very disturbing. It's also hard to get owners to be compliant about medical therapy if the patient is not consistently eating. We might instruct them to give 2 or 3 drugs, some with food and some without. Very quickly clients will get overwhelmed and say, "I stopped giving the antibiotic because I think it made his poor appetite worse."

Dr. Johannes: So much of the social interaction our clients experience with their pets is appetite-related, appetite-driven. Clients know their pets best. I myself have a Schnauzer that had pancreatitis, and if he doesn't eat his breakfast in 20 seconds, I know something's wrong.

Calls to Action

Dr. Larson: What are some key take-aways for general practitioners regarding management of inappetence and hyporexia, particularly in dogs?

Dr. Burney: If you can, detect the underlying cause. Sometimes an obvious lesion or condition is not the cause of a poor appetite. The other thought I would like to leave you with is that getting these patients to eat is important not only for the short term but for the long term. I have a number of patients with some degree of chronic malnutrition in which I am using ENTYCE®. Finally, remember how important it is to clients to see their pets eagerly eating. They want their pets to come into the kitchen looking for food and treats. They equate so much of a pet's quality of life to eating.

Dr. Freeman: One of my take-home points also would be thinking about patients in which ENTYCE can be used, which raises one issue: The fact that it's not just the animals with anorexia that can benefit. That's the smallest proportion. The much bigger populations are those with hyporexia and dysrexia—getting them to eat the food they need. The other point is that even if you don't have changes in appetite, start to be aware of muscle loss from cachexia and sarcopenia in every patient.

References

1. Johnson LN, Freeman LM. Recognizing, describing, and managing reduced food intake in dogs and cats. *J Am Vet Med Assoc*. 2017; 251(11):1260-1262.
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3. Freeman LM. Cachexia and sarcopenia: Emerging syndromes of importance in dogs and cats. *J Vet Intern Med*. 2012; 26(1):3-17.
4. WSAVA Nutritional Assessment Guidelines Task Force (Freeman L, Becarova I, Cave N, et al). *J Small Anim Pract*. 2011; 52:385-396.

entyce®

(capromorelin oral solution)

30 mg/mL

For oral use in dogs only

Appetite Stimulant

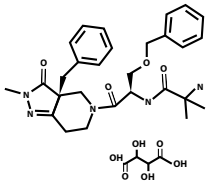
Caution:

Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

Description:

ENTYCE® (capromorelin oral solution) is a selective ghrelin receptor agonist that binds to receptors and affects signaling in the hypothalamus to cause appetite stimulation and binds to the growth hormone secretagogue receptor in the pituitary gland to increase growth hormone secretion. The empirical formula is $C_{28}H_{35}N_5O_4 \cdot C_4H_6O_5$ and the molecular weight 655.70. The chemical name is 2-amino-N-[2-(3aR-benzyl-2-methyl-3-oxo-2,3,3a, 4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-1R-benzyloxymethyl-2-oxo-ethyl]-isobutyramide L-tartrate.

The chemical structure of capromorelin tartrate is:



Indication:

ENTYCE (capromorelin oral solution) is indicated for appetite stimulation in dogs.

Dosage and Administration:

Administer ENTYCE orally at a dose of 3 mg/kg (1.4 mg/lb) body weight once daily.

To administer ENTYCE, gently shake the bottle, and then withdraw the appropriate amount of solution using the provided syringe. Rinse syringe between treatment doses.

The effectiveness of ENTYCE has not been evaluated beyond 4 days of treatment in the clinical field study (See Effectiveness).

Contraindications:

ENTYCE should not be used in dogs that have a hypersensitivity to capromorelin.

Warnings:

Not for use in humans. Keep this and all medications out of reach of children and pets. Consult a physician in case of accidental ingestion by humans. **For use in dogs only**

Precautions:

Use with caution in dogs with hepatic dysfunction. ENTYCE is metabolized by CYP3A4 and CYP3A5 enzymes (See Clinical Pharmacology).

Use with caution in dogs with renal insufficiency. ENTYCE is excreted approximately 37% in urine and 62% in feces (See Adverse Reactions and Clinical Pharmacology).

The safe use of ENTYCE has not been evaluated in dogs used for breeding or pregnant or lactating bitches.

Adverse Reactions:

In a controlled field study, 244 dogs were evaluated for safety when administered either ENTYCE or a vehicle control (solution minus capromorelin) at a dose of 3 mg/kg once daily for 4 days. Enrolled dogs had a reduced or absent appetite for a minimum of 2 days prior to day 0 and had various medical conditions: arthritis (40); gastrointestinal disease (24); allergy (22); dental disease (22); cardiovascular disease (16); renal disease (13); and others. Some dogs may have experienced more than one of the adverse reactions during the study. The following adverse reactions were observed:

Table 1: Adverse Reactions reported in dogs administered ENTYCE oral solution compared to vehicle control

Adverse Reactions	ENTYCE (n = 171) n (%)	Vehicle Control (n = 73) n (%)
GASTROINTESTINAL		
Diarrhea	12 (7.0 %)	5 (6.8 %)
Vomiting	11 (6.4 %)	4 (5.5 %)
Hypersalivation	4 (2.3 %)	0 (0.0 %)
Abdominal discomfort	2 (1.2 %)	0 (0.0 %)
Flatulence	2 (1.2 %)	0 (0.0 %)
Nausea	2 (1.2 %)	0 (0.0 %)
CLINICAL PATHOLOGY		
Elevated blood urea nitrogen	7 (4.1 %)	2 (2.7 %)
Elevated phosphorus	4 (2.3 %)	1 (1.4 %)
Elevated creatinine	1 (0.6 %)	1 (1.4 %)
OTHER		
Polydipsia	7 (4.1 %)	1 (1.4 %)
Lethargy/depression	2 (1.2 %)	0 (0.0 %)

The following adverse reactions were reported in < 1% of dogs administered ENTYCE: hyperactivity, increase fecal volume, increase gut sounds, and polyuria.

To report suspected adverse drug events and/or to obtain a copy of the Safety Data Sheet (SDS) or for technical assistance, call Aratana Therapeutics at 1-844-272-8262.

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

Clinical Pharmacology:

Following oral administration of ENTYCE at a dose of 3 mg/kg to 12 Beagle dogs, absorption of capromorelin was rapid with the maximum concentration (C_{max}) reached within 0.83 hr (T_{max}). After C_{max}, the plasma concentrations declined mono-exponentially with a short terminal half-life ($T_{½}$) of approximately 1.19 hrs. There were no gender differences in capromorelin pharmacokinetics. The exposure (C_{max} and AUC) of capromorelin increased with dose, but the increases were not dose proportional following single and repeat once daily administrations of capromorelin. There was no drug accumulation following repeat oral administration.

Table 2. Plasma PK parameters following oral administration of 3 mg/kg of ENTYCE

Parameter	Mean	SD
T_{max} (hr)	0.83	0.58
C_{max} (ng/mL)	330	143
AUC_t (ng*hr/mL)	655	276
AUC_{inf} (ng*hr/mL)	695	262
$T_{½}$ (hr)	1.19	0.17

The mean absolute oral bioavailability of capromorelin was 44%. The mean total plasma clearance and volume of distribution was 18.9 mL/min/kg and 2.0 L/kg, respectively. Capromorelin was not highly bound (unbound fraction 51%) to plasma protein. The protein binding was concentration-independent over the range of 10 to 1000 ng/mL. *In vitro* (human liver microsomes) and *in vivo* (rats) metabolism studies suggest that capromorelin is metabolized by hepatic enzymes, mainly CYP3A4 and CYP3A5. Therefore, drugs that inhibit CYP3A4 and CYP3A5 activity may affect capromorelin metabolism. Following oral administration of radio-labelled capromorelin to dogs, capromorelin was excreted in urine (37%) and in feces (62%) within 72 hours.

Effectiveness:

Laboratory Effectiveness Study: Twenty four healthy Beagle dogs (6 dogs per sex in each group) with normal appetite were randomized into two groups and dosed daily with ENTYCE (capromorelin oral solution) at 3 mg/kg/day or vehicle control (solution minus capromorelin) to compare food intake over a 4-day period. The dogs were 13 months of age and weighed between 6.5 and 12.5 kg at the time of randomization. Six dogs administered ENTYCE repeatedly exhibited salivation post dosing and two dogs administered vehicle control exhibited salivation only one time on study day 0. Emesis was observed in one dog administered ENTYCE on study day 1. Dogs administered ENTYCE at a dose of 3 mg/kg/day for 4 consecutive days had statistically significantly increased food consumption compared to the vehicle control group ($p < 0.001$).

Clinical Field Study: Effectiveness was evaluated in 177 dogs (121 dogs in the ENTYCE group and 56 dogs in the vehicle control group) in a double-masked, vehicle controlled field study. Dogs with a reduced appetite or no appetite, with various medical conditions, for a minimum of 2 days prior to day 0 were enrolled in the study. The dogs ranged in age from 4 months to 18 years. Dogs were randomized to treatment group and dosed once daily for 4 days with ENTYCE at 3 mg/kg or vehicle control. Dogs were assessed for appetite by owners on day 0 and day 3 ± 1 using an "increased", "no change" or "decreased" scoring system. Dogs were classified as a treatment success if the owner scored their dog's appetite as "increased" on day 3 ± 1. The success rates of the two groups were significantly different ($p = 0.0078$); 68.6% (n = 83) of dogs administered ENTYCE were successes, compared to 44.6% (n = 25) of the dogs in the vehicle control group.

Animal Safety:

In a 12-month laboratory safety study, 32 healthy Beagle dogs (4 dogs per sex per group) approximately 11-12 months of age and weighing 9-13.6 kg were dosed orally with capromorelin in deionized water daily at 0X (placebo), 0.3 (0.13X), 7 (3.07X), and 40 (17.5X) mg/kg/day. Administration of capromorelin was associated with increased salivation and reddening/ swollen paws, increased liver weights and hepatocellular cytoplasmic vacuolation. Treatment related decreases were seen in red blood cell count, hemoglobin and hematocrit in the 40 mg/kg group. Pale skin, pale gums, and decreased red blood cell count, hemoglobin and hematocrit were observed in one dog administered 40 mg/kg/day. Increases were seen in cholesterol, high density lipoproteins, and the liver specific isozyme of serum alkaline phosphatase in the 40 mg/kg group. Growth hormone and insulin-like growth factor 1 plasma levels were increased in all groups administered capromorelin. There were no effects noted on gross necropsy. Capromorelin levels were similar in plasma collected on days 90, 181, and 349 indicating no accumulation of drug.

Storage Conditions:

Store at or below 86° F (30° C)

How Supplied:

30 mg/mL flavored solution in 10 mL, 15 mL and 30 mL bottles with measuring syringe

NADA 141-457, Approved by FDA

US Patent: 6,107,306
US Patent: 6,673,929

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ARATANA THERAPEUTICS®

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