

WITH REDUCED APPETITE, THERE'S
**MORE THAN
MEETS THE EYE**

entyce[®]
(capromorelin oral solution)



Don't wait for weight loss.
Stimulate appetite early to treat
the whole picture.



APPETITE IS A KEY INDICATOR OF QUALITY OF LIFE



- Change in appetite is often the first and only sign a dog is sick
- Pet owners consider inappetence, weight loss and depression as unacceptable¹
- Pet owners are distressed by effects of inappetence and often perceive pet as suffering

WHAT IS INAPPETENCE?

Almost any disease can cause inappetence, which can manifest as:

Hyporexia Dog is eating but not obtaining adequate caloric intake

Dysrexia

- Unwilling to eat optimal diet
- Requires additional treats, topping or flavor enhancers to eat diet
- Loses interest in diet after eating it a few days (e.g., the picky eater)

Anorexia Dog is not eating food

IT IS IMPORTANT TO ASK PET OWNERS TO MONITOR ANY CHANGES IN THEIR DOG'S EATING BEHAVIOR.



COMMON CAUSES OF INAPPETENCE

Acute medical conditions

- Gastroenteritis, pain, post-surgery, psychological, among others

Chronic medical conditions and the clinical impact of inappetence



Chronic kidney disease

Higher BCS at diagnosis associated with significantly improved survival²



Congestive heart failure

Dogs that gained body weight had longer survival times³



Cancer

Nearly 40% of dogs experienced $\geq 5\%$ weight loss⁴

- Dogs underweight at diagnosis with lymphoma had shorter survival times⁵



Chronic gastrointestinal disease

Malnutrition in chronic GI disease is multifactorial

- Nutrient loss, malabsorption, lack of intake

Consequences of inappetence

Changes occur early, often before noticeable weight loss ($\geq 5\%$ weight loss is clinically significant)⁶

Decline in GI tract function

Decreased immune response

Impaired healing, recovery

EARLY RECOGNITION OF ANY CHANGES IN APPETITE IS ESSENTIAL. PROLONGED INAPPETENCE, IF LEFT UNTREATED, CAN BECOME MORE DETRIMENTAL TO THE PATIENT THAN THE UNDERLYING CONDITION.



Potential advantages of early intervention to improve nutritional intake

- Maintain strength & immune function while investigating a diagnosis
- Shorten hospital stay⁷
- Improve treatment outcomes
- Enhance patient quality of life
- Increase client satisfaction with decision to treat



Add ENTYCE[®] (capromorelin oral solution) at the first sign of decreased eating as part of an overall treatment plan

- ✓ Proven to **safely and effectively** stimulate appetite^{10,11}
- ✓ Demonstrated a significant **increase in food consumption**¹⁰
- ✓ Proven safe for **long-term use**¹¹
- ✓ **Convenient, once-daily dosing**
 - Available in 10, 15 and 30mL bottle sizes



**AVAILABLE THROUGH YOUR
ARATANA AUTHORIZED
DISTRIBUTOR**

IMPORTANT SAFETY INFORMATION: ENTYCE[®] (capromorelin oral solution) is for use in dogs only. Do not use in breeding, pregnant or lactating dogs. Use with caution in dogs with hepatic dysfunction or renal insufficiency. Adverse reactions in dogs may include diarrhea, vomiting, polydipsia, and hypersalivation. Should not be used in dogs that have a hypersensitivity to capromorelin. Please see the full Prescribing Information for more detail.

ENTYCE® (capromorelin oral solution) treated dogs demonstrated significant increases in appetite compared to placebo treated dogs in the Clinical Field Study⁹

Parameter	Capromorelin	Placebo	P-Value
Treatment success—single-question assessment %*	68.6	44.6	0.0078
Treatment success—owner appetite assessment, %**	56.2	26.8	0.0071
Percent change in owner appetite assessment, mean (±SD)	73.3 (±75.9)	37.6 (±53.9)	0.0125
Percent change in body weight, mean (±SD)	1.83 (±2.75)	0.11 (±3.61)	0.0004

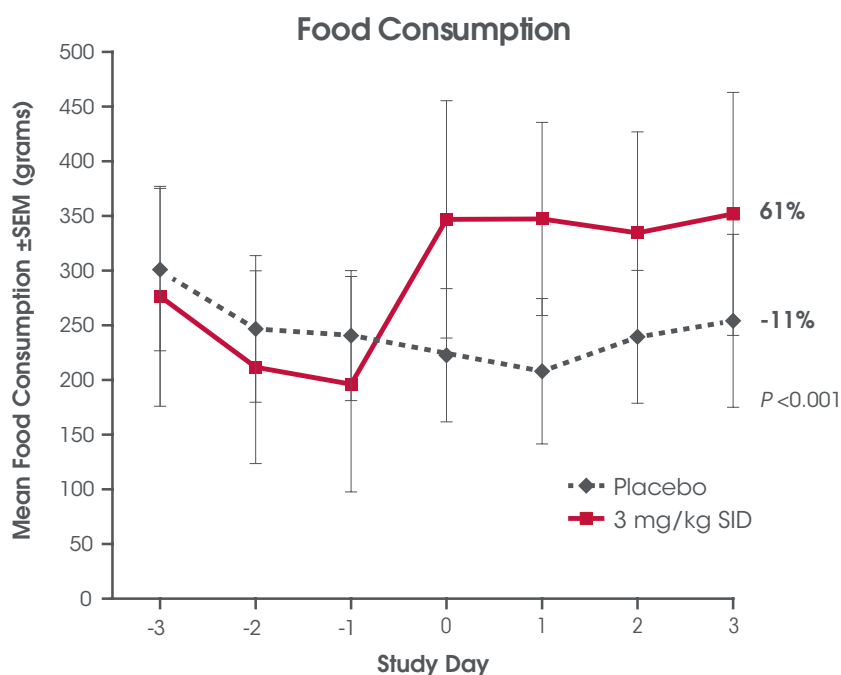
*A dog was considered a treatment success if the owner answered that their dog's appetite was increased in response to the question, "Do you feel that during the study (over the 4 ± 1 days of treatment) your dog's appetite was increased, no change or decreased?"

**Treatment success was defined as an increase in total score ≥5 from day 0 to day 3 ± 1 (scoring scale 5-25)

ENTYCE treated dogs demonstrated significantly increased food consumption compared to dogs that received placebo¹⁰

LABORATORY EFFECTIVENESS STUDY

Results demonstrated that ENTYCE-treated dogs had a 61% increase in food consumption vs. reduction of 11% in placebo-treated dogs ($P < 0.001$).



Study design: A randomized, masked, placebo-controlled study of 24 healthy beagle dogs, randomized 1:1. Study participants received ENTYCE 3 mg/kg once daily or placebo for 4 days. All dogs enrolled were observed for clinical signs throughout the course of the study. Physical exams were completed prior to and at the end of treatment. Blood was drawn before and after treatment for evaluation of serum chemistry and hematology parameters.

Demonstrated to be safe and well-tolerated for long-term use¹¹

In the 12-Month Laboratory Safety Study, the most common adverse events were mild emesis and loose stools in all groups, as well as excess salivation among some dogs receiving higher capromorelin doses.

Study design: A study of 32 beagle dogs that received either oral placebo or 0.3, 7, or 40 mg/kg capromorelin administered once daily for 12 consecutive months. Safety was evaluated by physical examinations, including electrocardiogram (ECG), ophthalmic examinations and comprehensive clinical pathology.

Shown to be safe and effectively stimulate appetite in dogs enrolled in a large multi-center Clinical Field Study¹⁰

Adverse reactions reported in dogs administered ENTYCE[®] (capromorelin oral solution) compared with vehicle control

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



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

Study design: A blinded, placebo-controlled, multi-site study of 244 client-owned dogs with inappetence of various etiologies, randomized 2:1. Study participants received ENTYCE 3 mg/kg once daily or placebo for 4 days. All dogs enrolled in the study were evaluated for adverse reactions throughout the course of the study.

Don't wait for weight loss.

Stimulate appetite early with ENTYCE[®] (capromorelin oral solution) as part of your overall treatment plan.

- ✓ Proven safe for long-term use¹¹
- ✓ Effectively stimulates appetite to help improve food consumption
- ✓ The ONLY FDA-approved appetite stimulant for dogs

Dose:

3 mg/kg (1.4 mg/lb)
body weight once daily



REFERENCES:

1. Williams J, Phillips C, Byrd HM. Factors Which Influence Owners When Deciding to Use Chemotherapy in Terminally Ill Pets. *Animals (Basel)*. 2017;7(3):E18.
2. Parker VJ and Freeman LM. Association between body condition and survival in dogs with acquired chronic kidney disease. *J Vet Intern Med*. 2011;25(6):1306-11.
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9. Zollers B, Wofford JA, Heinen E, Huebner M, Rhodes L. A Prospective, Randomized, Masked, Placebo-Controlled Clinical Study of Capromorelin in Dogs with Reduced Appetite. *J Vet Intern Med*. 2016;30(6):1851-1857.
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entyce[®]

(capromorelin oral solution)

30 mg/mL

For oral use in dogs only

Appetite Stimulant

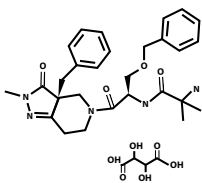
Caution:

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 C₂₈H₃₅N₅O₄·C₄H₆O₆ 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-benzyl-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 1-844-640-5500.

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_{1/2}) 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 _{1/2} (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: 6,673,929

US Patent: 9,700,591

Made in Canada



Additional information is available at www.aratana.com or by calling Aratana Therapeutics at 1-844-272-8262.

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