WITH REDUCED APPETITE, THERE'S

MORE THAN MEETS THE EYE

APPETITE IS A KEY INDICATOR OF QUALITY OF LIFE

Often first and only sign pet is sick

Pet owners consider inappetence, weight loss and depression in their dog as unacceptable side effects[1]

COMMON CAUSES AND CLINICAL IMPACT OF INAPPETENCE

Chronic kidney disease

- Higher BCS at diagnosis associated with significantly improved survival[2]

Chronic gastrointestinal disease

- Malnutrition in chronic GI disease is multifactorial
  - » Nutrient loss, malabsorption, lack of intake

Congestive heart failure

- Dogs that gained body weight had longer survival times[3]

Cancer

- Nearly 40% of dogs experienced ≥ 5% weight loss[4]
  - » Dogs underweight at diagnosis with lymphoma had shorter survival times[5]

WHY INTERVENE EARLY?

Changes occur early, often before noticeable weight loss

- Decline in GI tract function
- Decreased immune response
- Impaired healing, recovery

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

entyce®
(capromorelin oral solution)

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

- Proven safe for long-term use[6]
- Effectively stimulates appetite to help improve food consumption
- The ONLY FDA-approved appetite stimulant for dogs

entyce® (capromorelin oral solution)

ENTYCE treated dogs demonstrated significant increases in appetite compared to placebo treated inappetent dogs in the clinical field study[7]

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)

Most common side effects reported by pet owners in the study include:[7]

- Diarrhea
- Vomiting
- Hypersalivation
- Excessive drinking

Convenient, once-daily oral solution for treating inappetence

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

1. Williams J, Phillips C, Byrd HM. Factors Which Influence Owners When Deciding to Use Chemotherapy in Terminally Ill Pets. *Animals.* 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. 3. Slupe JL, Freeman LM, Rush JE. Association of Body Weight and Body Condition with Survival in Dogs with Heart Failure. *J Vet Intern Med.* 2008;22:561-565. 4. Michel KE, Sorenmo K, Shofer FS. Evaluation of body condition and weight loss in dogs presented to a veterinary oncology service. *J Vet Intern Med.* 2004;18(5):692-5. 5. Romano FR, Heinze CR, Barber LG, Mason JB, Freeman LM. Association between Body Condition Score and Cancer Prognosis in Dogs with Lymphoma and Osteosarcoma. *J Vet Intern Med.* 2016;30:1179–1186. 6. Zollers B, Huebner M, Armintrout G, Rausch-Derra LC, Rhodes L. Evaluation of the safety in dogs of long-term, daily oral administration of capromorelin, a novel drug for stimulation of appetite. *J Vet Pharmacol Ther.* 2017 Jun;40(3):248-255. 7. 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.

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 enclosed full Prescribing Information for more detail.

ARATANA THERAPEUTICS

entyce™

(capromorelin oral solution)

30 mg/mL

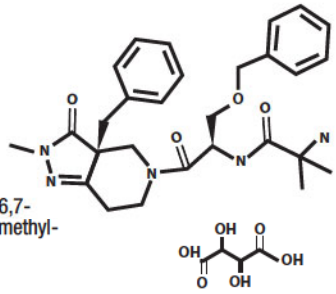
For oral use in dogs only

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 $C_{28}H_{36}N_5O_4 \cdot C_4H_6O_6$ 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 events, for technical assistance or to obtain a copy of the Safety Data Sheet (SDS), contact Elanco US Inc. at 1-888-545-5973. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or http://www.fda.gov/reportanimalae.

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

Approved by FDA under NADA # 141-457

Manufactured for:
Elanco US Inc.
Greenfield, IN 46140, USA
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Elanco™