WHY INTERVENE EARLY?

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

COMMON CAUSES AND CLINICAL IMPACT OF INAPPETENDE

Chronic kidney disease
- Higher BCS at diagnosis associated with significantly improved survival

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

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

Don’t wait for weight loss.
Stimulate appetite early to treat the whole picture.
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
- Effectively stimulates appetite to help improve food consumption
- The ONLY FDA-approved appetite stimulant for dogs

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

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

*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:
- 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


© 2019 ENTYCE is a registered trademark of Aratana Therapeutics, Inc. 11400 Tomahawk Creek Parkway Suite 340 Leawood, KS 66211
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_{46}H_{38}N_{4}O_{14}·C_{4}H_{6}O, 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-1H-pyrazolo[4,3-c]pyridin-5-yl)-1R-benzoxymethyl-2-oxo-ethyl]-isobutyramide-L-tartrate.
The chemical structure of capromorelin tartrate is:

![Chemical Structure Diagram]

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 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]

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_{AUC} 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®

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>C_{max} (ng/mL)</td>
<td>330</td>
<td>143</td>
</tr>
<tr>
<td>AUC (ng*h/mL)</td>
<td>655</td>
<td>276</td>
</tr>
<tr>
<td>AUC_{inf} (ng*h/mL)</td>
<td>595</td>
<td>262</td>
</tr>
<tr>
<td>T_{1/2} (hr)</td>
<td>1.19</td>
<td>0.17</td>
</tr>
</tbody>
</table>

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 2.01 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® 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 randomly to treatment groups 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 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 80°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.

Manufactured for:
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