entyce®
(capromorelin oral solution)
Technical Monograph
ENTYCE® (capromorelin oral solution): A U.S. Food and Drug Administration (FDA)-approved treatment for stimulation of appetite in dogs

ENTYCE® is the first drug developed specifically for appetite stimulation in veterinary medicine. The active ingredient in ENTYCE is capromorelin, a small-molecule ghrelin receptor agonist that mimics the effects of ghrelin. Several studies have been published that demonstrate its efficacy and safety in both laboratory dogs and client-owned dogs presenting to veterinary clinics with lack of appetite.¹⁻⁴

ENTYCE offers the convenience of once-daily oral administration and is supplied as a flavored liquid formulation. ENTYCE is available in 3 bottle sizes; each with an oral dosing syringe for ease of administration.⁵

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. See the package insert on page 30 for full product information.
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Introduction

Why Consider ENTYCE® (capromorelin oral solution)?

Inappetence is a common complaint in pets, and its effects are far reaching. The complicated nature of appetite control has resulted in therapeutic challenges in the past, and veterinarians have been limited to using unapproved drugs that may stimulate appetite as a side effect. ENTYCE was developed to stimulate appetite because its mechanism of action mimics an endogenous hormone that regulates appetite. ENTYCE is the first FDA-approved veterinary product labeled for stimulation of appetite in dogs and is an important tool in the medical management of conditions where appetite is reduced.

For additional information on inappetence in dogs, please see Appendix I on page 31.

The Role of Ghrelin in Appetite Control

The regulation of appetite and eating behavior is highly regulated and complex, and involves the coordination of many signals from the brain (mainly the hypothalamus), peripheral tissues (such as adipose tissue), and endocrine factors (such as ghrelin, leptin, and insulin) (Figure 1). The short-term control of appetite requires the gastric hormone, ghrelin, the so-called “hunger hormone,” which is integral to appetite regulation and the maintenance of homeostasis and energy metabolism.6

Restricting feeding increases ghrelin in healthy dogs, with levels peaking just before eating.7 Following release from the stomach, ghrelin exerts its effects by binding to the growth hormone secretagogue receptors (GHS-R) within the hypothalamus, which causes an increase in appetite.8,11 As a dog fasts, ghrelin levels rise, peaking just before eating and falling after a meal.7

In addition to its effect on appetite, ghrelin elicits increased growth hormone (GH) release and subsequent increased production of insulin-like growth factor (IGF-1) in the liver, and data shows that IGF-1 may increase muscle mass12. As IGF-1 levels increase and are moderately sustained, the normal negative feedback loop suppresses subsequent increases in GH release, thereby preventing overstimulation.

For additional information on control of appetite in dogs, please see Appendix II on page 34.
**Introduction** *(continued)*

**ENTYCE® (capromorelin oral solution) Mechanism of Action**

The active ingredient in ENTYCE is capromorelin, a potent and selective GHS-R agonist that mimics the action of endogenous ghrelin. Capromorelin binds to the GHS-R, a G protein–coupled receptor in the hypothalamus, which triggers appetite ([Figure 2](#)). As capromorelin binds to the GHS-R, it activates protein kinase C and stimulates GH secretion from the pituitary gland, resulting in elevation of circulating GH levels. In turn, GH release causes an increase in IGF-1 secretion from the liver. The GH-releasing activity of capromorelin has been demonstrated in vitro and in vivo in dogs.²

**Clinical Use of ENTYCE**

Inappetence is an exceedingly common clinical complaint in veterinary medicine. Inappetence may be the first, and sometimes only, sign an animal displays that indicates it is sick. Almost every disease can manifest with, or develop, decreased appetite (hyporexia), complete lack of appetite (anorexia), or changes in appetite (dysrexia). Decreased appetite can also be a side effect from the treatment of some diseases (eg, certain antimicrobials and chemotherapeutics). Prolonged inappetence, if left untreated, may become even more detrimental to the patient than the underlying primary disease.³ In a large clinical field study, ENTYCE was effective in stimulating appetite in inappetent dogs who had a variety of comorbidities.⁴ ENTYCE provides veterinarians an effective tool to manage the symptom of inappetence in dogs while working to diagnose the underlying chronic or acute condition.

*For additional information on inappetence in dogs, please see Appendix I on page 31.*
## ENTYCE Pharmacology

### Description

Capromorelin, the active ingredient of ENTYCE® (capromorelin oral solution), is an orally active small-molecule ghrelin receptor agonist belonging to a class of compounds that mimics the actions of the hormone ghrelin, classified as growth hormone secretagogues (GHS).\(^{14,15}\)

The chemical structure and nomenclature for capromorelin is shown in Figure 3. The empirical formula of capromorelin is: \(\text{C}_{28}\text{H}_{35}\text{N}_{5}\text{O}_{4}\cdot\text{C}_{4}\text{H}_{6}\text{O}_{6}\), and the molecular weight is 655.70 Daltons. Capromorelin has also been referred to as AT-002 and CP-424,391-18.\(^{16}\)

### Dosage Characterization

The therapeutic dose for ENTYCE of 3 mg/kg (1.4 mg/lb) orally once-daily (SID) was selected based on laboratory studies comparing food consumption and weight gain in healthy adult beagle dogs treated with varying dose regimens of capromorelin vs placebo.\(^{2}\)

One of the dose-finding studies evaluated changes in food consumption and body weight in four treatment groups of dogs: placebo (vehicle control) twice per day (BID), or capromorelin orally at 3 mg/kg SID, 4.5 mg/kg SID, or 3 mg/kg BID for 7 days. Table 1 summarizes the results for change in food consumption and change in body weight for all study groups. Statistically significant increases in food consumption were seen in all ENTYCE groups when compared to the vehicle control group.\(^{2}\)

### Table 1: Change in Food Consumption and Body Weight Following 7 Days of Treatment With Capromorelin or Placebo

<table>
<thead>
<tr>
<th>Percent Change From Baseline, Mean (SD)</th>
<th>Placebo BID</th>
<th>3.0 mg/kg SID</th>
<th>4.5 mg/kg SID</th>
<th>3.0 mg/kg BID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Food consumption</td>
<td>-13.5 (14.9)</td>
<td>57.7 (35.1)</td>
<td>37.9 (16.8)</td>
<td>36.4 (21.4)</td>
</tr>
<tr>
<td>Body weight</td>
<td>-1.2 (1.5)</td>
<td>4.5 (1.7)</td>
<td>3.8 (2.9)</td>
<td>4.2 (1.4)</td>
</tr>
</tbody>
</table>

2-amino-N-[2-(3aR-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-y])-1R-benzyl oxymethyl-yl-2-oxo-ethyl]-isobutyramide L-tartrate
ENTYCE Pharmacology (continued)

Pharmacokinetic Profile

The pharmacokinetic (PK) properties of ENTYCE® (capromorelin oral solution) in dogs were characterized in a laboratory study in healthy adult beagle dogs. A single dose of 3 mg/kg of ENTYCE was administered on day 0, followed by a washout period and another single dose on day 7. Blood samples were collected pre-dose and at 0.5, 1, 2, 4, 6, 8, 10, 12, and 24 hours post-dose. Mean PK parameters were calculated following analysis of capromorelin serum concentrations (Table 2).

### Table 2: Plasma PK Parameters Following Oral Administration of 3 mg/kg of ENTYCE in Dogs

<table>
<thead>
<tr>
<th>PK Parameter</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>C\textsubscript{max}, ng/mL</td>
<td>330</td>
<td>143</td>
</tr>
<tr>
<td>T\textsubscript{max}, hr</td>
<td>0.83</td>
<td>0.58</td>
</tr>
<tr>
<td>T\textsubscript{1/2}, hr</td>
<td>1.19</td>
<td>0.17</td>
</tr>
<tr>
<td>AUC\textsubscript{0-24 hr}, ng.hr/mL</td>
<td>655</td>
<td>276</td>
</tr>
<tr>
<td>AUC\textsubscript{inf}, ng.hr/mL</td>
<td>695</td>
<td>262</td>
</tr>
</tbody>
</table>

Absorption and Distribution

Following oral administration of ENTYCE at a dose of 3 mg/kg SID, capromorelin was rapidly absorbed, with peak serum concentrations (C\textsubscript{max}) reached within 0.83 hours (T\textsubscript{max}). After reaching C\textsubscript{max}, plasma concentrations declined exponentially with a terminal half-life (T\textsubscript{1/2}) of approximately 1.19 hours.

The mean absolute oral bioavailability of capromorelin following administration of ENTYCE was determined to be 44%. The volume of distribution, which represents drug distribution between plasma and the rest of the body, was 2.0 L/kg. Capromorelin was not highly bound to plasma protein, with an unbound fraction of 51%. The protein binding was concentration-independent over the range of 10 to 1000 ng/mL.

### Metabolism and Excretion

The mean total of plasma clearance of capromorelin, or the volume of plasma cleared of the drug per unit of time, is 18.9 mL/min/kg.

In vitro metabolism studies with human liver microsomes and in vivo metabolism studies in rats suggest that capromorelin is metabolized by hepatic enzymes, primarily CYP3A4 and CYP3A5. Therefore, drugs that inhibit CYP3A4 and CYP3A5 activity may affect capromorelin metabolism. Known inhibitors of CYP3A4 and CYP3A5 include ketoconazole, itraconazole, erythromycin, diltiazem, clarithromycin, grapefruit juice, nefazodone, ritonavir, telithromycin, and verapamil.

Following oral administration of radiolabeled capromorelin to dogs, capromorelin and its metabolites were excreted in feces (62%) and urine (37%) within 72 hours.
12-Month Laboratory Safety Study: Oral Toxicity Study in Beagle Dogs

The objective of the study was to evaluate the safety of capromorelin over 12 months at doses significantly higher than the clinical dose (3 mg/kg SID). This study did not use the final formulation of ENTYCE® (capromorelin oral solution). A PK bridging study compared the exposure to capromorelin from the service formulation used in this study to ENTYCE (see PK Bridging Study on next page for further information).

Study Design

Beagle dogs (n = 32) received either oral placebo or 0.3, 7, or 40 mg/kg capromorelin in solution administered by gavage SID for 12 consecutive months. Safety was evaluated by physical examinations, electrocardiogram (ECG), ophthalmic examinations, and comprehensive clinical pathology tests. Blood samples were collected periodically for determination of serum levels of capromorelin, GH, and IGF-1. Necropsies and histopathologic evaluations were performed at study termination.

Results

As expected, GH and IGF-1 levels were mildly increased in capromorelin-treated dogs. Adverse events were limited to mild emesis and loose stools in all groups, as well as excess salivation among some dogs receiving higher capromorelin doses (Table 3). Results of clinical pathology tests were generally within the reference ranges, although blood lipids and alkaline phosphatase levels were moderately increased among dogs receiving capromorelin. Capromorelin-treated dogs had slightly longer post-treatment PR intervals seen on ECG, but with no changes in cardiac histopathology. Drug-related increases in liver weight corresponded with increases in body weight. Postmortem findings were otherwise unremarkable.

Table 3: Adverse Events in Dogs Treated With Capromorelin or Placebo Over 12 Months

<table>
<thead>
<tr>
<th>Event, % of Dogs</th>
<th>Placebo (n = 8)</th>
<th>0.3 mg/kg (n = 8)</th>
<th>7 mg/kg (n = 8)</th>
<th>40 mg/kg (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emesis</td>
<td>75% (1-3)</td>
<td>63% (1-2)</td>
<td>63% (1-4)</td>
<td>75% (1-6)</td>
</tr>
<tr>
<td>Loose stools</td>
<td>100% (1-41)</td>
<td>100% (5-32)</td>
<td>100% (2-220)</td>
<td>100% (1-46)</td>
</tr>
<tr>
<td>Excess salivation</td>
<td>13% (4)</td>
<td>0</td>
<td>88% (1-104)</td>
<td>100% (34-354)</td>
</tr>
</tbody>
</table>

*Results in parentheses are reported as numbers of days in which adverse events were observed.

Conclusions

Capromorelin was well tolerated in dogs at daily doses up to 40 mg/kg for 12 months. When adjusting for differences between the capromorelin formulation in this study (aqueous solution of capromorelin base) and ENTYCE (flavored solution of capromorelin tartrate), the 40-mg/kg dose of capromorelin represents a dose 17.5 x the clinical dose. The lack of toxicity observed across multiple body systems when capromorelin was administered at doses substantially higher than the clinical dose over an extended period of time supports the wide safety margin for the use of capromorelin in dogs.
The objective of this crossover study in beagle dogs was to investigate and compare the PK parameters of capromorelin after a single oral administration of ENTYCE® (capromorelin oral solution) and a deionized water formulation used in the 12-month safety study, at 2 dose levels (3 mg/kg and 52.4 mg/kg).

Study Design
The study evaluated 2 different formulations of capromorelin. In the “deionized” formulation, the active pharmaceutical ingredient (API) was dissolved in deionized water. In the “flavored” formulation, the API was in an oral flavored solution. This flavored solution is the final market formulation of ENTYCE. Dogs received a single dose of each formulation of capromorelin (3 mg/kg or 52.4 mg/kg) with a 7-day washout period between dose administrations. A relative bioavailability analysis was performed using data from all dogs (n = 12) administered capromorelin at a dose of 3 mg/kg.

Results
Dogs administered 3 mg/kg of ENTYCE had a lower capromorelin exposure than the dogs administered 3 mg/kg of the API in deionized water (relative bioavailability based on geometric mean AUC[0-t] ratio, 74.4% [90% CI, 61.1%-90.6%]). Further, the capromorelin Cmax was lower following administration of ENTYCE compared to following administration of the API in deionized water (geometric mean Cmax ratio, 83.07% [90% CI, 64.20%-107.5%]). At the 3 mg/kg dose, the median Tmax and T1/2 following administrations of both formulations were similar (0.5 hours and 1 hour, respectively).

At the 52.4 mg/kg dose, there were a number of dogs in both dosing periods (9 dogs in the deionized group and 6 dogs in ENTYCE group) that had episodes of emesis within 0.5 hours after dose administration. The observed median Tmax at the 52.4 mg/kg dose was achieved within 0.5 hours (range, 0.5-2 hours). Because ≥ 1 emetic event occurred prior to Cmax, the dogs were considered to have missed the dose. Although a small number of dogs (3 dogs in the deionized group and 6 dogs in the ENTYCE group) provided evaluable PK data at the 52.4 mg/kg dose, the relative bioavailability for the 52.4 mg/kg dose was not calculated, as there were not sufficient dogs without emesis to perform any inferential analysis of variance.

Conclusions
This PK study adequately bridges the capromorelin exposure of ENTYCE to that of capromorelin in deionized water, as used in the 1-year oral toxicity study in beagle dogs for assessing target animal safety.1 This PK study showed that a 3 mg/kg dose of ENTYCE resulted in lower capromorelin exposure than that of capromorelin in deionized water. Further, the capromorelin Cmax was lower following administration of ENTYCE compared with capromorelin in deionized water (geometric mean Cmax ratio, 83.07% [90% CI, 64.20%-107.5%]). Therefore, drug exposure in the 1-year oral toxicity study in beagle dogs is representative for evaluating the margin of safety for the flavored oral solution formulation.
ENTYCE Safety (continued)

Clinical Field Study

The objective of this study was to assess the efficacy and safety of ENTYCE® (capromorelin oral solution) in inappetent dogs under field conditions when used as an appetite stimulant.

Study Design

This study enrolled client-owned dogs (N = 244) with decreased appetite for at least 2 days, including dogs with a variety of comorbid conditions. The dogs were randomized 2:1 to receive ENTYCE 3 mg/kg (n = 171) or vehicle control (n = 73) SID for 4 days. All dogs enrolled in the study were evaluated for adverse reactions throughout the study.

Results

The adverse reactions observed during the study are described in Table 4. Some dogs may have experienced more than 1 adverse reaction during the study.

Table 4: Adverse Reactions Reported in Dogs Administered ENTYCE Oral Solution Compared With Vehicle Control

<table>
<thead>
<tr>
<th>Organ System</th>
<th>Adverse Reaction</th>
<th>ENTYCE (n = 171)</th>
<th>Vehicle Control (n = 73)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal</td>
<td>Diarrhea</td>
<td>12 (7.0)</td>
<td>5 (6.8)</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>11 (6.4)</td>
<td>4 (5.5)</td>
</tr>
<tr>
<td></td>
<td>Hypersalivation</td>
<td>4 (2.3)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td></td>
<td>Abdominal discomfort</td>
<td>2 (1.2)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td></td>
<td>Flatulence</td>
<td>2 (1.2)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td>2 (1.2)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Clinical pathology</td>
<td>Elevated blood urea nitrogen</td>
<td>7 (4.1)</td>
<td>2 (2.7)</td>
</tr>
<tr>
<td></td>
<td>Elevated phosphorus</td>
<td>4 (2.3)</td>
<td>1 (1.4)</td>
</tr>
<tr>
<td></td>
<td>Elevated creatinine</td>
<td>1 (0.6)</td>
<td>1 (1.4)</td>
</tr>
<tr>
<td>Other</td>
<td>Polydipsia</td>
<td>7 (4.1)</td>
<td>1 (1.4)</td>
</tr>
<tr>
<td></td>
<td>Lethargy/depression</td>
<td>2 (1.2)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

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

There were no adverse reactions observed in clinical pathology parameters, with the exception of elevated blood urea nitrogen (BUN), creatinine, and phosphorus. These aberrations were reported in separate dogs, with the exception of 1 ENTYCE-treated dog, which experienced elevations in both BUN and phosphorus. The clinical significance of the observed elevations in BUN, creatinine, and phosphorus is unclear. In dogs with pre-existing azotemia (defined as creatinine ≥ 1.4 mg/dL according to the International Renal Interest Society threshold for stage 2 chronic kidney disease), both ENTYCE- and placebo-treated dogs experienced similar mean changes in BUN, creatinine, and phosphorus, which does not support a treatment-related effect. However, because elevations in BUN, creatinine, and phosphorus may be associated with renal disease, veterinarians should proceed with caution when prescribing ENTYCE for dogs with renal disease.

Conclusions

Administration of ENTYCE oral solution at a dose of 3 mg/kg SID for 4 days was shown to be safe and effective for appetite stimulation with minimal treatment-related adverse events in client-owned dogs.
7-Day Study Showing GH, IGF-1, and Cortisol Levels in Dogs

The objective of this laboratory study was to determine the effects in dogs of oral capromorelin at different doses for 7 days on food consumption, body weight, and serum levels of GH, IGF-1, and cortisol.

Study Design

Adult beagle dogs (n = 24) were randomized 1:1:1:1 to receive placebo BID or capromorelin 3.0 mg/kg SID, 4.5 mg/kg SID, or 3.0 mg/kg BID. Food consumption, body weight and serum capromorelin, GH, IGF-1, and cortisol were measured at intervals on days 1, 4, 7, and 9.

Results

Capromorelin increased food consumption (mean [SD] percent change, 3 mg/kg SID, 57.7% [35.1%]; 4.5 mg/kg SID, 37.9% [16.8%]; 3 mg/kg BID, 36.4% [21.4%]; placebo, −13.5% [14.9%]; Figure 4) and body weight (mean [SD] percent change, 3 mg/kg SID, 4.5% [1.7%]; 4.5 mg/kg SID, 3.8% [2.9%]; 3 mg/kg BID, 4.2% [1.4%]; placebo, −1.2% [1.5%]) compared with placebo. Treatment with capromorelin increased serum GH, which returned to baseline by 8 hours post-dosing (Figure 5). The magnitude of the GH increase was less on days 4 and 7 compared with day 1. IGF-1 levels increased on day 1 in capromorelin-treated dogs and were sustained through day 7 (Figure 5), but returned to baseline on day 9. Serum cortisol increased post-dosing and returned to baseline levels within 8 hours. Similar to GH, the magnitude of the cortisol increase was less on days 4 and 7 compared to day 1.
Conclusions

After the first dose of capromorelin, the expected high peak of GH was observed very quickly. This GH-releasing action is expected from a drug that binds the GHS-R. It would not be desirable to chronically stimulate the release of GH; however, it is important to note that IGF-1 levels presumably increase over the 8 hours following the first dose of capromorelin. This IGF-1 increase serves as a negative feedback mechanism, suppressing GH release. By days 4 through 7 of dosing, the sustained elevation in IGF-1 levels observed in capromorelin-treated dogs resulted in an attenuation of the GH peak observed after capromorelin was administered.

In order to maintain this negative feedback on the GH release, IGF-1 serum levels need to remain elevated in capromorelin-treated dogs. This study evaluated whether capromorelin needed to be dosed SID or BID to maintain elevated serum IGF-1 levels. The data show that SID dosing is sufficient. Further, there was no difference between dogs dosed at 3 mg/kg or 4.5 mg/kg SID, indicating that the 3 mg/kg dose is sufficient to maintain IGF-1 serum levels that can attenuate the GH peak and stimulate food consumption.

Based on increased food consumption, weight gain, and sustained IGF-1 serum levels, a dose of 3 mg/kg SID was chosen as the clinical dose of capromorelin.
ENTYCE Efficacy (continued)

Laboratory Effectiveness Study

This study was conducted to measure the effects of a daily 3 mg/kg oral dose of ENTYCE® (capromorelin oral solution) given over 4 days on food consumption and weight increase in healthy adult male and female beagle dogs.

Study Design

Twenty-four healthy beagle dogs were randomized 1:1 to receive a 3 mg/kg oral dose of ENTYCE or placebo SID for 4 days. Dogs were observed for clinical signs throughout the course of the study. Physical examinations 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.

Results

ENTYCE was well tolerated, with no abnormalities observed on physical examination or clinical pathology tests. Some dogs showed increased salivation. Dogs treated with ENTYCE had significantly increased mean (SD) food consumption compared with dogs that received placebo (Table 5 and Figure 6). Dogs treated with ENTYCE also had significantly increased mean body weight compared with dogs that received placebo (Table 5).

Table 5: Food Consumption and Body Weight Changes in Dogs Treated With Either ENTYCE or Placebo

<table>
<thead>
<tr>
<th></th>
<th>Percent Food Consumption Change, Mean (SD)</th>
<th>Percent Weight Increase From Day 0 to Day 3, Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ENTYCE</td>
<td>60.55 (39.87)</td>
<td>5.96 (1.76)</td>
</tr>
<tr>
<td>Placebo</td>
<td>−11.15 (14.23)</td>
<td>0.053 (1.14)</td>
</tr>
<tr>
<td>PValue</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Dogs (*n* = 6 males and 6 females per group) were treated for 4 days with either placebo or ENTYCE oral solution at 3 mg/kg/day.

Conclusions

This study demonstrates the effectiveness of ENTYCE oral solution as an appetite stimulant in dogs. Treatment resulted in dramatic increases in appetite, as measured by a 61% increase in food consumption compared with an 11% decrease in placebo. Additionally, the drug was well tolerated.
ENTYCE Efficacy *(continued)*

**Clinical Field Study**

This study evaluated the effectiveness and safety of ENTYCE® (capromorelin oral solution) for stimulation of appetite in client-owned dogs with reduced appetite.

**Study Design**

In this prospective, randomized, masked, placebo-controlled study, dogs of any age, breed, or sex were enrolled from 24 veterinary hospitals across the United States.

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Major Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduced appetite or no appetite for a minimum of 2 days prior to day 0</td>
<td></td>
</tr>
<tr>
<td>Owner Appetite Assessment score at screening of “Decreased”</td>
<td></td>
</tr>
<tr>
<td>General good health or stabilized for chronic conditions</td>
<td></td>
</tr>
<tr>
<td>Dogs intended for breeding, or pregnant or lactating female dogs</td>
<td></td>
</tr>
<tr>
<td>Dogs in crisis, moribund, or with serious and/or life-threatening conditions</td>
<td></td>
</tr>
<tr>
<td>Hospitalization within the prior 4 days</td>
<td></td>
</tr>
<tr>
<td>Active infection</td>
<td></td>
</tr>
<tr>
<td>Dogs in whom food intake was contraindicated (eg, suspected foreign body, gastric torsion, gastrointestinal surgery)</td>
<td></td>
</tr>
<tr>
<td>Regurgitation problems</td>
<td></td>
</tr>
<tr>
<td>Dental disease severe enough to impair food intake</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
</tr>
<tr>
<td>Dogs for whom the owner was unsure that they could reliably evaluate appetite (eg, multipet household)</td>
<td></td>
</tr>
</tbody>
</table>
| Dogs receiving prohibited medications

Dogs were randomized 2:1 to receive ENTYCE 3 mg/kg oral solution or placebo oral solution SID for 4 days. Owners completed evaluations of appetite at day 0 (first day of dosing) and day 3 ± 1. Two owner-evaluated measures of treatment effectiveness were used. The first was a single-question assessment: “Do you feel that during the study (over the 4 ± 1 days of treatment) your dog’s appetite was increased, had no change, or decreased?” A case was considered a treatment success if the owner answered that their dog’s appetite was increased post-treatment. The second was the Owner Appetite Assessment (see Appendix III for further information), which consists of 5 questions to evaluate a dog’s willingness to eat, hunger and begging behavior, behavior when anticipating meal time, behavior when food is presented, and the amount of food eaten. Treatment success was defined as an increase in total score ≥ 5 from day 0 to day 3 ± 1 (scoring scale, 5–25, with 25 representing an excellent appetite). Safety was evaluated by physical examinations, clinical pathology tests, adverse events, and owner observations.

**Results**

A total of 244 client-owned dogs reported by owners to be inappetent for ≥ 2 days were enrolled in the study, with 177 patients included in the effectiveness analysis (121 dogs in the ENTYCE treatment group and 56 dogs in the placebo treatment group). Enrolled dogs included those with a variety of comorbid conditions, including allergy, arthritis, cardiovascular disease, gastrointestinal disease, and renal disease.
ENTYCE® (capromorelin oral solution) treatment significantly improved appetite compared with placebo. Using the single-question assessment, a significantly higher proportion of dogs who received ENTYCE were classified as treatment successes compared with those who received placebo (68.6% vs 44.6%; *P* = 0.0078). Dogs in the ENTYCE group experienced a significantly greater mean (SD) percent change from baseline in Owner Appetite Assessment score compared with the placebo group (73.3% [75.9%] vs 37.6% [53.9%; *P* = 0.0125). Notably, a significantly higher proportion of ENTYCE-treated dogs had a change from baseline in Owner Appetite Assessment score ≥ 5 compared with placebo-treated dogs (56.2% vs 26.8%, respectively; *P* = 0.0071). ENTYCE-treated dogs also experienced a significantly greater increase in mean (SD) body weight compared with placebo-treated dogs (1.8% [2.8%] and 0.1% [3.6%], respectively; *P* = 0.0004). Overall, ENTYCE was well tolerated, with a low incidence of adverse events associated with drug treatment.

**Table 6: Effectiveness Outcomes in Dogs Treated With ENTYCE or Placebo Over 4 Days**

<table>
<thead>
<tr>
<th></th>
<th>ENTYCE</th>
<th>Placebo</th>
<th><em>P</em> Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment success — single-question assessment, %&lt;sup&gt;a&lt;/sup&gt;</td>
<td>68.6</td>
<td>44.6</td>
<td>0.0078</td>
</tr>
<tr>
<td>Treatment success — Owner Appetite Assessment, %&lt;sup&gt;b&lt;/sup&gt;</td>
<td>56.2</td>
<td>26.8</td>
<td>0.0071</td>
</tr>
<tr>
<td>Percent change in body weight, mean (SD)</td>
<td>1.8 (2.8)</td>
<td>0.1 (3.6)</td>
<td>0.0004</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>
</tbody>
</table>

<sup>a</sup> 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?”

<sup>b</sup> Treatment success was defined as an increased in total score ≥ 5 from day 0 to day 3 ± 1 (scoring scale 5-25).

**Conclusions**

These results support the findings from previous studies in healthy dogs and demonstrate that ENTYCE is an effective treatment for stimulation of appetite in dogs. This study is the first to demonstrate that a ghrelin receptor agonist, ENTYCE, can stimulate appetite and increase body weight in a large population of client-owned dogs with reduced appetite of varying etiologies. In addition, the results demonstrate that owners can evaluate relative changes in their dog’s appetite using a single-question assessment (“Do you feel that during the study your dog’s appetite was increased, no change, or decreased?”) or an assessment questionnaire (Owner Appetite Assessment) of the dog’s behavior. Taken together, these findings demonstrated that ENTYCE was safe and effective for stimulating appetite in a diverse population of inappetent dogs.
Frequently Asked Questions

Use of ENTYCE® (capromorelin oral solution)

Q: How quickly does ENTYCE stimulate appetite?
A: Onset of action was not measured in the pivotal efficacy study in inappetent dogs. Based on the Laboratory Effectiveness Study, a dramatic increase in food consumption was seen from Study Day -1 to Study Day 0 (Day 0 was the first day of dosing). This would imply that the time to onset is at least within 24 hours of administration in healthy dogs.

In another food consumption laboratory study, growth hormone and cortisol concentrations peaked at 30 minutes post oral capromorelin dose. While this does not directly correlate with onset of action, it implies that capromorelin very quickly binds the GHS-R in the hypothalamus when administered orally. Taken with the results of the above study, it would be reasonable to conclude that the appetite simulation effect should be seen within 24 hours, and perhaps even sooner in healthy dogs. The effect in clinically inappetent dogs is unknown, however it would not be surprising to see results quickly based on this data.

Q: Can I use ENTYCE longer than four days?
A: There are no restrictions on the label for the length of time that a dog may be treated with ENTYCE. ENTYCE should be used daily for as long as needed at the discretion of the attending veterinarian. This includes use in patients with chronic conditions that may benefit from long-term appetite stimulation, e.g., patients with cancer, heart, kidney, or GI disease.

Q: If a dog takes the drug more than 4 days, will the effect wear off?
A: While the pivotal efficacy trial was 4 days in duration, in other studies the effectiveness of ENTYCE has been evaluated up to 7 days with continued positive effects on appetite.

Q: Can I use an every other day dose or start and stop ENTYCE in response to a dog’s appetite?
A: This has not been evaluated. However, it is not recommended. After a dose of capromorelin, the expected high peak of GH was seen very quickly. It would not be desirable to stimulate pulsatile, super-physiologic levels of endogenous GH chronically, and therefore, it is important to remember that over the 8 hours after the dose of capromorelin, the level of IGF-1 increases. This IGF-1 increase serves as a negative feedback signal, suppressing GH release. This study also evaluated whether capromorelin needed to be dosed once or twice a day to maintain an elevated serum IGF-1 level, and the data clearly show that once a day dosing is sufficient, indicating that the 3 mg/kg dose is adequate to keep IGF-1 serum levels high enough to attenuate the GH peak and also to stimulate food consumption.

Q: Can I give ENTYCE on food instead of in the mouth?
A: This has not been evaluated. In theory, in an inappetent dog it would be best to give it directly into the mouth prior to a meal.

Q: Does it matter the time of day I give ENTYCE?
A: No, however, it is best to give it daily approximately 24 hours apart.

Q: Is there potential that use of ENTYCE could mask the underlying disease causing inappetence?
A: There are certain medications that can prevent the diagnosis of certain diseases (e.g., prednisone masking lymphoma). The use of ENTYCE should not mask or prevent diagnosis of the underlying illness. However, there could be concern that use of ENTYCE could delay definitive diagnosis of the underlying disease if the chief complaint is simply inappetence and no further workup occurs. It is important to arrive at a diagnosis whenever possible.
Frequently Asked Questions (continued)

Q: Is there potential that ENTYCE® (capromorelin oral solution) may not work in some patients?
A: The presence and severity of underlying disease conditions will impact ENTYCE’s ability to stimulate appetite in an individual patient, and if the underlying condition is severe enough, there is a potential it may not be effective in those patients. This underscores the importance of trying to arrive at a diagnosis of the underlying disease whenever possible. Expert consensus suggests that intervention to provide nutritional support is indicated within 3-5 days in patients that have not eaten sufficient amounts (including the time of reduced appetite at home before presentation), which could include certain types of feeding tubes or intravenous nutrients.

Q: Why are there precautions against using in patients with renal insufficiency or hepatic dysfunction on the package insert?
A: In the clinical field study, there were no adverse events in clinical pathology parameters except for elevated values of blood urea nitrogen (BUN), creatinine and phosphorus. These adverse events reports were in separate dogs, except for one ENTYCE-treated dog which experienced adverse events for both elevated BUN and elevated phosphorus. The clinical significance of the elevations in BUN, creatinine and phosphorus is unclear, but was not deemed to be clinically relevant. In dogs with pre-existing azotemia (defined as creatinine ≥ 1.4 mg/dL, which is the cutoff for the definition of International Renal Interest Society (IRIS) stage 2 CKD) the mean change in creatinine, BUN, and phosphorus was similar in the ENTYCE and placebo treated dogs, which does not support a treatment related effect. There is no evidence to suggest that ENTYCE causes or worsens renal disease.

Hepatic dysfunction
A: Precautionary language against use in dogs with hepatic dysfunction is included based on metabolism studies that suggests capromorelin is metabolized by hepatic enzymes, mainly through the CYP3A4 and CYP3A5. Therefore, drugs that inhibit CYP3A4 and CYP3A5 activity may affect capromorelin metabolism.

Q: Do I have to be concerned about the release of GH in my patients that are on ENTYCE?
A: A known secondary effect of using ENTYCE is the release of GH, which then triggers the release of IGF-1 from the liver. Due to a normal physiologic process of negative feedback by IGF-1, increased levels of GH are not sustained. In the 7-day dose confirmation study, after the first dose of ENTYCE, the expected high peak of GH was seen very quickly. This GH releasing action is expected from a drug that binds the GHS receptor. It would not be desirable to stimulate the release of such a super-physiological amount of GH chronically, and therefore, it is important that over the 8 hours after the first dose of ENTYCE, the concentration of IGF-1 increases. The IGF-1 increase serves as negative feedback, suppressing GH release. Clearly by 4 to 7 days of dosing, the sustained elevation in IGF-1 concentrations seen in the ENTYCE treated dogs result in an attenuation of the GH spike observed after the dose of ENTYCE is administered. This study further investigated whether ENTYCE needed to be dosed once or twice daily to maintain elevated serum IGF-1 concentrations, and clearly showed that once daily dosing is sufficient.

Q: Will ENTYCE interfere with insulin in the management of diabetes mellitus or could it cause a dog to become diabetic?
A: Capromorelin has not been evaluated in dogs diagnosed with diabetes mellitus, even if well managed. Dogs with diabetes mellitus were excluded from the field study. While excess growth hormone may be considered diabetogenic, or associated with insulin resistance, in our safety and efficacy studies no dogs developed diabetes mellitus.
Q: Should I caution owners that their dogs might salivate after dosing? Is this expected?
A: Excess salivation has been noted in several of the studies evaluating safety and efficacy of ENTYCE® (capromorelin oral solution), yet importantly in the field study there were very few reports of excessive salivation. This might be expected in a small number of dogs due to the pharmacologic action of ENTYCE, causing a feeling of hunger. Additionally, dogs may have growth hormone secretagogue receptors within salivary glands as has been demonstrated in people.⁰¹

Q: What is the flavor of ENTYCE?
A: Vanilla (synthetic flavoring agent).

Q: What are the storage requirements for ENTYCE?
A: The package insert advises to store at or below 86°F (30°C). It is not necessary to refrigerate after opening.

Q: What is the shelf-life for ENTYCE?
A: Two years from the manufacture date.

Q: How do I report an adverse reaction or a product defect?
A: Please refer any suspected adverse reactions or product defects to the Pharmacovigilance Department at 1-844-640-5500 or pv@aratana.com.

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 on page 30.
References

References (continued)

References (continued)


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Cummings DE. Ghrelin and the short- and long-term regulation of appetite and body weight. Physiol Behav. 2006;89(1):71-84.


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Bibliography (continued)


Bibliography (continued)


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Zollers B, Allen J, Kennedy C, Rhodes L. Safety of the ghrelin agonist, capromorelin, administered daily to cats for 91 days at an oral dose of 6 mg/kg. Presented at: 2015 American College of Veterinary Internal Medicine Forum; June 3-6, 2015; Indianapolis, IN [abstract NM08].


Zollers B, Rhodes L, Rausch-Derra LC, Armintrout G, Bell M. Safety of the ghrelin agonist, capromorelin, administered daily to beagle dogs for 1 year. Presented at: 2015 American College of Veterinary Internal Medicine Forum; June 3-6, 2015; Indianapolis, IN [abstract NM05].


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 (Cmax) reached within 0.83 hr (Tmax). After Cmax, the plasma concentrations declined mono-exponentially with a short terminal half-life (t1/2) of approximately 1.19 hrs. There were no gender differences in capromorelin pharmacokinetics. The exposure (Cmax 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>Tmax (hr)</td>
<td>0.83</td>
<td>0.58</td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td>655</td>
<td>276</td>
</tr>
<tr>
<td>AUCinf (ng*hr/mL)</td>
<td>695</td>
<td>262</td>
</tr>
<tr>
<td>T½ (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/hr/100 kg and 21.5 L/kg, respectively. Capromorelin was not highly bound (unbound fraction 55%) 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 (rat) 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/Efficacy 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 solution) at a dose of 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 5.5 and 12.5 kg at the time of randomization. 10 dogs administered ENTYCE repeatedly exhibited increased food post dosing and two dogs administered vehicle control exhibited only one time on study day 0. Emsys was observed in one dog administered ENTYCE on study day 2. Dogs administered ENTYCE had a dose of 3 mg/kg/day for 4 consecutive days and had statistically significantly increased food consumption compared to the vehicle control group (p < 0.005).

Clinical Field Study: Effectiveness was evaluated in 177 dogs (123 in the ENTYCE group and 54 in the vehicle control group) in a double-blind, 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 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); 56.8% (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 11.2 months of age and weighing 9.1 to 11.6 kg were dosed orally with capromorelin in dosed water daily at OR (galoide), 0.3 (0.390), 1.0 (0.397), and 4.0 (1.75) mg/kg/day. Administration of capromorelin was associated with increased salivation and salivary flow rates, 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 549 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 50 mL bottles with measuring syringe

NADA 141-457, Approved by FDA
US Patent: 6,793,919
US Patent: 7,100,591
Made in Canada

Additional information is available at www.aratana.com or by calling Aratana Therapeutics at 1-844-270-8362.

Manufactured for: Aratana Therapeutics, Inc.
Leawood, KS 66221

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Appendix I: Inappetence in Dogs

Causes of Inappetence
Hyporexia, anorexia, or dysrexia in dogs can occur when there is a disturbance anywhere along the pathway affecting psychologic events, peripheral physiology, and metabolic events or neurotransmitter and metabolic interactions in the brain. The causes of inappetence are numerous and can be divided into 2 main categories: pseudoinappetence and true inappetence.

Pseudoinappetence can be due to physical problems that affect eating, such as oral pain, obstruction from a mass, or prehension difficulty. For example, masticatory muscle myositis can affect appetite because animals are unable to chew normally. Some dogs may choose not to eat due to an unpalatable diet. Dogs can also develop food aversions—ie, if dogs are offered a particular food type when ill, they may refuse the same diet when recovered because they associate the food with the illness.

True inappetence can be divided into primary and secondary causes. Primary causes include problems in smelling food—if animals cannot smell due to an upper respiratory tract infection, they are often unlikely to eat. Neurologic disease (eg, brain lesions affecting the appetite center in the hypothalamus), environmental challenges, and pet-to-pet interactions can also adversely affect appetite. Secondary causes of inappetence are diverse and common. Systemic disease causes inappetence in a multitude of ways. Specifically, chronic illnesses including kidney disease and cancer, as well as nausea, fever, pain, dehydration, respiratory disease, or medications can be involved.

Inappetence is a commonly described side effect of many chemotherapeutics in dogs; however, its true incidence is not well documented. A prospective, multicenter clinical survey was completed to assess occurrence and clinical impact of inappetence in dogs receiving chemotherapy. Owner-assessed evaluation of inappetence may be helpful in predicting subsequent body weight loss, prompting earlier clinical intervention.

Consequences of Inappetence
Prolonged inappetence can result in either a hypermetabolic state or a hypometabolic state; either condition can seriously endanger a pet’s life. A sustained hypermetabolic state in veterinary patients is usually the result of a systemic septic condition (eg, septic peritonitis). The insult (sepsis) causes a systemic inflammatory response secondary to elevated cytokine activity and exaggerated release of stress hormones (eg, catecholamines, glucagon, cortisol), which predisposes one to profound catabolism. If the hypermetabolic state continues without modulation, immunosuppression, depletion of nutrients at the tissue and cellular levels, organ failure, and/or death may eventually occur as sequelae. A hypometabolic state is usually the result of prolonged food deprivation (ie, starvation), which can lead to complications such as hyperthermia, lean muscle mass loss and muscle breakdown, hypoventilation, and cardiac failure. Lean muscle catabolism may also lead to impaired wound healing and altered immune system function, and it may adversely affect drug metabolism.

Humans with severe weight loss from anorexia nervosa suffer from bradycardia, hypothermia, and hypoventilation. These changes result from a decrease in resting metabolic rate, which occurs quickly, within a few days of cessation of food intake. Hypometabolism is a consequence of decreased insulin activity and decreased glucose utilization, with subsequent loss of lean body mass. Sarcopenia, or skeletal muscle loss, leads to poor shivering ability and reduced respiratory muscle function, resulting in hyperthermia and hypoventilation. Over time, decreased myocardial mass and ventricular contractility occur, leading to decreased cardiac output and, in some patients, overt heart failure.
Additionally, in humans there are numerous documented negative consequences and outcomes of prolonged malnutrition and/or anorexia, including protein-energy wasting, susceptibility to infection, altered gastrointestinal tract functionality (resulting in decreased motility), chronic wounds, decreased immune system function, prolonged hospital stays, and increased risk of mortality. The health of the gastrointestinal tract also depends on adequate oral intake of food; decreased appetite disrupts the gastrointestinal tract flora, and increased permeability can result as the tight junctions between enterocytes weaken, resulting in translocation of gut microbiota into systemic circulation.

A singular, major consequence of pet inappetence is the caregiver’s perception of quality of life. Eating and enjoyment when eating are of universal significance. Although caregivers may not fully understand the diagnosis or magnitude of the disease (if identified), they certainly understand the importance of proper nourishment. Therefore, a pet’s lack of appetite, or decreased appetite, can be especially distressing and often perceived as evidence of suffering. There are several nonvalidated health-related quality of life scoring systems available online, all of which include the pet owner’s perceptions surrounding the pet’s appetite and demonstrate how appetite is an important component of quality of life. In the future, it will be interesting to observe the evolution and possible application of web-based and wearable technologies as tools to measure a dog’s quality of life, particularly surrounding appetite. As an effective therapeutic that stimulates a dog’s appetite, ENTYCE® (capromorelin oral solution) may provide a feeling of empowerment and relief to the owner, knowing that their beloved dog may eat reliably while further work-up or treatment of the underlying disease is pursued.

Management of Inappetence

The World Small Animal Veterinary Association (WSAVA) has described nutrition as the 5th vital sign. The WSAVA 5th Vital Assessment Group (V5) has used the science-based Nutritional Assessment Guidelines from the American Animal Hospital Association (AAHA) to develop their own global Nutritional Assessment Guidelines as an easy-to-use tool to help veterinarians around the world optimize the health and well-being of pets. The document focuses on ensuring adequate and appropriate nutrition for small animals. Aratana’s quest to transform dogs’ lives through the treatment of inappetence using ENTYCE helps veterinarians by providing them with a tool to help meet these guidelines.

The scientific evidence of the benefits of early nutritional intervention in veterinary patients is growing. There are numerous reports of the positive outcomes of nutritional support. In particular, early nutritional support (within 12 to 24 hours), regardless of route (enteral or parenteral) significantly shortens hospitalization times in dogs. Enteral nutrition maintains gastrointestinal barrier function and is associated with improved blood flow to the gastrointestinal tract, liver, and kidneys. Enteral nutrition may also improve immunologic control and mitigate the systemic inflammatory response by the introduction of food into the intestinal lumen. Importantly, it has been demonstrated that there is a relationship between the type of nutritional support provided, the energy intake (percentage of maintenance energy requirement [MER]), and outcome of discharge from hospitalization. For example, pets receiving between 67% and 100% of their MER had a > 90% chance of discharge from hospitalization, while those who received 0% to 33% of their MER had an approximately 63% chance of discharge. Similarly, a pet eating voluntarily had a > 90% chance of discharge from hospitalization, while those that required force feeding or enteral or parenteral support had a likelihood of discharge of 75%, 72%, and 62%, respectively. Clearly there is an advantage to early and appropriate nutritional support of ill and hospitalized pets—ENTYCE was developed to assist in the management of inappetence by stimulating appetite in dogs.
Appendix I: Inappetence in Dogs (continued)

Importance of “Asking the Right Questions” Regarding Appetite

It is imperative to ask open-ended questions when probing about a pet’s appetite. For example, asking, “What happens when you offer your pet food?” will be more informative than asking, “Is your pet eating?” The former will allow for a few minutes of dialogue that may reveal whether a pet has a finicky appetite, is not finishing its meals, requires coaxing or hand-feeding, is vomiting or regurgitating, while the latter will only result in a “yes” or “no” answer and will not necessarily offer any additional insight.

The veterinarian’s focus when faced with an inappetent dog is usually to identify and address the underlying cause. Some factors that contribute to inappetence (e.g., nausea, fever, pain, and dehydration) can be treated and corrected. If the dog is in stable condition, tempting it with different foods can be tried and could be combined with ENTYCE® (capromorelin oral solution). The use of ENTYCE can be helpful in a variety of clinical presentations that include inappetence, specifically while investigating the cause. In some situations, the underlying reason for inappetence cannot be identified or corrected, and in these patients, long-term support of their nutritional intake is needed in order to maintain their quality of life.13,41 Prolonged inappetence may warrant the placement of a feeding tube, which is an invasive procedure and may be objectionable to some owners. Although the clinical and laboratory dog studies of ENTYCE were over a duration of 4 days, there is no label restriction on the duration of use, so veterinarians can use their judgment regarding how long a dog may be dosed effectively for appetite stimulation. Veterinarians can refer to the 1-year oral toxicity study in beagle dogs, which demonstrated no safety concerns when capromorelin, the active ingredient in ENTYCE, was administered over a long duration (12 months), to help understand the potential long-term safety of ENTYCE.
Appendix II: Control of Appetite in Dogs

The regulation of appetite and eating behavior is highly regulated and complex, and involves the coordination of many signals from the brain (mainly the hypothalamus), peripheral tissues (e.g., adipose tissue), and the gut (e.g., ghrelin, a hormone secreted by endocrine cells in the stomach). Regulating the amount and frequency of food intake is critical in maintaining health and optimal body condition. The short-term control of appetite requires the gastric hormone ghrelin, or the so-called “hunger hormone,” the only known orexigenic hormone. During periods of fasting, ghrelin levels increase, peaking just before eating and subsequently falling after a meal. Following secretion from the stomach, ghrelin exerts its effects by binding to GHS-Rs within the hypothalamus, which causes an increase in appetite. As a dog eats, the production of ghrelin is inhibited, and appetite decreases. This system of negative feedback regulates appetite by modulating ghrelin secretion.

Discovery of Ghrelin

In the late 1970s and early 1980s, a group of synthetic opioid peptide derivatives was developed and shown to stimulate the release of GH in vitro through an unknown mechanism. Subsequent research demonstrated that these GH release-inducing molecules, termed GH secretagogues, were active in vivo in a variety of animal models, including rats and dogs, as well as in humans. Pharmaceutical research sought to further characterize these molecules and the mechanism by which they stimulate GH release, with the goal of developing orally-active small molecules for the stimulation of GH release to improve bone density, lean muscle mass, and strength in elderly patients. In 1996, a G protein-coupled receptor in the pituitary and hypothalamus of pigs and humans was cloned and identified as the target receptor for the GH secretagogues, and thus it was termed the GHS-R. The search for the endogenous ligand for GHS-R resulted in the discovery of ghrelin in 1999. The first indication of the role of ghrelin in appetite control came from a study in 2000 that showed that administration of ghrelin caused dose-dependent increases in body weight and food consumption in mice. A rapidly growing number of studies in both animals and humans have since defined in detail the links between ghrelin and appetite regulation.

Physiologic Roles of Ghrelin

Ghrelin is a 28-amino acid peptide that is produced mainly in the stomach, although smaller amounts are also produced in the intestine, pancreas, and hypothalamus. The active form accounts for only 10%-30% of circulating ghrelin and requires acylation by an enzyme called ghrelin O-acyltransferase. Ghrelin is a key factor in the regulation of energy metabolism and affects multiple pathways, including GH secretion, food intake, body weight, energy expenditure, glucose homeostasis, and the sensation of hunger. In human studies, ghrelin has been implicated in the control of diverse processes outside of energy metabolism, including learning and memory, sleep/wake rhythm, aging, thymopoiesis, depression, psychological stress, mood, and anxiety. In addition, ghrelin has anti-inflammatory properties and serves as a link between the immune system and energy metabolism. For example, ghrelin downregulates the production of proinflammatory cytokines, including interleukin (IL)-1β, IL-6, and tumor necrosis factor α through GHS-R expressed on human T lymphocytes and monocytes, and has been shown to attenuate ischemia- or reperfusion-induced pancreatitis and endotoxin-induced anorexia in mice.
Appendix II: Control of Appetite in Dogs (continued)

The Role of Ghrelin in Appetite Control

Ghrelin is produced primarily in the stomach, although low levels can also be detected in the small intestine and in some tissues outside the gastrointestinal tract, including the hypothalamus and pancreas. During periods of fasting, ghrelin secretion from the stomach is increased, through a mechanism that is not currently well understood. The sympathetic nervous system may play an important role in ghrelin stimulation, as activation of gastric sympathetic nerves increases ghrelin secretion in rats, and studies have shown that epinephrine and norepinephrine directly stimulate ghrelin secretion through the β1 receptor on ghrelin-producing cells.

Ghrelin produced in the stomach travels to the hypothalamus, where it binds GHS-R, a G protein–coupled receptor primarily expressed in the hypothalamus and often located on presynaptic nerve endings. Binding of ghrelin to GHS-R increases intracellular Ca²⁺ through the phospholipase C-protein kinase C pathway. This rise in intracellular Ca²⁺ activates calmodulin kinase kinase 2 (CaMKK2), which in turn activates adenosine monophosphate (AMP)–activated protein kinase (AMPK). AMPK mediates the orexigenic and anorexigenic effects of several hormones and compounds, including leptin, insulin, glucose, and ghrelin. Ghrelin-induced AMPK activity inhibits de novo fatty acid synthesis pathways in the ventromedial nuclei of the hypothalamus, which stimulates hunger.

Ghrelin also upregulates the expression of UPC2, an inner-membrane mitochondrial protein that modulates energy expenditure, which increases mitochondrial respiration and proliferation. In addition, ghrelin modulation of UPC2 activity enhances expression of neuropeptide Y (NPY) and agouti-related peptide (AgRP) within the arcuate nucleus (ARC). Ghrelin-enhanced NYP/AgRP expression inhibits ARC pro-opiomelanocortin neurons and paraventricular nuclei corticotropin- and thyrotropin-releasing hormone positive anorectic neurons in the hypothalamus, leading to enhanced food intake.

In addition to stimulation of appetite, ghrelin-induced GH release leads to increased production of IGF-1, a somatomedin essential for somatic growth. Elevated GH and IGF-1 levels in transgenic mice have been shown to increase overall growth. IGF-1 has also been shown to enhance the differentiation of muscle cells in vitro. Administration of GH to beagle dogs resulted in elevated IGF-1 levels, which corresponded to a significant increase in body weight and increased muscle mass due to hypertrophy of muscle fibers.

Complex interactions between nutrient intake, hormone production, and neural signals contribute to the decline of ghrelin levels after feeding. Ghrelin levels decrease in proportion with the amount of calories consumed, and specific nutrient content of meals can affect ghrelin levels. For example, several studies in humans have demonstrated that glucose and long- and short-chain fatty acids suppress ghrelin secretion, while medium-chain fatty acids increase the levels of circulating acylated ghrelin.

Meal ingestion stimulates the production of gastrointestinal and pancreatic hormones that play a role in ghrelin suppression. For example, ghrelin levels are inversely related to insulin levels, which decrease during fasting and increase after eating. Ghrelin levels are reduced upon insulin administration in rodents and humans, and this relationship is mediated through a glucose-independent mechanism. Ghrelin stimulates the release of GH, which then inhibits ghrelin in a negative feedback loop. GH administration was shown to decrease plasma ghrelin levels in rats and suppress ghrelin secretion from gastric explants. In addition, GH stimulates lipolysis, which increases levels of free fatty acids, and can cause insulin resistance, leading to increased insulin levels, both of which suppress circulating ghrelin.

Given the multitude of molecules and systems involved in appetite control, it is not surprising that appetite can become dysregulated in a variety of disease states. In spite of this complexity, ENTYCE® (capromorelin oral solution) demonstrates stimulation of appetite in inappetent dogs with a variety of underlying conditions.
Appendix III: Owner Appetite Assessment Questionnaire

A questionnaire was developed with 5 questions that allowed the owner to evaluate a dog’s eating behavior and appetite. Each question could be scored from 1 to 5. The scores for each of the 5 questions were added to give a total appetite score, with the lowest total score (5) corresponding to the worst appetite and the maximum score (25) corresponding to the best appetite. Each dog was classified as a treatment success or treatment failure, with treatment success defined as an increase in total appetite score of ≥ 5 points from day 0 to day 3 ± 1.

<table>
<thead>
<tr>
<th>Owner Appetite Assessment Questionnaire</th>
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<tbody>
<tr>
<td><strong>Willingness to eat:</strong></td>
</tr>
<tr>
<td>1. Always have to coax to eat or refuses food</td>
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<tr>
<td>2. Often have to coax to eat</td>
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<tr>
<td>3. Sometimes have to coax to eat</td>
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<tr>
<td>4. Never have to coax to eat</td>
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<tr>
<td>5. Never coax as dog always eats with enthusiasm</td>
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<tr>
<td><strong>Anticipating meal time:</strong></td>
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<tr>
<td>1. Avoids or hides when food bowl is filled</td>
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<tr>
<td>2. Little interest in meal time</td>
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<td>3. Comes to eat when called</td>
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<tr>
<td>4. Anticipates meal time</td>
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<tr>
<td>5. Runs to the food bowl</td>
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<td><strong>Hunger/begging behavior:</strong></td>
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<tr>
<td>1. Never seeks food, never begs</td>
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<tr>
<td>2. Rarely seeks or begs for food</td>
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<tr>
<td>3. Sometimes seeks or begs for food when sees, smells, or hears food</td>
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<tr>
<td>4. Always seeks food when sees, smells, or hears food</td>
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<tr>
<td>5. Actively seeks food even when your pet does not see, smell, or hear food</td>
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<tr>
<td><strong>When food is placed in front of dog:</strong></td>
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<tr>
<td>1. Avoids or refuses food</td>
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<tr>
<td>2. Slow to eat food</td>
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<tr>
<td>3. Eats food offered in reasonable time</td>
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<tr>
<td>4. Eats food offered quickly</td>
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<td>5. Eats food offered rapidly, with enthusiasm</td>
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<td><strong>Your dog:</strong></td>
</tr>
<tr>
<td>1. Eats no food without being force fed</td>
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<td>2. Eats half or less of food offered</td>
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<td>3. Eats most food offered</td>
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<tr>
<td>4. Eats all food offered</td>
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<tr>
<td>5. Eats all food offered and begs for more</td>
</tr>
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