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_{44}H_{55}N_{3}O_{23}C_{6}H_{3}O, and the molecular weight 665.70. The chemical name is 2-amino-N-[2-[[3R-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-1,4-pyrazolo[4,3-c]pyridin-5-yl]-1R-benzyloxymethyl-2-oxo-ethyl]isobutyramide L-tartrate.

The chemical structure of capromorelin tartrate is:

![Chemical Structure of Capromorelin Tartrate]

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

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

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 and six dogs administered vehicle control were evaluated 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 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 9-13.6 kg were dosed orally with capromorelin in deionized water daily at 0X (placebo), 0.3 (0.1X), 7 (0.7X), 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 1-844-727-8262.

Manufactured for:
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