Inappetence in Dogs

Inappetence refers to a spectrum of changes in appetite, ranging from hyporexia (ie, eating less), dysrexia (ie, intermittent or altered eating), or anorexia (ie, eating nothing). All types of inappetence can affect a dog’s ability to obtain the nutritional intake needed to maintain optimal health. Following is a discussion of the consequences that can occur with inappetence, as well as treatment approaches and use of the FDA-approved appetite stimulant ENTYCE® (capromorelin oral solution).

Dr. Larson: Can you explain your definition of inappetence?

Dr. Natalie Marks: I think inappetence is a really new topic for most of us. I have been guilty of writing down in my SOAP that if a dog is not eating, it is anorectic. And I think a lot of us do that by habit. But there are really 3 different forms that we need to be aware of because we also need to educate our clients on what this looks like. Anorexia, I think most of us can agree, is a complete lack of eating, and that is pretty easy to get from a client; it is also very easy for us to assess when they answer history questions. But the other 2 are really important to know because a lot of owners feel their dog is just a picky eater and that is normal for them. Well, it’s not normal. We need to understand if they are truly hyporexic. This is why it is so important to ask them not just what they are eating but how much they are eating. Clients need to understand the importance of measuring out food, especially in a multiple-dog or multiple-cat household. But it is also important to know if there is a change in the pattern of eating; that’s called dysrexia. So, as an example, if you have a pug that is a Hoover, but all of a sudden the client comments, “Yeah, he is eating all of his food, but it’s taking all day,” that’s a change, and we should be noting that. Especially if all of a sudden all they are eating is human treats and they are not eating their dog food. They are still eating, but they are not eating in the same pattern. And all of those categories are very important to recognize.

Dr. Clifford: One of the things I think is important is the idea of making sure the staff understands the concepts Dr. Natalie Marks just defined. Often, it is the nursing staff going in first to talk to the owners. In our respective institutions, we don’t have a universal questionnaire we can all look to underline or take from. So I
We need to change the mindset of the owner that any change in eating is not normal—that it is not expected even as the patient is getting older.

—Dr. Clifford

think that is a great opportunity for veterinarians and staff to use the appetite assessment questionnaire that Aratana has created to help pet owners identify, monitor, and track changes in their dog’s eating behavior.

Dr. Stanley Marks: I think many of us are guilty of not obtaining a comprehensive dietary history when it comes to food intake and the specific nature or type of food that the patient is in fact ingesting. And it is especially important to consider this when we look at certain disease states. For example, we tend to think about a patient with chronic kidney disease having vomiting as a potential presenting problem. If you look at the literature, in fact, weight loss and hyporexia are far more prevalent than vomiting in cats with CKD IRIS stages 3 and 4. And so that part of the history is critically important for me as I assess the severity of the patient’s disease state and also helps guide me with my considerations for my workup on that patient, and also on what potential therapeutic interventions I might consider.

Dr. Natalie Marks: I think it’s also very important to remember that a lot of our patients coming in for routine wellness exams are going to have some form of inappetence as part of their history—it’s not just sick patients with a 3-day history of not eating. These are questions we need to be asking every client for every patient. Many of our small terriers are going to come in with signs of inappetence, and we are missing that, and we could be looking and intervening early and finding disease that is there, and then we can reverse before it becomes too severe to treat.

Dr. Stanley Marks: It just seems surreal that if any of us had a child that was eating 50% of its normal food intake, we would panic, and within 24 hours we would be wanting to know what was going on. Are you painful? Do you have indigestion? Do I need to take you to a doctor right now, because it’s been 24 hours and you are not eating normally? And yet, for an animal, it has become acceptable to give it time to see if the hyporexia will resolve, and that’s the wrong approach. I think as a profession we’ve been guilty of not being proactive enough and intervening later rather than earlier. We should be thinking about appetite stimulation during the workup of that patient. So let’s start early and not wait for the diagnosis. We’ve got to change this mindset of “wait and see” to be proactive as a profession.

Dr. Clifford: Along those lines, changing the mindset with the owner. Think about it: How many people have had an older patient brought in and the owner says, “You know, he hasn’t been eating that much, but I figured it’s just because he is old.” Everybody has had the owner come in and say that. So changing the mindset of the owner that any change in eating is not normal—that is not to be expected even as the patient is getting older.

Dr. Natalie Marks: And to believe your owners, because I have been guilty of that, too. I have a client who has 3 Yorkies, and one of the Yorkies eats 8 kibbles a day. She measures them out, and she came to me and said, “You know what? Jimmy is eating only 7 kibbles a day.” She knew there was something wrong. So we do have to believe there are owners out there that are really that in tune to their pet’s appetite, and you need to believe them and take that seriously, because it does mean something.
Dr. Larson: Can you talk about specific diseases in dogs that you commonly see causing inappetence?

Dr. Clifford: We know that with a number of cancers, patients may come in not eating. It could be a systemic cancer like lymphoma or leukemia, or it could be a solid tumor or a large mast cell tumor that is causing a GI ulceration, or a bone tumor. Through treating my patients, I can cause inappetence. Loss of appetite is not just with chemotherapy. For instance, when I am using lomustine, I use a hepatoprotectant that must be given on an empty stomach, and I find patients don’t eat as well as a result. Pain medications are additional concomitant medications used in my cases, and these can also affect appetite. Or they are on additional pain medications or antibiotics, so it’s 2-fold. Many cancers will affect appetite by virtue of their size or systemic effects but then cause the patient to be inappetent. But then many of the therapies can lead to it, and that’s where I tend to be very proactive.

So, one of the things you are going to see from all of us throughout this is the idea of early intervention. Often I will get them started on an appetite stimulant while I am getting treatment started or while I’m just doing diagnostics in the beginning. That way, I can have it on board as early as possible.

Dr. Stanley Marks: When we looked at the last year of use of capromorelin at the UC Davis Veterinary Medical Teaching Hospital, we observed 200 dogs that had been given the drug for a variety of reasons. But the common themes over and over again were CKD, pancreatitis, inflammatory bowel disease, congestive heart failure, end-of-life care, and pain causing hyporexia. These are complex diseases that can be challenging to diagnose and manage, and appetite stimulation is one pivotal piece of this puzzle that we should think about in all of these cases.

Dr. Larson: Can you expand on other medications that sometimes can affect appetite?

Dr. Stanley Marks: As an internist and gastroenterologist, I use medications every day that can induce hyporexia, anorexia, and nauseousness in my patients. Think about all the opioids that we use before we induce a patient for a surgical procedure. Many of the analgesics that we use every day for the management of pain can also cause ileus, gastroparesis, and nauseousness in the animal. In addition, the antibiotics that we use so commonly to manage an infection often cause hyporexia. To a lot of people, that reduction of food intake by 40% or 50% might be acceptable, but it shouldn’t be to us. If you can counteract that adverse effect with a drug given once daily that mitigates the hyporexia, it’s a win–win situation, especially for the owner, because they perceive that hyporexia emotionally.

The other important point that I want to stress is this: A lot of the medications that we give every single day must be given with a meal for optimal absorption. If my patient is not eating, it can affect the absorption and effectiveness of the medication. So it really is pivotal for us to think about this phenomenon.

Dr. Larson: One other important point is this concept of early recognition. Studies have shown that even after only 24 hours of not eating normally, there is pathology occurring in the GI tract. So by the time a patient gets to you, often days to weeks later, there may be significant GI changes. Can you expand on this concept?

Dr. Stanley Marks: One has to think about the integrity of the intestinal mucosal barrier. And what one sees quite rapidly in rodent models, in people, and in the dog and the cat is a fairly rapid denudation or atrophy of the intestinal villi; that is commensurate with a bowel that becomes far more permeable or leaky within 5 days of anorexia—that’s been very well published. You now have to concern yourself with potential bacterial and endotoxin translocation in that patient, and that is a real concern, especially when you have a patient with pancreatitis, intestinal lymphoma, or severe IBD that can further compromise the intestinal mucosal barrier. Feline hepatic lipidosis is a metabolic disorder associated with the prolonged (4-6 weeks) lack of food intake.
**It is so important to have the entire team in the hospital ready to ask the right questions, from the time the appointment is scheduled to the time that you are asking the history in the exam room.**

—Dr. Natalie Marks

Dr. Natalie Marks: I think it’s very important to not only stress to the client that they did a good thing bringing their pet in for not eating because we don’t know how long that’s been going on at home, and the earlier we can intervene, the better. But you need them to also allow you to do that diagnostic workup so you can find the diseases that Dr. Stanley Marks referenced and also be able to do that very thorough physical exam, which a lot of times will find the cause of inappetence. A full oral cavity exam—there are so many cats with resorptive lesions that are not eating, and it’s very difficult sometimes to see that on oral exam. A painful spine with IVDD, an anal sac tumor that we’re missing—there are so many things, and we need to really go through that physical with the client and stress to them that as a team we are on board. Their pet is inappetent, there is something wrong here, and we are going to find it together.

Dr. Larson: Say a dog is presented to you—can you give a good example of what that looks like in that initial appointment?

Dr. Natalie Marks: It is so important to have the entire team in the hospital ready to ask the right questions, from the time the appointment is scheduled to the time that you are asking the history in the exam room. What is that dog eating? How is it eating? How much is it eating? Is there any change in how that dog is eating? Are there any new treats introduced? Do you have to hand feed? All of these questions need to be asked, because a lot of people don’t understand that hand feeding shouldn’t have to happen. And then again, as I mentioned, that thorough physical exam—looking at every body part and explaining to the owner what you are looking for. I think a little off tangent but important: We don’t communicate to clients the value of our physical exam. It is so important. We are the only profession, I feel, that does a full thorough physical exam. We need to keep doing that and looking for causes of inappetence and discussing that there is something off here. Even if that dog is coming in for vaccinations and a heartworm test; if there is something that triggers off in that history-taking for appetite, we need to explain why that is not normal and go through the appropriate diagnostics based on what we are finding.

Dr. Stanley Marks: Just take a few minutes to look up the WSAVA Nutritional Assessment Guidelines. There is a panel of international nutrition experts who created a document for us to review that dovetails beautifully into what Dr. Natalie Marks just mentioned as part of a physical exam. So the body condition score (BCS), the muscle condition score (MCS), the body weight, plus the questions that Dr. Natalie Marks mentioned earlier form a comprehensive packet that we should be collecting on every single patient at every single visit. And I think a lot of us do not recognize the value of that BCS. You could have 2 Labrador retrievers that weigh 65 pounds; one is obese and the other one has an optimal BCS of 4/9, yet they both weigh the exact same amount.

Dr. Larson: What do we do once we have identified that this dog is not eating normally?

Dr. Clifford: For me, most of the time it’s going to be a cancer patient, so clearly routine blood work and further assessment with diagnostic imaging. If I know what the true cause is, then really what it comes down to is the idea of
treating right away, because oftentimes their inappetence is going to be secondary to the disease process, whichever cancer they may be suffering from. I have a double-edged sword in that I’m giving medications that I know can certainly affect the appetite. That’s where I, without question, always start with early intervention. And owners are on board with it, because one of the things they do not want to see is loss of appetite. We will talk about this multiple times—that owners can handle vomiting, but they can’t handle not eating, at least certainly in oncology patients. So for me it’s getting something on board right away as I’m doing my diagnostics and initial therapy.

Dr. Natalie Marks: In general practice, I want to encourage everyone that your minimum database is not just a CBC/chemistry. Please make sure it’s a full CBC, a full chemistry panel with electrolytes and a thyroid, and that you are getting a blood pressure and a urinalysis. Because we are missing hypertension; we are missing any kind of sediment changes in the urinalysis that could cue you in to disease process. Make sure you are looking for any signs of retinal detachment, again looking for signs of hypertension leading down that path. I can’t tell you how many times I’ve diagnosed Addison’s in a dog that just comes in with inappetence by electrolyte changes and further testing. You might need imaging, whether its radiography or ultrasound, and certainly moving on from there. But I can’t stress enough how many times—again, I’m guilty of it myself—we’re just doing a CBC/chemistry and missing some of those very key data points that are going to help steer you down the right diagnostic pathway.

Dr. Stanley Marks: I’m going to make it even more simple: The history and physical examination are undervalued by many physicians and veterinarians. History and physical examination contribute the bulk of the diagnosis in many of our patients. The blood work, to me, is the icing on the cake. If you are not spending enough time in your clinical practice recognizing the art of the history and performing a comprehensive physical exam, you are compromising your ability to make a diagnosis. The physical exam should comprise a thorough oral examination, and if the patient is aggressive or fractious, it should be sedated if feasible.

And the lab work complements the history and physical exam. And I love the fact that Dr. Natalie Marks stressed the importance of a urinalysis. The urine specific gravity is the poor man’s test for renal disease. Don’t do it once; do it consistently, so you can look at trends.

Patients with esophagitis secondary to gastroesophageal reflux can also be hyporexic or anorexic. One should observe the patient for evidence of odynophagia, ptyalism, hard swallowing, regurgitation, and coughing associated with drinking or eating. Intestinal disease can cause hyporexia in the absence of primary GI signs (eg, vomiting, diarrhea), and it is important to carefully evaluate serum albumin, globulin, and cholesterol concentrations and measure serum cobalamin concentration. Do not forget about the importance of a rectal exam on all canine patients. It is a frequently ignored part of a physical exam in the veterinary profession, and it is concerning. The rectal examination allows one to evaluate the colorectum for benign polyps or malignant tumors; evaluate the size, symmetry, and contour of the prostate gland; palpate the urethra; and assess the appearance of feces on the rectal glove for the presence of blood, foreign material, etc.

Dr. Larson: Let’s talk about what specific treatments look like and things we would have used in the past that we thought would help stimulate appetite.

Dr. Clifford: One of the interesting points was oncologists and internists were surveyed before ENTYCE had come out, asking what do you tend to use for appetite stimulant? And what was number one at that point that came out was an antiemetic, which I thought was very fascinating. Clearly times have changed, but there is still a large number of clinicians who will jump to antiemetics in those patients.

Dr. Stanley Marks: Antiemetics inhibit the vomiting reflex via different mechanisms. Maropitant, one of the most ubiquitous drugs used by many veterinarians, is a highly effective antiemetic. That
Early intervention and use of appetite stimulants during your diagnostic workup are very helpful, because the earlier we intervene, the better chance of success.

—Dr. Natalie Marks

Drug does not resolve nauseousness in the dog or cat based on studies published to date. So I may inhibit vomiting effectively, but I still have a dog that is hypersalivating, lip smacking, and pacing anxiously due to nauseousness. Ondansetron, a 5-hydroxytryptamine_{3} receptor antagonist, appears to be more effective for managing nauseousness and is a potent antiemetic.

Antiemetics are also administered injudiciously to many veterinary patients. A patient that is vomiting once- to twice-weekly likely does not need antiemetic therapy because the drug could muddy the water and make it more challenging to evaluate the dog’s response to primary therapeutic interventions (eg, diet change, antibiotic therapy, corticosteroids).

Of equal importance, acid suppressants like famotidine and omeprazole are also commonly administered injudiciously to our patients. A consensus statement was published in the Journal of Veterinary Internal Medicine in 2018 looking at the rational use of gastrointestinal protectants in dogs and cats. They are one of the most overprescribed and misused drugs in the human and veterinary professions. So think about modifying the patient’s environment and managing blood pressure and pain in an effort to optimize the medical management of our patients.

Dr. Clifford: Does the severity of how the patient presents, though, play a role in that? Because if they are truly coming in anorexic for several days, you may have to do more of a shotgun approach of everything.

Dr. Stanley Marks: Absolutely. It is often a multimodal approach. But I do want to recognize that if we are not addressing pain while giving an appetite stimulant, we are not doing the patient and the owner much of a service.

Dr. Natalie Marks: Early intervention and use of appetite stimulants during your diagnostic workup are very helpful, because the earlier we intervene, the better chance of success. I want to also point out a couple of things that have worked in our practice that people sometimes forget about. Nutrition is imperative to wound healing, and we are all doing surgeries in our practices, using opioids and other types of medications during procedures, where those patients develop inappetence postsurgically. We are using appetite stimulants postsurgically in the recovery period when those patients are going home and seeing tremendous response from our clients who are seeing their pets eating the next day. As Dr. Clifford mentioned, when a pet is not eating, that is very emotionally draining on the pet parent. And the more we can intervene, both helping that emotional bond and also helping that patient recover from surgery faster because they are getting back to eating faster and getting that nutrition for wound healing, the better the outcome for everyone involved.

We also use appetite stimulants for chronic boarders. Many of us have boarding patients, or patients that go to kennels, where as soon as they enter that kennel, they don’t eat for several days. Well, why not intervene in a multimodal approach, also addressing the anxiety and stress, by giving that option of an appetite stimulant so they don’t have to go through a tremendously long boarding experience, not eating in any of those forms of inappetence? So there are a lot of different ways that appetite stimulants play a role in daily practice, not just in those chronic diseases but also in acute situations and behavioral stresses.
Dr. Clifford: My ER service is definitely one where everybody is on an antiemetic, and everyone is on an antacid as well. So I think there is always room for improvement; there is no doubt about that.

Dr. Stanley Marks: We are well aware of the potential benefits of consuming a probiotic prior to or concurrently with an antibiotic in effort to mitigate antibiotic-associated diarrhea. There is a plethora of research in the human field, in particular, studying prevention of diarrhea by preemptively taking a probiotic. When we give a patient amoxicillin/clavulanic acid, we can also see hyporexia commonly, yet we don’t think about the potential benefits or value of preemptively giving that patient an appetite stimulant to mitigate the hyporexia. It is well worth asking, “Might I be able to prevent that hyporexia in my patient by intervening sooner rather than later?”

Dr. Larson: There is only one FDA-approved veterinary appetite stimulant for dogs, which is ENTYCE. What are some success stories using ENTYCE?

Dr. Stanley Marks: Clinicians at the University of California, Davis, see very complex cases, typically as a referral, and these patients have multi-organ disease. So, it’s not uncommon to see a patient with a chronic enteropathy such as IBD, concurrent pancreatitis, or renal disease and heart failure. These patients are receiving a slew of different drugs to try and manage each of these different disorders. And we have recognized that, with the advent of ENTYCE, in a fairly large percentage of these patients that have been hyporectic or anorectic, there is a dramatic response to food intake. The beauty of the drug, too, is that it typically works quickly. Unlike other appetite stimulants like cyproheptadine that take several days for us to observe an effect, we’re typically seeing an effect within 30 minutes or an hour in our patients following administration of ENTYCE. Despite the complexity of the diseases in many of these patients, we still do see a subset of patients with chronic pancreatitis, CKD, and congestive heart failure that are on multiple drugs and that respond favorably to administration of ENTYCE, which is incredibly rewarding, especially for the pet owner.

Dr. Natalie Marks: One of my biggest success stories is Roosevelt (Rosie). He is a now 15-year-old shih tzu that has been in stage B2 congestive heart failure and stage 3 IRIS kidney disease for almost 9 months. He has a dad who is a first-time pet owner at 72. As Rosie has been aging and we have been dealing with chronic disease and concurrent disease, the owner has been asking me what I am looking for. “What are signs that this is time, because I have never gone through this?” All of us have mentioned that if a dog is not eating, that is a big sign. Rosie started to become hyporexic, understandably. He is on a multimodal cocktail for congestive heart failure and also lots of things to try and help his kidney disease. And when ENTYCE came out, I said, “I think I have something we can try to give Rosie a better quality of life,” because he was getting to that point. We started ENTYCE on a Friday; Saturday afternoon, he sends me a video of them in Lincoln Park, and he is sitting there drinking a coffee and Rosie has food in a bowl, and the bowl looks almost empty, and he has this big thumbs up.

That dog went from being hyporexic for almost 2 weeks to eating 2 full meals a day. And the amazement and the incredible emotional kind of joy that we are able to now provide to him and Rosie for whatever time they have left is really why we do this, right? We now have this great new tool in our toolbox for those kinds of cases where we are dealing with chronic diseases where they are on a multimodal approach and they are also dealing with potentially new diseases and new ailments. Acutely, we see lots of dietary indiscretions after holidays and vacations. I had an Australian shepherd named Merlin who got into the garbage after Thanksgiving and ate 3 full plates of turkey and stuffing and cranberry. He came in with severe gastroenteritis. For those kinds of cases, I think in the past I would have just said, “Well, let’s just let it take its course.” That dog was not eating and was of course vomiting and having lots of diarrhea. Those are the cases where we have a great new tool, again, to intervene, not only with an antiemetic but with concurrent use of an appetite stimulant to get them home and feeling better quicker. They don’t have to wait that 2 to 3 days until everything reregulates and hope that they are going to start eating slowly again.

There are a lot of different ways that appetite stimulants play a role in daily practice, not just in those chronic diseases but also in acute situations and behavioral stresses.

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We want them to get in and get eating. We want the pet to get healthy nutrition again. We tried ENTYCE with Merlin, and his mom said that within 18 hours he had started eating a gastrointestinal-friendly food. So I want to stress again that there are a lot of different indications for ENTYCE, both from acute and chronic cases, but early intervention is key.

Dr. Stanley Marks: The ease and ability to give a drug like ENTYCE should not preclude us from trying to find a specific diagnosis. Another key point to consider is that renal disease typically requires administration of a protein-restricted, phosphorus-restricted, and sodium-restricted diet. And to many of our patients, the reduced palatability of some of these diets can exacerbate the reduced food intake with the kidney disease. Administration of ENTYCE can help maintain adequate caloric intake and possibly increase survival when feeding a protein-restricted renal diet to our patients.

Reference

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

KEY TAKEAWAYS

➤ It is important to recognize and differentiate the 3 forms of inappetence: anorexia, hyporexia, and dysrexia.

➤ Early intervention is key; clinicians should obtain a comprehensive patient history regarding food intake and diet.

➤ Patients receiving drug therapy (eg, antibiotics, opioids, chemotherapeutics) for other conditions may also need to receive an appetite stimulant to prevent inappetence.

➤ In addition to treating chronic disease, appetite stimulants can help in acute cases and cases involving behavioral stressors (eg, boarding).

ENTYCE
The active ingredient in ENTYCE, capromorelin, is a ghrelin-receptor agonist that mimics ghrelin, the main hunger hormone. ENTYCE is FDA approved and has been demonstrated through clinical studies to safely and effectively stimulate appetite in dogs. ENTYCE can be used as long as needed for most situations when a dog is not eating normally, including during the diagnostic phase of the workup, and can continue as part of the treatment plan if indicated.
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 C₂₈H₂₈N₂O₅, and the molecular weight: 465.50. 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.

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 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

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>ENTYCE (n = 171) n (%)</th>
<th>Vehicle Control (n = 73)</th>
</tr>
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<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>
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<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 < 3% of dogs administered ENTYCE: hyperactivity, increased fecal volume, increased 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 1-844-272-8262.

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 (Cmax) reached within 0.83 hr (Tmax). After Cmax, the plasma concentrations declined mono-exponentially with a short terminal half-life (T½) 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>
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<tbody>
<tr>
<td>Tmax (hr)</td>
<td>0.83</td>
<td>0.58</td>
</tr>
<tr>
<td>Cmax (mg/mL)</td>
<td>330</td>
<td>143</td>
</tr>
<tr>
<td>AUC (ng·hr/mL)</td>
<td>655</td>
<td>276</td>
</tr>
<tr>
<td>AUC0-48 (ng·hr/mL)</td>
<td>695</td>
<td>262</td>
</tr>
<tr>
<td>T½ (hr)</td>
<td>1.19</td>
<td>0.17</td>
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</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 2.0 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. Emsosis 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 16 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 (0.13X), 1 (0.3X), 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 for dogs administered ENTYCE or vehicle control.

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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