INTENDED USE
ENTERAGAM is a medical food product intended for the dietary management of chronic diarrhea and loose stools. ENTERAGAM must be administered under medical supervision.

DESCRIPTION
Each ENTERAGAM PACKET (10 g net weight) contains a light-colored powder consisting of 5 g of serum-derived bovine immunoglobulin/protein isolate (SBI), 5 g dextrose (also known as glucose) and trace amounts of sunflower lecithin.

SBI is composed of >90% protein which consists primarily of immunoglobulins (e.g. >50% IgG) along with other proteins and peptides that are similar to those commonly consumed by humans in beef products.

ENTERAGAM does not contain any milk-derived ingredients such as lactose, casein, or whey. ENTERAGAM is gluten-free, dye-free, and soy-free.

DIRECTIONS FOR USE
Add at least 4 oz of liquid (water or other liquid as preferred) to a cup or glass
- Note that warm liquids may help the product dissolve more quickly
- Do not dissolve in hot liquids as this may degrade the proteins in the product
Pour content of packet into liquid and stir until fully mixed (do not shake).
Consume all the solution immediately.
Alternatively, product can be mixed with soft foods such as pudding or yogurt.

DOSING
The recommended starting dose of ENTERAGAM is based on the number of loose or watery stools experienced per day.

<table>
<thead>
<tr>
<th># of loose/watery stools per day</th>
<th># of packets per day</th>
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<tbody>
<tr>
<td>5 or fewer</td>
<td>1 to 2 packets</td>
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<tr>
<td>6-10</td>
<td>2 packets</td>
</tr>
<tr>
<td>11-15</td>
<td>3 packets</td>
</tr>
<tr>
<td>16+</td>
<td>4 packets</td>
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</table>

Once stools normalize (1-2 stools per day with good consistency which typically occurs within 2-4 weeks), the daily intake can be decreased to 1 packet per day. Intake may be increased during flare ups or decreased for mild constipation. There is no restriction on the length of time ENTERAGAM may be consumed.

Pediatric Patients – Children 2 years and older can be administered one half (1/2) PACKET of ENTERAGAM once daily (or in divided doses) in liquids or soft food according to the healthcare provider’s instructions.

MEDICAL FOODS
ENTERAGAM is a medical food as defined by the Orphan Drug Act. Medical supervision is required.

The term medical food, as defined by the Orphan Drug Act [(21 U.S.C. 360ee(b)(3)) of 1988, is “a food which is formulated to be consumed or administered enterally under the supervision of a physician and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation.” Ingredients in medical foods must be generally recognized as safe (GRAS) and/or approved food additives.

ENTERAGAM is manufactured in compliance with current Good Manufacturing Practice (cGMP) for medical foods.

Generally Recognized as Safe
The ingredients in ENTERAGAM are Generally Recognized as Safe (GRAS). GRAS is a statutory safety standard that the FDA requires of all ingredients added to food products. Therefore, ENTERAGAM is safe for use in the general population.

CHRONIC DIARRHEA
A variety of intestinal disorders [e.g., irritable bowel syndrome with diarrhea (IBS-D), inflammatory bowel disease (IBD)] are associated with chronic diarrhea and loose stools. While the pathophysiological mechanisms that cause the chronic diarrhea and loose stools associated with intestinal disorders are not well understood, there is evidence that exposure to external antigens (foreign substances such as food ingredients like lactose), toxins, or other environmental insults (including infection) can elicit changes in the lining of the intestine that alter its ability to absorb key nutrients (e.g., protein, carbohydrate, fat, vitamins, minerals) and water. Malabsorption of such nutrients can lead to malnutrition or protracted undernutrition and play a central role in contributing to or even exacerbating chronic diarrhea and loose stools in patients with intestinal disorders.
**PHARMACOLOGY**

**Mechanism of Action**
Immunoglobulins found in SBI have been shown to bind to certain microbial components with immune-activating potential from a variety of bacteria, fungi, and viruses, including those implicated in human disease. Unlike common dietary proteins, SBI contains concentrated amounts of unique proteins that may aid in the management of chronic diarrhea or loose and frequent stools. While the mechanism of action of ENTERAGAM has not been fully elucidated, this binding of inflammatory antigens may prevent their passage into the lamina propria, presumably due to steric exclusion. The resultant dampening of immune response in the gut-associated lymphoid tissue (GALT) is believed to allow for restoration of intestinal homeostasis, leading to resumption of normal gut function and nutrient absorption.

This combined effect of SBI fulfills a distinctive nutritional requirement associated with various GI conditions where chronic diarrhea or loose stools is present that cannot be provided by normal dietary proteins alone.

**Digestibility**
Digestion of the protein content in SBI followed by significant absorption of amino acids has been shown to occur in healthy volunteers. A percentage of SBI survives through the stomach and into the small as well as large intestines. Whole proteins such as the immunoglobulins present in SBI and other foods (i.e., milk and meat) are not known to be absorbed into the blood stream without first being digested to the amino acid level.

**Survival and Elimination**
The unique compositional structure of immunoglobulins helps them avoid degradation during gastrointestinal transit in order to reach the areas of the intestines where they can impart the intended benefit. Differences in survival through the GI tract may occur as a result of variations in transit time because of co-administration with proton pump inhibitors, GI infection, hydration state, or disease resulting in diarrhea. Previous studies using immunoglobulin preparations similar to SBI have shown that up to 50% of orally-administered immunoglobulins survive initial digestive processes in the stomach. Transit time following oral ingestion of bovine immunoglobulins occurs between 6 and 40 hours, depending on the health of the individual. In infants with diarrhea, approximately 5-12% of orally-administered immunoglobulins are excreted in feces. Other studies in adults with compromised GI tracts show that approximately 10-20% of orally-administered immunoglobulins are excreted in the feces.

**PRECAUTIONS AND WARNINGS**
ENTERAGAM contains beef protein; therefore, patients who have an allergy to beef or any component of ENTERAGAM should not take this product.

**Pregnancy, Labor and Delivery and Nursing Mothers**
ENTERAGAM has not been studied in pregnant women, in women during labor or delivery or in nursing mothers. The choice to administer ENTERAGAM during pregnancy, labor or delivery, or in nursing mothers is at the clinical discretion of the prescribing physician.

**Pediatric Use**
ENTERAGAM has not been studied specifically in clinical trials in pediatric populations. However, four case reports have been presented where ENTERAGAM was used successfully in five older infants or children to help manage diarrhea or chronic loose and frequent stools associated with various disorders; no AEs were reported in any of these pediatric patients following use of 5-10 g SBI per day. In addition, immunoglobulin preparations similar to SBI (0.18 to 1.0 g total protein per day) have been evaluated in two clinical studies involving a total of 117 infants and children; no AEs were reported for up to 8 months of immunoglobulin therapy.

**DRUG AND FOOD INTERACTIONS**
No significant interactions of ENTERAGAM with commonly prescribed medications or therapies have been reported. There are no known adverse food interactions with ENTERAGAM.

**ADVERSE EVENTS/REACTIONS**
As previously stated, the ingredients in ENTERAGAM are Generally Recognized as Safe (GRAS) for use in the general population. The most commonly reported (incidence of 2-5%) adverse events (AEs) in clinical studies with SBI have included mild nausea, constipation, stomach cramps, headache, and increased urination. There were no serious adverse events (SAEs) associated with the use of SBI at doses up to 20 g per day in published clinical studies involving over 346 participants.

Post-marketing surveillance – Since ENTERAGAM was introduced in 2013, it is estimated that nearly 3 million doses of product have been administered to over 22,000 patients in the United States. The overall adverse event (AE) rate is less than 0.2%. The most common AEs reported by patients administered ENTERAGAM include mild nausea, constipation, headache, increased urination, increased diarrhea and joint pain. No serious AEs have been attributed to ENTERAGAM during post-marketing surveillance.

To report SUSPECTED ADVERSE REACTIONS, contact Entera Health, Inc. at 1-855-4ENTERA (1-855-436-8372) or FDA at 1-800-FDA-1088 (1-800-332-1088) or www.fda.gov/medwatch.
## SAFETY

### Table 1. Clinical Safety Experience (Data on file)

<table>
<thead>
<tr>
<th>Population Studied</th>
<th>Safety Summary</th>
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<tr>
<td>Normal, Healthy Adult Volunteers</td>
<td>Forty-one (41) healthy adults were administered doses of SBI of 5 g, 10 g or 20 g for 15 days. Two (2) subjects withdrew due to AEs: one due to abdominal cramping; another due to abdominal cramping, bloating and diarrhea. Adverse events that occurred at an incidence of ≥ 10% in the dose groups were as follows (presented as number of subjects for 5.0 g, 10 g or 20 g daily): abdominal cramps (3, 0, 1), constipation (2, 0, 1), diarrhea (2, 0, 0), flatulence (0, 0, 2), cold (2, 0, 0), upper respiratory tract infection (0, 2, 0), and headache (2, 1, 0).</td>
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<tr>
<td>Irritable Bowel Syndrome (IBS) and Small Intestinal Bacterial Overgrowth (SIBO)</td>
<td>Forty-four (44) adult subjects administered either 5 or 10 g of SBI per day for 6 weeks. SBI was well-tolerated with no SAEs reported. Three (3) subjects withdrew from the study due to nausea. In a second retrospective chart review, fifteen (15) adult subjects diagnosed with IBS-D were administered SBI 5 g BID. Three AEs (nausea, sores on tongue, metallic taste in mouth) experienced by one subject were reported as possibly related to SBI. No SAEs were reported. The following AEs were reported: headache (2 subjects), cramping (2 subjects), nausea (2 subjects), gas (2 subjects) and one subject for each: back pain, stomach flu, bloating, leaking, sinus infection, acid reflux, cold sore and sick. Ten (10) adult subjects with IBS-D or IBS with bloating/distention were administered 5 g of SBI per day. SBI was well-tolerated with no reported AEs when taken up to 28 weeks. A third study evaluated medical charts for twenty-six (26) adult subjects with SIBO administered 10 g of SBI per day for 4 weeks. Three (3) subjects discontinued due to AEs: one with constipation, another with diarrhea and another with nausea and constipation. A fourth chart review evaluated twenty-eight (28) adult subjects with IBS-D administered 5 g of SBI per day for 16 weeks. Two (2) subjects reported AEs: one with hardened stool and another with increased stool frequency.</td>
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<tr>
<td>Inflammatory Bowel Disease</td>
<td>Forty-five (45) adult subjects with IBD (n=38 diagnosed with Crohn’s disease and n=7 with ulcerative colitis) were administered 5 g of SBI per day for 12 weeks. A retrospective chart analysis showed SBI was well-tolerated with no reported AEs. In a second retrospective chart review, four (4) adult subjects diagnosed with Crohn’s disease and three (3) subjects with ulcerative colitis who were not fully managed on traditional therapies were administered either 5 or 10 g per day for 3 to 9 months. Results showed that SBI was well-tolerated with no reported AEs. A third study evaluated medical charts for two (2) adult subjects diagnosed with ulcerative colitis not fully controlled on traditional therapies. Subjects were administered SBI using different dosing regimens: one was given 5 g QID for one week followed by 5 g BID of SBI; another received 5 g BID for 8 weeks followed by 5 g daily thereafter. Each subject maintained SBI therapy along with other therapies for over 12 months with no reported AEs.</td>
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<tr>
<td>Human Immunodeficiency Virus</td>
<td>In a pilot study, eight (8) HIV-positive subjects were administered 2.5 g SBI twice a day for 8 weeks. SBI was well-tolerated with no SAEs reported. Five (5) subjects continued on therapy for up to 48 weeks. The most commonly reported AEs included worsening or reoccurrence of diarrhea (5 AEs reported by 4 subjects), constipation (2 subjects), and worsening neuropathy (3 AEs reported by 2 subjects). AEs reported by subjects (n=1 for each) included: sinus infection, throat infection, gastrointestinal reflux disease, flatulence, worsening lower back pain, groin pain, nausea, bronchitis, acute ear infection, and infection on finger. None of the reported AEs were deemed related to SBI and no subjects discontinued due to an AE. In a dual phase multicenter, outpatient study, one hundred and three (103) HIV+ adult subjects were administered SBI 2.5 g or 5.0 g BID for up to 24 weeks. One subject withdrew due to an AE, diarrhea. AEs reported by &gt;2% were: arthralgia (n=10 subjects), myalgia (n=8 subjects), anxiety (n=6 subjects), headache (n=4 subjects), toothache (n=4 subjects), dizziness (n=3 subjects), and nausea (n=3 subjects). The related AEs: constipation (n=2 subjects), flatulence (n=2 subjects) and one (1) subject for upper abdominal pain, abnormal feces, dyspepsia, oral leukoplakia, nausea, rectal tenesmus and headache.</td>
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</table>
NONCLINICAL DATA

Animal and in vitro models support the above proposed mechanism of action of ENTERAGAM.

The antibodies contained in SBI have been shown to bind, in vitro, to many different microbial components from multiple bacterial, fungal, and viral organisms. Indeed, SBI binding has been confirmed for lipopolysaccharide (LPS), peptidoglycan, zymosan, flagellin, cyclic diadenylate monophosphate, cytosine phosphate-linked guanine, muramyl dipeptide, rotaviral enterotoxin NSP4 and C. difficile toxin A and B. These antigens are capable of activating the intestinal immune system if allowed access through a compromised intestinal epithelial barrier.

In a co-culture model of damaged intestinal epithelium, SBI was shown to block (presumably through steric exclusion) movement of an endotoxin mimic (Pam3CSK4) across compromised tight junctions.

Two different animal models have been utilized to assess the effect of SBI on managing gut barrier function. In the mdr1a/- mouse model of spontaneous colitis, alterations in gut barrier allow bacteria and other luminal antigens (factors associated with GI immune cell activation) to cross the epithelium. When SBI was included in the diet of mdr1 mice the expression of mucosal TNF-α, IFN-γ, and inducible nitric oxide synthase was significantly decreased (all P < 0.005). In addition, consumption of SBI also led to decreased crypt permeability, mitigation of the reduction of tight junction protein (E-cadherin and zona occluden-1) expression and attenuated the loss of muc2 and trefoil factor 3 expression. Together these findings are consistent with the hypothesis that SBI supports intestinal barrier function.

In a separate study, colitis was induced in altered Schaedler flora (ASF) mice who were administered dextran sodium sulfate (DSS), and E. coli (LF82, a strain originally isolated from a Crohn’s patient known to exacerbate the inflammatory condition). SBI significantly maintained colon mucosal height (p < 0.05), cecal stromal structure (p < 0.05), and colonic glandular tissue (p < 0.05) in DSS-LF82 mice treated with SBI compared to control mice given DSS-LF82 and treated with hydrolyzed collagen. Western blot analysis also demonstrated that SBI binds to multiple components of each ASF species and LF82 E. coli.

CLINICAL EXPERIENCE

Provided below is a listing of published clinical findings for SBI that support the dietary management of chronic diarrhea and loose stools in a wide variety of patient types. In addition to the cases outlined below, SBI has been used successfully in several other GI disorders with chronic diarrhea and loose stools (e.g. radiation and chemo-induced diarrhea, infectious diarrhea).

Irritable Bowel Syndrome with Diarrhea (IBS-D)


Inflammatory Bowel Disease (IBD), Ischemic Colitis and Microscopic Colitis with Chronic Diarrhea


Good L, Panas R. Case Series Investigating the Clinical Practice Experience of Serum-Derived Bovine Immunoglobulin/Protein Isolate (SBI) in the Clinical Management of Patients with Inflammatory Bowel Disease.


Good L, Panas R. Remission of Pouchitis in Patients Following Serum-Derived Bovine Immunoglobulin/Protein Isolate (SBI) Therapy. *Inflammatory Bowel Diseases.* 2016; doi: 10.1097/01.MIB.0000480104.33028.4a.


**Fecal Incontinence with Chronic Diarrhea**

Good L, Panas R. Management of Severe Watery Stools with Fecal Incontinence in Ileorectal Anastomosis Patient with Serum-Derived Bovine Immunoglobin Therapy. Poster presented (#842) at 2015 ACG Annual Scientific Meeting, Honolulu, HI. October 19, 2015.


**Celiac and Non-Celiac Gluten Sensitivity with Chronic Diarrhea**

Iduru S, Burnett BP. Management of Celiac Disease and Non-Celiac Gluten Sensitivity with Serum-Derived Bovine Immunoglobulin/Protein Isolate. Poster presented (#1343) at 2015 ACG Annual Scientific Meeting, Honolulu, HI. October 19, 2015.

Good L, Panas R. Nutritional Management of Celiac Disease using Serum-derived Bovine Immunoglobulin/Protein Isolate in a Patient with Poor Gluten-Free Diet Compliance. Poster presented (#627) at 2015 ACG Annual Scientific Meeting, Honolulu, HI. October 18, 2015.

**Other Enteropathy with Chronic Diarrhea**


Mah’moud M, Anderson M, Young HE. Use of Serum-Derived Bovine Immunoglobulin/Protein Isolate (SBI) for the Management of DMARD-Induced Chronic Loose and Frequent Stools. Poster presented (#1018) at 2015 ACG Annual Scientific Meeting, Honolulu, HI. October 18, 2015.

Roy J, Klein GL, Young HE. Clinical Management of Mastocytic Enterocolitis with Serum-Derived Bovine Immunoglobulin/Protein Isolate. Poster presented (#1483) at 2015 ACG Annual Scientific Meeting, Honolulu, HI. October 20, 2015.

**Pediatric Studies**


**HIV-Associated Enteropathy with Chronic Diarrhea**


Asmuth DM, Stombaugh J, Ma ZM, Albanese A, et al. Changes in stool microbiota, bacterial translocation and mucosal immunity after oral serum-derived bovine immunoglobulin (SBI) administration. 20th Conference on...


Shaw AL, Burnett BP, Weaver EW. Serum-Derived Bovine Immunoglobulin Protein Isolate, a New Medical Food for the Clinical Dietary Management of HIV-Associated Enteropathy. Presented at the 26th ANAC Conference, November 23, 2013, Atlanta, GA.


All published and presented, peer-reviewed data is available upon request.

REFERENCE
1. 21 USC Section 360ee(b)(3).