EnteraGam®
(serum-derived bovine immunoglobulin/protein isolate, SBI)

PRODUCT INFORMATION

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 amount 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 contents 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.

# of loose/watery stools per day	# of packets per day
5 or fewer	1 to 2 packets
6-10	2 packets
11-15	3 packets
16+	4 packets

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.1 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

Unlike common dietary proteins, SBI contains a specially formulated concentrated food-based source of immunoglobulin that may aid in the management of chronic diarrhea or loose and frequent stools. Immunoglobulins found in SBI have been shown to bind to microbial components with immune-activating potential from a variety of bacteria, fungi and viruses, including those implicated in human disease. 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's action on the intestinal tract 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 or by increased intake of foods which contain immunoglobulin (i.e., milk).

Digestibility

Following ingestion, proteins are subject to chemical and enzymatic degradation in the GI tract, resulting in small peptides and individual amino acids that are able to cross the epithelial barrier and become absorbed into the blood stream. Absorption of peptide sequences from foreign proteins into the bloodstream can result in a risk of acute allergic response (i.e., anaphylaxis). The digestion and safety of SBI (5 g, 10 g, or 20 g per day for 14 days) was studied in 42 normal healthy volunteers. Results of the study showed a significant dose-dependent increase in the plasma concentra- tions of both total and essential amino acids. Despite this extensive digestion, bovine IgG was found in the feces of subjects, thereby, demonstrating that the disulfide bond-stabilized molecule is capable of surviving transit through the GI tract to regions where therapeutic response may be initiated. No adverse events suggestive of allergic reaction were reported in the study; moreover, quantifiable bovine IgG was not present in patient plasma samples.

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 been specifically studied in two well-controlled pediatric IBS-D clinical trials. The age ranges in these two studies were 13.5± 3.6 yrs and 14.5±2.2 yrs, respectively. In addition, four case reports have been presented where ENTERAGAM was used successfully in older infants (>6 mo) or children (2 to 18 yrs) to help manage diarrhea or chronic loose and frequent stools associated with various disorders; one ccc coo nausea and one case of emesis were reported in pediatric patients following use of 5-10 g SBI per day.

Immunoglobulin preparations similar to SBI (0.18 to 1.0 g total protein per day) have also been evaluated in two clinical studies involving a total of 117 infants and children (>6 mo to 25 mo); 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.

PRODUCT SAFETY: ADVERSE EVENTS / ADVERSE REACTIONS

As previously stated, the ingredients in ENTERAGAM are Generally Recognized as Safe (GRAS) for use in the general population. The safety profile of the product has been documented in clinical trials and retrospective chart reviews that describe adverse events (AEs)/adverse reactions in almost 1,500 subjects/patients.

Clinical Trials

In well-controlled clinical trials (6) and open-label studies (4) completed to date under IRB approved protocols, 874 subjects or patients have received at least one dose of SBI or ENTERAGAM. The most common AEs reported in each study are shown in Table 1 and include abdominal cramps, constipation, diarrhea, flatulence, headache, and nausea. The majority of these AEs were judged by the investigators as mild or moderate in intensity. Four serious adverse events (SAEs) reported in the clinical trials and none were attributed to SBI.

Retrospective Chart Reviews

Reviews of medical charts of 621 patients where ENTERAGAM was used in the management of chronic diarrhea and loose stools have resulted in numerous publications that are listed at the end of this document. These publications, comprised of posters, abstracts as well as peer-reviewed manuscripts, cover a wide variety of disease states such as: IBS-D, IBD, lymphocytic colitis, fecal incontinence, celiac disease (as well as non-celiac gluten sensitivity), short bowel syndrome, chronic pancreatitis, pancreatic insufficiency, drug-induced diarrhea, mastocytic enterocolitis and infectious enteropathy (e.g., C. difficile infection, HIV enteropathy, norovirus and cryptosporidium) and more. Out of 621 patients published in these studies, there were 29 total AEs and no SAEs. Constipation was most predominant (11) followed by nausea (7). There were 2 reports each for mild cramping, mild abdominal pain, insufficient response, and mild diarrhea or loose stools. One report each for headache, frequent urination, and metallic taste were also recorded.

Post-Marketing Surveillance

Since ENTERAGAM was introduced in 2013 through 2017, over 8 million packets of ENTERAGAM have been administered to at least 31,260 patients. There have been 191 side effects from 114 unique patients reported to the manufacturer during this period. Therefore, the cumulative frequency of adverse events (serious and non-serious) was 0.4%. The most common AEs reported by patients administered ENTERAGAM included in order mild constipation (23), headache (13), mild diarrhea (11), nausea (8), abdominal pain (8), abdominal distention (7), and hives (7). 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.

TABLE 1. CLINICAL SAFETY EXPERIENCE

Population Studied	Data Source	Safety Summary
Normal, Healthy Adult Volunteers	Clinical Trial	Forty-one (41) healthy adults were received SBI (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 in more than one subject 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), sinus infection (1, 1, 0), upper respiratory tract infection (0, 2, 0), and headache (2, 1, 0). All AEs were mild to moderate in intensity and no SAEs were reported.
Irritable Bowel Syndrome (IBS) and Small Intestinal Bacterial Overgrowth (SIBO)	Clinical Trial	Forty-four (44) adult IBS-D subjects received SBI (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. Fifteen (15) adult subjects diagnosed with IBS-D received SBI (5 g BID) for 8 weeks. Three AEs (nausea, sores on tongue, metallic taste in mouth) experienced by one subject were reported as possibly related to SBI. The majority of AEs were mild to moderate in intensity. No SAEs were reported. The following AEs were reported: headache (2 subjects), cramping (2 subjects), nausea (2 subjects), gas (2 subjects) and one subject each for: back pain, stomach flu, bloating, leaking, sinus infection, acid reflux, cold sore and malaise.
	Retrospective Chart Review	Twenty-six (26) IBS-D or IBS-M (mixed diarrhea / constipation pattern) patients were prescribed ENTERAGAM (10 g SBI per day) for 4 weeks. Eleven patients were found to have small intestinal bacterial overgrowth (SIBO) prior to being administered ENTERAGAM. Two (2) patients were lost to follow up leaving twenty-four (24) in the final analysis. Three (3) of these patients discontinued product due to AEs: constipation (1 patient), diarrhea (1 patient), and nausea and constipation (1 patient). Twenty-eight (28) adult subjects with IBS-D were prescribed ENTERAGAM (5 g of SBI per day) for 16 weeks. Two (2) subjects reported AEs: hardened stool (1 patient) and increased stool frequency (1 patient).
Inflammatory Bowel Disease	Retrospective Chart Review	Two case reports: One adult patient with ischemic colitis was prescribed ENTERAGAM (5 g SBI per day) for 4 weeks. Patient reported AE of cramping, resulting in dose decrease to 2.5 g SBI per day. Patient was followed for one year with no subsequent AEs reported. The other patient, diagnosed with pan ulcerative colitis, was prescribed ENTERAGAM (5 g SBI BID) for 8 weeks, then 5 g SBI per day for a year. No AEs were reported for this patient.
Other Diarrheal Conditions	Retrospective Chart Review	Two case reports of adults with post-infectious (*Clostridium difficile*) IBS-D. One patient who was prescribed ENTERAGAM (10 g SBI per day for 4 weeks) but following a urinary tract infection and constipation, dose was reduced to 5 g SBI per day. No AEs were reported with other patient who was prescribed ENTERAGAM (20 g SBI per day).
Human Immunodeficiency Virus	Clinical Trial	Eight (8) HIV-positive subjects received SBI (2.5 g BID) for 8 weeks. Five (5) subjects continued on therapy for up to 48 weeks. The majority of AEs were mild to moderate in intensity and no SAEs were reported. 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). Other AEs reported by subjects included: sinus infection, throat infection, gastroesophageal 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. One hundred and three (103) adult HIV-positive subjects received SBI (2.5 g or 5.0 g BID) for up to 24 weeks. One subject withdrew due to an AE, diarrhea. The majority of AEs were mild to moderate in intensity. Three subjects experienced four SAEs (alcohol abuse, peripheral neuropathy, cerebral hemorrhage and subarachnoid hemorrhage) and all events were reported as unrelated to SBI. The

		most commonly reported AEs included: arthralgia (10 subjects), myalgia (8 subjects), anxiety (6 subjects), headache (4 subjects), toothache (4 subjects), dizziness (3 subjects), and nausea (3 subjects). The related AEs included: constipation (2 subjects), flatulence (2 subjects) and one subject each for upper abdominal pain, abnormal feces, dyspepsia, oral leukoplakia, nausea, rectal tenesmus and headache.

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 typically released upon the death of these microbes in the intestine. 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 components, also known as antigens, are capable of activating the intestinal immune system if allowed access through a damaged 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) (an antigen) 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 mdr1a mice, the expression of mucosal TNF-α, IL-6, IL-2, IL-17, IFN-γ, and inducible nitric oxide synthase was significantly decreased (all $p < 0.005$) while there was an increase in anti-inflammatory TGFβ. In addition, consumption of SBI led to decreased crypt permeability, mitigation of the reduction of tight junction protein (E-cadherin and zona occluden-1) expression, attenuated loss of muc2 and trefoil factor 3 expression, and a reduction in neutrophil recruitment and activation in mesenteric lymph nodes and lamina propria. 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 PUBLICATIONS

Provided below is a listing of published clinical studies and retrospective chart reviews involving almost 1,500 subjects and/or patients administered SBI that support its use in the dietary management of chronic diarrhea and loose stools in a wide variety of patient types.

Irritable Bowel Syndrome with Diarrhea (IBS-D)

Wilson D, Evans M, Weaver E, et al. Evaluation of serum-derived bovine immunoglobulin protein isolate in subjects with diarrhea-predominant irritable bowel syndrome. Clin Med Insights: Gastroenterol. 2013; 6:49-60. doi: 10.4137/C-Gast.S13200

Weinstock LB, Jasion VS. Serum-derived bovine immunoglobulin/protein isolate therapy for patients with refractory irritable bowel syndrome. Open J Gastroenterol. 2014;4:329-334. doi: 10.4236/ojgas /2014.410047

Hilal R, Mitchell P, Guerra E, Burnett BP. Case series of 10 drug-refractory IBS patients who respond to oral serum-derived bovine immunoglobulin/protein isolate (SBI). Open J Gastroenterol. 2014;4:321-328. doi: 10.4236/ojgas.2014.410046

Crawford C, Panas R. Post-Infectious Irritable Bowel Syndrome with Functional Diarrhea Following C. difficile Infections: Case Studies of Responses using Serum-Derived Bovine Immunoglobulin. Gastro and Hepatology Res. 2015; 4(4):1577-1581. doi: 10.17554/j.issn.2224-3992.2015.04.483

Good L, Rosario R, Panas R. New therapeutic option for irritable bowel syndrome: Serum-derived bovine immunoglobulin: case study. World J Gastroenterol. 2015; 21: 3361-3366. doi: 10.3748/wjg.v21.i11.3361

Shafran I, Burgunder P, Young H. Nutritional Management of Refractory IBS-D Patients by the Medical Food Serum-Derived Bovine Immunoglobulin (SBI) in a 28-Patient Cohort. The James W. Freston Conference, Chicago, IL; August 29, 2015.

Arrouk R, Herdes R, Karpinski AC, Hyman PE. Serum-Derived Bovine Immunoglobulin (SBI) for Children with Diarrhea Predominant Irritable Bowel Syndrome (d-IBS). Ped Health Med Thera. 2018; In Press.

Good L, Shaw A, Wei D, Vasquez RE, et al. Oral serum bovine immunoglobulin improves IBS-D symptoms analyzed from patient medical charts. Biol Med Case Rep. 2017;1(1):16-23.

Rana A, Fernandez M, Wang Z, Hyams JS. Safety, Tolerability, and Efficacy of Serum-Derived Bovine Immunoglobulin in Children with Diarrhea-Predominant Irritable Bowel Syndrome. Gastroenterol. 2017;152(5):S652. doi: 10.1016/S0016-5085(17)32299-0

Shaw A, Tomanelli A, Bradshaw TP, et al. Impact of Serum-derived Bovine Immunoglobulin/Protein Isolate Therapy on Irritable Bowel Syndrome and Inflammatory Bowel Disease: A Survey of Patient Perspective. Patient Preference and Adherence. 2017; 11:1-7. doi: 10.2174/PPA.S134792

Valentin N, Camilleri M, Carlson P, et al. Potential mechanisms of effects of serum-derived bovine immunoglobulin/protein isolate therapy in patients with diarrhea-predominant irritable bowel syndrome. Physiol Rep. 2017;5(5). pii: e13170. doi: 10.14814/phy2.13170.

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

Awad A, Jasion VS. Use of a nutritional therapy, serum-derived bovine immunoglobulin/protein isolate (SBI), to achieve improvement in two different cases of colitis. Journal of Gastrointestinal Digestive Systems. 2015;5:2.doi: 10.4172/2161-069x.1000274

Beaurele BD, Burnett BP, Dryden GW. Successful management of refractory ulcerative colitis with orally administered serum-derived bovine immunoglobulin therapy. Clinical Case Reports and Reviews. 2015;1(4):90-92. doi: 10.15761/CCRR.1000130.

Frissora C, Shafran I, Silver S, et al. Clinical Management of Lymphocytic Colitis with Serum-Derived Bovine Immunoglobulin/Protein Isolate (SBI). Poster presented (#806) at ACG Annual Scientific Meeting, Honolulu, HI. October 19, 2015.

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. J Gastrointest & Dig Systems 2015; 5(2). doi: 10.4172/2161-069X.1000268

Good L, Burnett BP. Management of Loose, Frequent Stools and Fecal Incontinence in a Chronic Mesenteric Ischemia Patient with Oral Serum-Derived Bovine Immunoglobulin. Clin Med Insights: Gastroenterology. 2015; 8:7-11. doi: 10.4137/CGast.S21307

Shafran I, Burgunder P, Wei D, et al. Management of inflammatory bowel disease patients with oral serum-derived bovine immunoglobulin. Therapeutic Advances in Gastroenterology. 2015; 1-9. doi: 10.1177/ 1756283X15593693.

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.

Shafran I, Young HE, Wei D, et al. Pilot Pharmacoeconomic Analysis of Serum-derived Bovine Immunoglobu- lin Use in IBD. Am J Pharm Benents. 2016;8(2):e34-e41.

Soriano RA, Ramos-Soriano A. Clinical and Pathologic Remission of Pediatric Ulcerative Colitis with Serum-Derived Bovine Immunoglobulin Added to Standard Treatment Regimen. Case Reports Gastroenterol. 2017; 1-8. doi: 10.1159/000475923.

Tyson C, Shafran I, Hilal R, et al. Economic and clinical impact of serum-derived bovine immunoglobulin/ protein isolate (SBI) in the management of chronic diarrhea in inflammatory bowel disease (IBD). Value in Health. 2017; 20(9):A633-A634. doi: 10.1016/j.jval.2017.08.1432.

Good L, Panas R. Long-term management of pouchitis-associated diarrhea with the serum-derived bovine immunoglobulin/protein isolate. J Clin Exp Gastroenterol. 2018; In Press.

Liaquat H, Ashat M, Stocker A, et al. Efficacy of Serum Derived Bovine Immunoglobulin in Patients with Refractory Symptoms of Inflammatory Bowel Disease. Am J Med Sci. 2018; In Press.

Shafran I, Hilal R, Chalasani R, et al. Economic and Clinical Impact of Serum-derived Bovine Immunoglobulin / Protein Isolate (SBI) in Management of Inflammatory Bowel Disease. Clinical Therapeutics. 2018; In Press

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 Immunoglobulin Therapy. Poster presented (#842) at ACG Annual Scientific Meeting, Honolulu, HI. October 19, 2015.

Gilmore K, Burnett BP. Management of Fecal Incontinence in Patients Administered a Medical Food: Serum-Derived Bovine Immunoglobulin/Protein Isolate. Poster presented (#Tu1394) at 2016 DDW, San Diego, CA, May 22-24, 2016. doi: 10.1016/S0016-5085(16)33019-0

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.

Chronic Diarrhea with Other Conditions, Cachexia and Hepatic Studies

Hilal RE. A case of short bowel syndrome managed with a prescription medical food product, serum-derived bovine immunoglobulin/protein isolate (SBI). Presented at 2014 ACG Annual Scientific Meeting, Philadelphia, PA, October 17-22, 2014.

Hilal R, Young HE. Serum-Derived Bovine Immuno-globulin/Protein Isolate for the Management of Diarrhea Associated with Chronic Pancreatitis and Pancreatic Insufficiency: A Novel Approach. Poster presented (#756) at 2015 ACG Annual Scientific Meeting, Honolulu, HI. October 18, 2015.

LeVine M, Burnett BP, Good L. Management of Antibiotic-Associated Diarrhea after C. diffi cile Infection with Serum-Derived Bovine Immunoglobulin Preparation. Poster presented (#1731) at ACG Annual Scientific Meeting, Honolulu, HI. October 20, 2015.

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 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.

Chemotherapy-Induced Diarrhea

Arikapudi S, Rashid S, Al Almomani LA, et al. Serum bovine immunoglobulin for chemotherapy-in- duced gastrointestinal mucositis. Amer J Hospice and Palliative Med. 2017;1049909117735831. doi: 10.1177/1049909117735831

Pediatric Studies

Dave' M, Fourment C, Burnett BP. Resolution of Antibiotic-Induced and Idiopathic Diarrhea in Infants with a Serum-Derived Bovine Immunoglobulin Preparation. Poster session presented at Digestive Disease Week (DDW) 2015. Washington, D.C. May 16-19.

Dave' M, Burnett BP. Oral Serum-derived Bovine Immunoglobulin Therapy to Help Achieve Clinical Remission with Associated Decreases in Fecal Calprotectin in a Pediatric Ulcerative Colitis Patient. NASPGHAN Annual Mtg, Washington, D.C. Oct 7-11, 2015.

Dave' M, Burnett BP. N of 1 Spontaneous Trial Demonstrates Efficacy of Serum Bovine Immunoglobulin for Emesis (Potential Cyclic Vomiting) and Gastrointestinal Symptoms in an Autistic Patient. NASPGHAN Annual Mtg, Washington, D.C. Oct 7-11, 2015.

Taxman TL, Panas RM. Efficacy of Serum-derived Bovine Immunoglobulin/Protein Isolate (SBI) in Pediatric Patient with Acute Diarrhea Due to Small Intestinal Bacteria Overgrowth. Poster session presented at Digestive Disease Week (DDW). Washington, D.C. May 16-19, 2015.

Infection-Associated Chronic Diarrhea

Asmuth D, Ma Z-M, Albanese A, et al. Oral serum-derived bovine immunoglobulin improves duodenal immune reconstitution and absorption function in patients with HIV enteropathy. AIDS 2013; 27(14):2207-2217. doi: 10.1097/QAD.0b013e328362e54c

Asmuth DM, Ursell L, Ma Z-M, et al. Duodenal Lamina Propria CD4+ T-lymphocyte (CD4+ LPL) Increases following Oral Serum-Derived Bovine Immunoglobulin (SBI) Administration Leads to Reduced Enterocyte Damage and Improved Collagen Turnover in HIV-Enteropathy. Presented at the 53rd Interscience Conference on Antimicrobial Agents and Chemotherapy. September 10-13, 2013, Denver, CO.

Ursell L, Siewe B, Sandler N, et al. Serum-Derived Bovine Immunoglobulin (SBI)-Induced Changes in Stool Microbiota Correlate with Levels of Bacterial Translocation (BT) and Reduced Mucosal Damage. Presented at the 53rd Interscience Conference on Antimicrobial Agents and Chemotherapy. September 10-13, 2013, Denver, CO.

Asmuth D, Somsouk M, Hunt P, et al. Serum-derived bovine immunoglobulin isolate increases peripheral and mucosal CD4+ T-cell counts. (poster) 2015 Amer Assoc of Immunologists (AAI); New Orleans, LA, May 8-12, 2015.

Asmuth DM, Somsouk M, Hunt P, et al. Serum-Derived Bovine Immunoglobulin Protein Isolate Increases Peripheral and Mucosal CD4+ T-cell counts in Patients with HIV Enteropathy. Oral presentation at IAS 2015; Vancouver, BC, July 19-22, 2015.

Asmuth D, Sandler-Utay N, Somsouk M, et al. Oral Bovine Immunoglobulin Reduces Immune Activation in HIV+ Non-Responders. Poster presented at IAS 2016; Boston, MA, Feb 22-25, 2016.

Asmuth DM, Hinkle JE, La Marca A, et al. Evaluation of Oral Serum-Derived Bovine Immunoglobulins in Patients with HIV-Associated Enteropathy. HIV Clinical Trials, 2017;18(5-6):205-213.

Ferm S, Varadi N, Fisher C, Gutkin E. Serum-derived bovine immunoglobulin as novel adjunct in complicated *Clostridium difficile* colitis treatment. *ACG Case Rep J.* 2017;4:e64. doi: 10.14309/crj.2017.64.

Gelfand MS, Cleveland KO. Oral serum-derived bovine immunoglobulin for management of infectious diarrhea due to norovirus and cryptosporidiosis in solid organ transplant patients. Infect Dis Clin Practice. 2017; 25(4):218-220. doi: 10.1097/IPC.0000000000000479

Kumar V, Zhou E, Yuliya A, et al. Serum Derived Bovine Immunoglobulin (SBI) Is Safe and Well Tolerated in Patients with Recurrent C. difficile Infection (RCDI) Treated Medically. Poster presented (P100) at ACG Annual Scientific Meeting, Orlando, FL. October 15, 2017.

Silver HS, Burnett BP. C. difficile infection (CDI) unresponsive to antibiotics resolved by co-administration of serum-derived bovine immunoglobulin/protein isolate, a nutritional support product: A case study. Adv Res Gastroenterol Hepatol. 2017;6(2): ARGH.MS.ID.555685.

Zhou E, Kumar V, Yuliya A, et al. Serum Derived Bovine Immunoglobulin (SBI) Is Safe and Well Tolerated in Patients Undergoing Fecal Microbiota Transplant (FMT) for Recurrent C. difficile Infection (RCDI). Poster presented (P99) at ACG Annual Scientific Meeting, Orlando, FL. October 15, 2017.

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

HOW SUPPLIED / STORAGE AND HANDLING

†Product #	Description	Size
53703-100-03	ENTERAGAM Commercial Product	30 packets per carton
53703-100-11	ENTERAGAM Professional Samples *NOT FOR SALE*	30 packets per carton

†Entera Health, Inc. does not represent this product code to be a National Drug Code (NDC) number. Instead, Entera Health has assigned a product code formatted according to standard industry practice to meet the formatting requirements of pharmacy and health insurance computer systems.

Store packets at 20-25°C (68-77°F): excursions permitted between 15-30°C (59-86°F). [see USP Controlled Room Temperature]

Manufactured by:
Entera Health, Inc.
Ankeny, Iowa 50021

Entera Health®

REFERENCES

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

For more information, visit www.EnteraGam.com or cal: 1-800-436-8372. ENT.PL001.USA.20 Rev. 02/2020