

## HIGHLIGHTS OF PRESCRIBING INFORMATION

**VISBIOME™ EXTRA STRENGTH** (*L. acidophilus* DSM24735, *L. plantarum* DSM24730, *L. paracasei* DSM24733, *L. delbrueckii* subsp. *bulgaricus* DSM24734, *S. thermophilus* DSM24731, *B. longum* DSM24736, *B. breve* DSM24732, *B. infantis* DSM24737)

Live, lyophilized, probiotic cultures for oral administration.

**VISBIOME EXTRA STRENGTH is a medical food as defined by the Orphan Drug Act. Physician supervision required.**

### Dispense By Prescription

#### RECENT MAJOR CHANGES

Reference Section	8/2016
Intended Use	8/2016

#### INTENDED USE

VISBIOME EXTRA STRENGTH is a medical food intended for the dietary management of dysbiosis associated with irritable bowel syndrome (IBS), ulcerative colitis (UC), pouchitis, and hepatic encephalopathy (HE). VISBIOME EXTRA STRENGTH is a non-drug therapy that addresses distinct nutritional requirements, to promote microbial balance in people with IBS, UC, pouchitis, and HE that cannot be addressed by modification of the diet alone.

#### DOSAGE AND ADMINISTRATION

- Mix into 3-6 oz. cold water or any cold, non-carbonated beverage
- Stir contents until mixed
- Promptly drink all contents (mixture may settle on bottom of glass over time)
- Alternatively, the product can be mixed with cold food such as yogurt or applesauce.
- Adjustment of the intestinal flora can take a few days or weeks; it may take up to one month for the colonization of the gut to become optimally stable, if consumed on a regular basis.

#### DOSAGE FORM AND STRENGTH

Each packet contains 900 billion ( $900 \times 10^9$ ) colony forming units (CFUs) of probiotic bacterium. Inactive ingredients: maltose and silicon dioxide.

#### CONTRAINDICATIONS

VISBIOME EXTRA STRENGTH should not be used in premature infants in the Neonatal Intensive Care Unit (NICU) setting.

#### WARNINGS AND PRECAUTIONS

VISBIOME EXTRA STRENGTH contains milk. VISBIOME EXTRA STRENGTH may contain trace amounts of lactose (less than 0.1 g per 100 g) and dehydrated skim milk or milk protein (casein and beta-lacto globulin of less than 2 mg/kg).

#### ADVERSE REACTIONS

Mild abdominal bloating has been occasionally reported during the first few days of consuming VISBIOME EXTRA STRENGTH. This is generally a readjustment of the microflora, which usually diminishes within 3-4 days. If bloating persists, the patient should reduce their intake for a few days.

**To report SUSPECTED ADVERSE REACTIONS, contact EXEGI PHARMA, LLC at 1-844-FIT-GUTS (1-844-348-4887) or the FDA at 1-800-FDA-1088 (1-800-332-1088) or [www.fda.gov/medwatch](http://www.fda.gov/medwatch)**

#### DRUG INTERACTIONS

There are no known adverse drug interactions associated with consumption of VISBIOME EXTRA STRENGTH. The bacterium in VISBIOME EXTRA STRENGTH may be inactivated by certain antibiotics. Do not consume VISBIOME EXTRA STRENGTH within four (4) hours of taking antibiotics.

#### USE IN SPECIFIC POPULATIONS

The probiotic formulation in VISBIOME EXTRA STRENGTH has been the subject of studies in adults and children between the ages of 1.7 - 17 years. If you are pregnant or nursing, please consult with your healthcare provider.

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## FULL PRESCRIBING INFORMATION

### 1. INTENDED USE

1.1 VISBIOME EXTRA STRENGTH is a specially formulated probiotic medical food for the dietary management of dysbiosis associated with irritable bowel syndrome (IBS), ulcerative colitis (UC), pouchitis, and hepatic encephalopathy (HE). Visbiome is a non-drug therapy that addresses distinct nutritional requirements, to promote microbial balance in people with IBS, UC, pouchitis, and HE that cannot be addressed by modification of the diet alone.

1.2 VISBIOME EXTRA STRENGTH is intended for the clinical dietary management of patients, who because of therapeutic or chronic medical needs, have special medically determined nutrient requirements, the dietary management of which cannot be achieved by the modification of the normal diet alone.

**VISBIOME EXTRA STRENGTH, as a medical food, must be used under physician supervision.**

**VISBIOME EXTRA STRENGTH is dispensed by prescription.**

### 2. DOSAGE AND ADMINISTRATION

FOR ORAL ADMINISTRATION. Consume ¼ to 4 packets daily as directed by your physician. VISBIOME EXTRA STRENGTH can be mixed into cold water or any cold, non-carbonated beverage and consumed promptly. Adjustment of the intestinal flora can take a few days or weeks; it may take up to one month for the colonization of the gut to become optimally stable, if consumed on a regular basis.

Recommended daily intake for Adults – Consult with your physician	
For the Dietary Management of:	Packets Per Day**
Irritable Bowel Syndrome	¼ - ½ (225 - 450 billion)
Hepatic Encephalopathy	½ - 1 (450 - 900 billion)
Ulcerative Colitis (maintenance)	½ - 1 (450 - 900 billion)
Pouchitis (maintenance or prevention)	1 - 2 (900 - 1,800 billion)
Active Ulcerative Colitis (flaring)	2 - 4 (1,800 - 3,600 billion)

\*\* Each Packet Contains 900 Billion Live Bacteria (Colony Forming Units – CFUs)

### 3. DOSAGE FORMS AND INGREDIENTS

#### 3.1 DOSAGE FORM:

VISBIOME EXTRA STRENGTH is a powder consisting of eight (8) strains of live, lyophilized, probiotic bacteria. Each packet contains at least 900 billion ( $900 \times 10^9$ ) colony forming units (CFUs).

VISBIOME EXTRA STRENGTH is soluble in water. Each carton of VISBIOME EXTRA STRENGTH contains 30 packets.

#### 3.2 INGREDIENTS:

VISBIOME EXTRA STRENGTH contains a proprietary blend of live, lyophilized, probiotic bacteria - *Lactobacillus acidophilus* DSM24735™, *lactobacillus plantarum* DSM24730™, *lactobacillus paracasei* DSM24733™, *lactobacillus delbrueckii* subsp. *bulgaricus*\* DSM24734™, *streptococcus thermophilus* DSM24731™, *bifidobacterium longum*± DSM24736™, *bifidobacterium breve* DSM24732™, *bifidobacterium infantis*± DSM24737™.

±Recently reclassified as *Bifidobacterium lactis*

\*Recently reclassified as *Lactobacillus helveticus*

Other Ingredients: – VISBIOME EXTRA STRENGTH contains the following inactive ingredients: maltose and silicon dioxide.

The designation numbers for the strains in Visbiome are trademarks of ExeGi Pharma, LLC.

### 4. CONTRAINDICATIONS

VISBIOME EXTRA STRENGTH should not be used in premature infants in the Neonatal Intensive Care Unit (NICU) setting.

## 5. WARNINGS AND PRECAUTIONS

- VISBIOME EXTRA STRENGTH contains milk.
- VISBIOME EXTRA STRENGTH may contain trace amounts of lactose (less than 0.1 g per 100 g) and dehydrated skim milk or milk protein (casein and beta-lacto globulin of less than 2 mg/kg).

### Allergens:

The table below indicates the presence (as added component) of the following allergens and products thereof:

Yes	No	Allergen	Description
	X	Wheat	
	X	Other cereals containing gluten	
	X	Crustacean shellfish	
	X	Eggs	
	X	Fish	
	X	Peanuts	
	X	Soybeans	
X		Milk (including lactose)	Used as fermentation nutrient
	X	Nuts	
	X	Celery	
	X	Mustard	
	X	Sesame seeds	
	X	Sulfur dioxide and sulfites (> 10 mg/kg)	
	X	Lupine	
	X	Mollusks	

## 6. ADVERSE REACTIONS

Mild abdominal bloating has been reported occasionally during the first few days of consuming VISBIOME EXTRA STRENGTH. This is generally a readjustment of the microflora, which usually diminishes within 3 - 4 days. If bloating persists, the patient should reduce their intake for a few days and consult with their physician.

## 7. DRUG INTERACTIONS

There are no known adverse drug interactions associated with consumption of VISBIOME EXTRA STRENGTH. Some strains of bacterium in VISBIOME EXTRA STRENGTH may be inactivated by certain antibiotics. Do not consume VISBIOME EXTRA STRENGTH within four (4) hours after taking antibiotics.

## 8. USE IN SPECIFIC POPULATIONS

The probiotic formulation in VISBIOME EXTRA STRENGTH has been the subject of studies in adults and children between the ages of 1.7 - 17 years. If you are pregnant or nursing, please consult with your healthcare provider.

## 9. SAFETY AND OVERDOSAGE

Probiotics have a long history of safe use, having been consumed for health benefit and as part of fermented foods for millennia.<sup>1,2,3,4</sup> Many bifidobacteria and lactobacilli species are normal, nonpathogenic inhabitants of the human gastrointestinal tract, oral cavity, skin, and vagina.<sup>1,2,5,6</sup> Documented cases of infection attributable to probiotic intake are limited to individual case reports, primarily associated with the use of probiotics in severely immunocompromised patients, , but never reported for VISBIOME EXTRA STRENGTH.

The probiotic bacteria in VISBIOME EXTRA STRENGTH are non-pathogenic, non-toxicogenic and Generally Recognized as Safe (GRAS) as food ingredients.

The De Simone Formulation in VISBIOME EXTRA STRENGTH has been the subject of over 60 clinical studies involving over 3,900 adult and pediatric patients (ages 1.7 - 17). The most common reported adverse events are abdominal bloating and/or gas, generally reported within the first few days of probiotic consumption.

VISBIOME EXTRA STRENGTH has been administered in clinical evaluation in daily dosages of up to 3,600 billion ( $360 \times 10^{10}$ ) colony forming units (CFUs) per day for 12 weeks.

## 10. MEDICAL FOOD STATUS

The Orphan Drug Act of 1988 defines “medical food” as “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” 21 U.S.C. 360ee(b)(3). FDA regulations 21 C.F.R. 101.9(j)(8) set forth additional criteria for makers of medical food products.

VISBIOME EXTRA STRENGTH is a medical food as defined by the Orphan Drug Act and additional FDA regulations. VISBIOME EXTRA STRENGTH is specially formulated and processed to provide a precise mixture of certain bacterial species to the gastrointestinal tract. The gastrointestinal microflora, or “microbiome”, is important for the normal functioning of the human gastrointestinal tract.<sup>7,8,9</sup> Patients with irritable bowel syndrome (IBS), ulcerative colitis (UC), and pouchitis have documented deficiencies in luminal concentrations of lactobacilli and bifidobacteria compared with healthy individuals.<sup>10,11,12,13,14,15</sup> In addition, frequent and/or long-term use of antibiotic treatment in these patient populations can further exacerbate deficiencies in the microbiome. Likewise, the gut microbiome of patients with hepatic encephalopathy (HE), and associated liver conditions such as cirrhosis, have been shown to be significantly altered compared to controls.<sup>16,17,18,19,20,21</sup> For example, in patients with liver cirrhosis, differences in colonic mucosal microbiota are found in patients with the cirrhosis plus HE versus those with cirrhosis without HE.

IBS, UC, pouchitis, and HE patients, thus, have distinct nutritional requirements that differ from the general population and thus require the consumption of high levels of probiotic bacteria to maintain an adequate and balanced microflora. In these patients, sufficient adjustment of the microflora cannot be achieved through modification of the normal diet.

VISBIOME EXTRA STRENGTH is intended for those with irritable bowel syndrome (IBS), ulcerative colitis (UC), pouchitis, or hepatic encephalopathy (HE) who are receiving active and ongoing medical supervision with regular instruction on the use of medical foods.

## 11. CLINICAL DATA

VISBIOME EXTRA STRENGTH was created by Professor Claudio De Simone M.D. Over 25 years ago, Professor De Simone invented a proprietary blend of probiotic strains and collaborated with VSL Pharmaceuticals, Inc. to market the invention as “VSL#3®” a trademark owned by VSL Pharmaceuticals, Inc. In 2014, Professor De Simone decided to leave VSL Pharmaceuticals and is now collaborating with ExeGi Pharma, LLC to produce VISBIOME EXTRA STRENGTH, a probiotic using the same proprietary blend of probiotic strains that De Simone originally invented.

VISBIOME EXTRA STRENGTH contains the same strains in the same concentrations and proportions, and is therapeutically equivalent to, the VSL#3® probiotic as produced before January 31, 2016. *VSL#3® is a registered trademark and is manufactured exclusively for, VSL Pharmaceuticals, Inc. Visbiome is manufactured exclusively for ExeGi Pharma, LLC and is not affiliated with, endorsed by, or distributed by VSL Pharmaceuticals, Inc. ExeGi Pharma, LLC and VSL Pharmaceuticals, Inc. are different companies and have no affiliation with each other.*

VISBIOME EXTRA STRENGTH is produced in the U.S. using dairy ingredients. In August 2016, VSL Pharmaceuticals announced that they moved the production of VSL#3 probiotic from the U.S. to Italy, and declared that they had eliminated any trace of dairy in the manufacturing process.

ExeGi takes the position that all studies performed on the VSL#3 product, manufactured using dairy ingredients, are relevant to the evaluation of the efficacy and safety of VISBIOME EXTRA STRENGTH.

### 11.1 Clinical Experience - Irritable Bowel Syndrome (IBS) Dietary Management

The De Simone Formulation has been the subject of over 60 published clinical trials in human subjects, with extensive clinical research in the dietary management dysbiosis associated with irritable bowel syndrome (IBS), ulcerative colitis (UC), pouchitis, and hepatic encephalopathy (HE).

The De Simone Formulation has been the subject of clinical trials involving over 250 adult and pediatric patients in the dietary management of dysbiosis associated with IBS.<sup>22,23,24,25</sup> In one study, 25 patients with diarrhea-predominant IBS received placebo or the De Simone Formulation for eight weeks. Patients receiving the probiotic experienced a statistically significant reduction in abdominal bloating.<sup>23</sup> In a second study, 48 patients with Rome II IBS were randomized in a double-blind design to the probiotic or placebo. Patients receiving the De Simone Formulation experienced a statistically significant reduction in flatulence (p=0.01).<sup>22</sup> The De Simone Formulation was well tolerated with no adverse events reported in either IBS studies.

### 11.2 Clinical Experience - Ulcerative Colitis (UC) Dietary Management

The De Simone Formulation has been the subject of published clinical studies in ulcerative colitis involving nearly 500 adult and 47 pediatric patients.<sup>26,27,28,29,30</sup> In these studies, the daily consumption of the De Simone Formulation was associated with effective dietary management of ulcerative colitis.

In one study, involving 90 adult patients, the De Simone Formulation plus low-dose balsalazide was compared to balsalazide, or mesalamine alone in the dietary management of acute ulcerative colitis. The De Simone Formulation plus low-dose balsalazide was superior to balsalazide and mesalamine alone in achieving dietary management of remission (85.7% vs. 80.8% vs. 72.7%;  $p < 0.02$ ), with improved time to remission (4 days vs. 7.5 vs. 13;  $p < 0.001$ ).<sup>27</sup> In a second study involving 32 adult patients with acute UC, dietary management with the De Simone Formulation resulted in a combined 77% remission/response rate with no adverse effects, as measured by UCDAI score (53% remission, 24% response).<sup>26</sup>

In the dietary management of ulcerative colitis (UC), the De Simone Formulation was also shown to help achieve remission when added to standard therapies (mesalazine, azathioprine, or 6-mercaptopurine). In a multicenter, randomized, double-blind, placebo-controlled trial ( $n=147$ ) patients consuming the De Simone Formulation had significantly higher remission rates vs. placebo (43% vs. 16%;  $p < 0.001$ ). In the same study, UCDAI scores showed a significant decrease by 50% from baseline ( $p < 0.001$ ).<sup>29</sup>

### 11.3 Clinical Experience - Pouchitis Dietary Management

In three double-blind, placebo-controlled trials and one open trial, the De Simone Formulation has been shown to aid in the dietary management of pouchitis.<sup>31,32,33</sup> In Gionchetti *et al.* (2000), 40 patients with chronic relapsing pouchitis were randomized to the probiotic or placebo after one month of antibiotic treatment. In the dietary management of remission 20 patients consuming the probiotic were still in remission after nine months compared to zero in the placebo group ( $p < 0.001$ ).<sup>31</sup> The formulation found in VISBIOME EXTRA STRENGTH is recognized as an effective tool for the dietary management of pouchitis by the American College of Gastroenterology,<sup>34</sup> German Association of Gastroenterology,<sup>35</sup> the British Society of Gastroenterology,<sup>36</sup> the European Crohn's and Colitis Organization (ECCO)<sup>37</sup>, and The Cochrane Collaboration.<sup>38</sup>

### 11.4 Clinical Experience - Hepatic Encephalopathy (HE) Dietary Management

In the dietary management of dysbiosis associated with hepatic encephalopathy (HE), the De Simone Formulation has been the subject of multiple controlled clinical studies involving over 750 patients.<sup>39,40,41,42</sup> In one placebo-controlled trial involving 160 cirrhotic patients, those consuming the De Simone Formulation for dysbiosis experienced a reduced incidence of HE, reduced ammonia levels, and improvements in psychometric test compared to controls. Seven patients in the probiotic group experienced overt HE vs. 14 in the control group ( $p < 0.05$ ).<sup>42</sup> In a second study, 235 cirrhotic patients who had prior episodes of HE were evaluated after consuming the De Simone Formulation, lactulose or no therapy. There was a significant difference in the development HE in the probiotic vs. no treatment groups ( $p = 0.02$ ) and in the lactulose vs. no treatment group ( $p = 0.001$ ) but no difference between the probiotic group vs. lactulose ( $p = 0.134$ ).<sup>40</sup>

### 11.5 Clinical Experience - Pediatric

The De Simone Formulation was the subject of two trials involving patients between the ages of 1.7 and 17 years of age with active ulcerative colitis (UC). In one trial, 29 patients were randomized to receive dietary management with the De Simone Formulation or placebo concomitantly with standard UC treatment (steroids, 5-ASA). Of the 29 patients (92.8%) of those treated with the De Simone Formulation and standard therapy achieved remission vs. four patients (36.4%) in placebo arm ( $p < 0.001$ ). In addition, 21.4% of patients consuming the De Simone Formulation and standard UC therapy and 73.3 % patients consuming placebo and standard therapy relapsed within 1 year of follow-up ( $p = 0.014$ ). At six months, 12 months, or at time of relapse, endoscopic and histological scores were lower in the probiotic group than in placebo group.<sup>29</sup>

In a second study in pediatric patients with mild to moderate acute UC, the De Simone Formulation was administered open-label for eight weeks. 13 patients (56%) achieved remission and the combined remission/response rate was 61%.<sup>43</sup>

A third open-label study was conducted in 59 pediatric patients with irritable bowel syndrome (IBS). In this study, probiotics reduced the intensity and frequency of abdominal pain and bloating after six weeks.<sup>44</sup>

## 12. HOW SUPPLIED/STORAGE AND HANDLING

- VISBIOME EXTRA STRENGTH is a light colored powder consisting of  $900 \times 10^9$  (900 billion) probiotic bacteria per packet.
- VISBIOME EXTRA STRENGTH contains a proprietary blend of live, lyophilized, probiotic bacteria - *Lactobacillus acidophilus* DSM24735™, *lactobacillus plantarum* DSM24730™, *lactobacillus paracasei* DSM24733™, *lactobacillus delbrueckii* subsp. *bulgaricus*\* DSM24734™, *streptococcus thermophilus* DSM24731™, *bifidobacterium longum*<sup>±</sup> DSM24736™, *bifidobacterium breve* DSM24732™, *bifidobacterium infantis*<sup>±</sup> DSM24737™
- VISBIOME EXTRA STRENGTH is soluble in water.
- VISBIOME EXTRA STRENGTH is shipped and stored cold to ensure maximum potency (39 - 46° F / 4 - 8° C)
- VISBIOME EXTRA STRENGTH can be stored at room temperature for up to one week without adversely impacting potency
- VISBIOME EXTRA STRENGTH contains the following inactive ingredients: maltose and silicon dioxide.
- Each carton of VISBIOME EXTRA STRENGTH contains 30 packets.

Product Code	Carton Size
69355-0516-01	30 packets per carton

Store at (39 - 46° F / 4 - 8° C). Do not freeze.

<sup>‡</sup>Recently reclassified as *Bifidobacterium lactis*

<sup>\*</sup>Recently reclassified as *Lactobacillus helveticus*

The designation numbers for the strains in Visbiome are trademarks of ExeGi Pharma, LLC.

### 13. DAIRY, GLUTEN, AND KOSHER STATUS

- **Dairy Status** - Contains milk. VISBIOME™ EXTRA STRENGTH may contain trace amounts of lactose (less than 0.1 g per 100 g) and dehydrated skim milk or milk protein (casein and beta-lacto globulin of less than 2 mg/kg).
- **Gluten Status** - VISBIOME™ EXTRA STRENGTH is gluten free.
- **Halal Status** - VISBIOME™ EXTRA STRENGTH is Halal certified.
- **Kosher Status** - VISBIOME™ EXTRA STRENGTH is Kosher certified.

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