VSL#3®
THE LIVING SHIELD®

PRODUCT INFORMATION SHEET

VSL#3® is a probiotic medical food intended for the dietary management of Irritable Bowel Syndrome (IBS) [1-3], Ulcerative Colitis (UC)[4-8] or an ileal pouch[9-11].

Description

VSL#3® is a potent probiotic medical food formulated to provide a mixture of 8 individual strains of live, freeze-dried lactic acid bacteria per packet or capsule. VSL#3® is available in 3 different concentrations.

a) VSL#3® Capsules: 112.5 billion CFU* per capsule
b) VSL#3® Unflavored: 450 billion CFU* per packet
c) VSL#3® Double Strength (DS): 900 billion CFU* per sachet

**CFU, colony-forming units.*

VSL#3® products are manufactured in accordance with Current Good Manufacturing Practice for foods, using ingredients that are listed by the U.S. Food and Drug Administration (FDA) as food or food additives, or are "Generally Recognized as Safe" (GRAS)[56] food substances. The lactic acid bacteria in VSL#3® have a long history of use in foods[15,34].

Directions

VSL#3® can be mixed with any cold, noncarbonated beverage and then consumed. VSL#3® can also be mixed into any cold food such as yogurt, ice cream, or applesauce, and then consumed. VSL#3® should be taken as directed by a physician. Adjustment of the intestinal flora can take a few days or weeks; it may take up to 1 month for the colonization of the gut to become optimally stable. Heated beverages are not recommended because exposure to heat and moisture may reduce bacterial viability and activity.

Lactic acid bacteria (8 strains of probiotic bacteria)

- *L. acidophilus*
- *L. plantarum*
- *L. paracasei*
- *L. delbrueckii subsp. bulgaricus***
- *S. thermophilus*
- *B. longum**
- *B. breve*
- *B. infantis**

*Reclassified as *B. lactis*
**Reclassified as *L. helveticus*

All ingredients

a) VSL#3® Capsules: Lactic acid bacteria, hydroxylpropylmethylcellulose (HPMC vegetarian capsule), cornstarch, magnesium stearate, silicon dioxide, stearic acid, microcrystalline cellulose.
b) VSL#3® Unflavored Packets: Lactic acid bacteria, cornstarch, silicon dioxide.
b) VSL#3® DS sachets: Maltose, lactic acid bacteria, cornstarch, silicon dioxide.

Allergen Status

All formulations of VSL#3® contain none of the following: wheat, gluten (other cereals), soy, milk (including lactose), crustacean shellfish, eggs, peanuts, nuts, fish, celery, mustard, sesame seeds, sulfur dioxide and sulfites (>10 mg/kg), lupin, mollusks. VSL#3® contains cornstarch, an inactive ingredient, which is generally well-tolerated.

GMO Status

All formulations of VSL#3® do not consist of, nor contain, nor are produced from genetically modified organisms according to the definitions of Regulation (EC) 1829/2003 and Regulation (EC) 1830/2003 of the European Parliament and the Council of 22 September 2003.

All formulations of VSL#3® are Kosher and Halal-certified.

Probiotic Medical Food

As a probiotic medical food, VSL#3® is specially formulated and processed to provide a precise mixture of certain bacterial species with potential synergistic relationships. The importance of the gastrointestinal microflora in the normal functioning of the human gastrointestinal tract is well recognized[12-15]. Several studies demonstrate that patients with IBS, UC or an ileal pouch have decreased luminal concentrations of lactobacilli and bifidobacteria compared with healthy individuals[16-23]. Patients with IBS, UC or an ileal pouch may benefit from consuming high levels of probiotic bacteria so as to maintain the appropriate quantity and balance of beneficial microflora in their gastrointestinal tract. This is particularly important for patients with UC or an ileal pouch in view of their frequent and often long term antibiotic treatment. Hence, IBS, UC and ileal pouch patients have a distinct nutritional requirement that differs from normal individuals. Daily consumption of high levels of probiotic bacteria is needed to maintain adequate and balanced colonization in the gastrointestinal tract, and this cannot be achieved simply by modification of the normal diet.

VSL#3® is for the dietary management of IBS, UC or ileal pouch patients under the care of a physician.

Interactions with other medications

VSL#3® is believed to be compatible with most types of drugs. If taken with antibiotics, VSL#3® should be consumed in-between antibiotic doses thereby maximizing the probiotic effect.

Side Effects

Mild abdominal bloating has been reported in the first few days of consuming VSL#3®. This is usually a transitory phenomenon due to the changing intestinal microflora. If you experience bloating, you may need to reduce your daily intake to allow for this adjustment. Please report any unexpected reaction after starting VSL#3® to Alfasigma USA, Inc. by calling (toll free) (866) 634-2765.

Precautions

Please keep this product out of reach of children. Pregnant or lactating women should consult with a physician or healthcare professional before using this or any other medical food product.

Clinical Experience

VSL#3® has been the subject of extensive clinical research in the dietary management of IBS, UC and an ileal pouch. In one study, the consumption of VSL#3® was associated with a 39% reduction in bloating in patients with diarrhea-predominant IBS[2]. In the same study, fecal urgency scores showed a trend toward reduction vs. placebo. In a second study, the consumption of VSL#3® was associated with reduced flatulence (gas) by 25% vs. placebo [3]. In both IBS studies, the consumption of VSL#3® was well tolerated with no adverse events reported. In a pediatric IBS study[1], the consumption of VSL#3® was significantly superior to placebo ($p < 0.05$) in the primary endpoint, the subjective assessment of relief of symptoms; as well as in 3 of 4 secondary endpoints: abdominal discomfort ($p < 0.05$), abdominal bloating/gassiness ($p < 0.05$), and family assessment of life disruption ($p < 0.01$). No significant difference was found ($p < 0.06$) in the stool pattern. No untoward adverse effect was recorded in any of the patients. The World Gastroenterology Organization Global Guideline for Irritable Bowel Syndrome, April 2009 states that VSL#3® has "clinical trial evidence of efficacy for bloating, distension, and flatulence"[24]. Published studies[4-8] suggest that daily ingestion of VSL#3® can aid in the dietary management of UC in both adults and pediatric patients. These studies have also demonstrated that VSL#3® can be utilized along with standard pharmaceutical UC therapies such as 5-ASA, immunosuppressants, immunomodulatory drugs and steroids[4,5,8]. An adult study concluded that 77% of the patients consuming VSL#3® in the dietary management of active UC had a positive response to the product with no adverse events[6]. In a second study with VSL#3® in dietary management of adult UC patients intolerant or allergic to 5-ASA, 75% of patients had a positive response to the product for 12 months[7]. A pediatric study looked at maintenance of remission in children aged between 2 and 16, with UC[4]. All 29 patients responded to the inflammatory bowel disease (IBD) therapy. Remission was achieved in 13 children (92.8%) treated with traditional IBD therapy and VSL#3® and in 4 children (36.4%) treated with placebo and traditional IBD therapy ($P<0.001$). Overall, 3 of 14 (21.4%) children treated with traditional IBD therapy and VSL#3® and 11 of 15 (73.3%) children treated with placebo and traditional IBD therapy relapsed within 1 year of follow-up ($P=0.014$; RR=0.32; CI=0.025-0.773; NNT=2). Of the relapsed children, all 3 children treated with VSL#3® and 6 of 11 (54.5%) children treated with placebo relapsed within 6 months of diagnosis. At 6 months, 12 months, or at time of relapse, endoscopic and histological scores were significantly lower in the VSL#3® group than in the placebo group ($P<0.05$). There were no biochemical or clinical adverse events related to VSL#3®. In a second pediatric study, 13 of 18 children completed 8 weeks of VSL#3® treatment and 5 patients were withdrawn due to lack of improvement[5]. Remission (defined as SCCAI ≤3) was achieved in 56% of children (n = 10); response (decrease in SCCAI ≥2, but final score ≤5) in 6% (n = 1); and no change or worsening in 39% (n = 7). Post-VSL#3® treatments demonstrated a bacterial taxonomy change in rectal biopsy. VSL#3® was well tolerated in clinical trials and no biochemical and clinical adverse effects attributed to VSL#3® were identified. The American Academy of Pediatrics in its "Clinical Report - Probiotics & Prebiotics in Pediatrics" 2010 mentions VSL#3® as showing 'promising results' for children with UC[25]. VSL#3® is also recognized for the dietary management of UC in the following guidelines: WGO Global Guidelines October, 2011 - Probiotics and Prebiotics[26]; the European Crohn's and Colitis Organization (ECCO) and the European Society of Pediatric Gastroenterology Hepatology and Nutrition (ESPGHAN - Management of Pediatric Ulcerative Colitis: Joint ECCO and ESPGHAN Evidence-Based Consensus Guidelines, September, 2012[27]; and the Second European evidence-based Consensus on the diagnosis and management of ulcerative colitis part 2: Current management[28]. Three doubleblind, placebo-controlled trials have been published that show that VSL#3® aids in the dietary management of pouchitis[9-11]. VSL#3® is the only probiotic recognized as an effective tool for the dietary management of pouchitis by The American College of Gastroenterology April, 2010[29]. The use of VSL#3® for the dietary management of pouchitis is also mentioned in the German Society of Digestive and Metabolic Diseases, 2004[30]; The British Society of Gastroenterology, 2011[31]; WGO Global Guidelines October, 2011 - Probiotics and Prebiotics[26] and the Cochrane Library, June 2010 in its review of the use of probiotics for the dietary management of pouchitis[32]. A recent meta-analysis looked at of the effect of probiotics in remission of UC and in maintaining of therapy in UC and pouchitis. Only VSL#3® maintained remission rates compared to controls in patients with active UC. VSL#3® significantly reduced the clinical relapse rates for maintaining remission in patients with pouchitis[33].

Recommended Daily Intake

Adult intake: VSL#3® is designated for the dietary management of UC, an ileal pouch and IBS. Daily intake ranges from 225 to 3,600 x 10^9 CFU. Consuming VSL#3® has been shown to aid in the dietary management of UC in both adults and pediatric patients. VSL#3® has been found useful following IPAA surgery for UC. It has also been shown to reduce symptoms in mild pouchitis, and to reduce relapse of pouchitis symptoms following antibiotic-induced remission. VSL#3® may also decrease bloating and flatulence in patients with IBS.

Table 1: Adult Recommended Daily Intake[2,3,6-11,55]

For the Dietary Management of	VSL#3® Capsules (112.5 Billion CFU/ capsule)	VSL#3® Unflavored (450 Billion CFU/pkt)	VSL#3®DS (900 Billion CFU/ sachet)
Irritable bowel syndrome	2-4 (225-450)	0.5-1 (225-450)	N/A
Ulcerative colitis (maintenance)	4-8 (450-900)	1-2 (450-900)	0.5 -1 (450-900)
Pouchitis	N/A	2-4 (900-1800)	1-2 (900-1800)
Active ulcerative colitis (flaring)	N/A	4-8 (1800-3600)	2-4 (1800-3600)

CFU, colony-forming units; N/A, not applicable.

Pediatric Intake: VSL#3® is also designated for the dietary management of UC or IBS in children. VSL#3® was the first probiotic medical food to be utilized in a pediatric, randomized, placebo-controlled, double-blind, crossover trial that suggested the safety and efficacy of a highly concentrated mixture of probiotic bacterial strains in active UC and demonstrated its role in maintenance of remission[4].

For children, the amount consumed per day varies by age, weight and clinical study[6-11, 55].

Table 2: Pediatric Recommended Daily Intake

Recommended intake by age (in years)	Dietary Management of active (flaring) ulcerative colitis (Billion CFU)		
	VSL#3® Capsules	**VSL#3® Unflavored**	**VSL#3®DS**
≤ 5	1-2 (112-225)	N/A	N/A
6-11	4-8 (450-900)	1-2 (450-900)	0.5-1 (450-900)
12-17	8-16 (900-1800)	2-4 (900-1800)	1-2 (900-1800)
Recommended intake by age (in years)	**Dietary Management (maintenance) of ulcerative colitis (Billion CFU)**		
	VSL#3® Capsules	**VSL#3® Unflavored**	**VSL#3®DS**
≤ 5	1-2 (112-225)	N/A	N/A
6-11	2-4 (225-450)	0.5-1 (225-450)	N/A
12-17	4-8 (450-900)	1-2 (450-900)	0.5-1 (450-900)
Recommended intake by age (in years)	**Dietary Management of Irritable Bowel Syndrome (Billion CFU)**		
	VSL#3® Capsules	**VSL#3® Unflavored**	
≤ 5	1-2 (112-225)	N/A	
6-11	2-4 (225-450)	0.5-1 (225-450)	
12-17	4-8 (450-900)	0.5-2 (225-900)	

CFU, colony-forming units; N/A, not applicable.

Storage

VSL#3® consists of live, lyophilized bacteria. It should be stored at a cold and stable temperature. VSL#3® products if unopened and stored under refrigeration (36-46°For 2-8°C), are guaranteed through the "Best if used by" date. VSL#3® can be stored at room temperature (77°F) for up to 2 weeks without having a major effect on potency. If it is left at room temperature for longer periods of time or exposed to excessive heat, the number of beneficial bacteria in VSL#3® can become greatly reduced. Studies have not been conducted on the effects of freezing on VSL#3®. But repeating changes in temperature such as freezing, refrigerating and refreezing can stress the bacterial cell membranes, which are vital to the life of the bacteria. Therefore, VSL#3® can be stored until needed in the freezer, but once it has been frozen and then thawed, it should then be maintained at refrigeration temperature and not be refrozen.

Safety

Probiotics, including the strains in VSL#3®, have a long history of safe use in foods[34]. The safety of VSL#3® is well established by the substantial historical use of the contained microorganisms in fermented dairy products[35,36]. Many probiotic species are integral to the production of fermented foods and have been consumed safely as part of these foods for millennia[15]. Furthermore, many bifidobacteria and lactobacilli species are normal, nonpathogenic inhabitants of the human gastrointestinal tract, oral cavity, skin, and vagina[15,37-39]. While theoretically probiotic species could act as opportunistic pathogens, epidemiological surveillance data indicate that the risk of infection from consumption of lactobacilli is negligible[35,40]. In the available literature, documented cases of infection attributable to probiotic treatment are rare and limited to case reports. These case reports are primarily associated with patients having compromised immune systems or other major health problems[41-45]. Each strain of probiotic bacteria in VSL#3® is both non-pathogenic and non-toxigenic. The use of these particular strains in VSL#3® medical foods has been confirmed as generally recognized as safe (GRAS)[56] for use in foods. The lactic acid bacteria in VSL#3® have a long history of use in foods. Studies of VSL#3® have been conducted in several animal models of colitis and inflammatory liver disease[46-51, 56]. In experimental animal models of colitis, there are serious derangements in epithelial permeability and barrier function, causing the animals to be particularly vulnerable to bacterial translocation. These studies demonstrate that VSL#3® normalizes gut permeability and barrier function[52-54]. Thus, despite increased gut permeability and inadequate barrier function the probiotics contained within VSL#3® do not translocate from the gut lumen and act opportunistically when ingested by animals with colitis.

How Supplied

SKU (Single keeping Unit)	Units per box or bottle	UPC
VSL#3® Capsules	60 capsules	7-45749-01781-9
VSL#3® Unflavored	30 packets	7-45749-01780-2
VSL#3®DS	20 sachets	7-45749-01782-6

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56. Generally recognized as safe (GRAS) is an American Food and Drug Administration (FDA) designation that a chemical or substance added to food is considered safe by experts. www.fda.gov.

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