Medical Policy Reference Manual
Medical Policy

1.02.025 Probiotics

Original MPC Approval: 10/14/2015
Last Review Date: 09/01/2022
Last Revision Date: 03/01/2023

Description

The National Institutes of Health (NIH) National Center for Complementary and Integrative Health define probiotics as live microorganisms that are intended to have health benefits. Many of the microorganisms in probiotic products are the same as or similar to microorganisms that naturally live in the body. Probiotics can be bacteria or yeast, the most common being lactobacillus, bifidobacterium, bacillus coagulans and saccharomyces boulardi.

Many probiotics are sold as dietary supplements. Dietary supplement labels may make claims about how the product affects the structure or function of the body without U.S. Food and Drug Administration (FDA) approval, but they cannot make health claims (claims that the product reduces the risk of a disease) without the FDA's consent.

Researchers have studied probiotics in a variety of health problems, including:

- Digestive disorders such as diarrhea caused by infections, antibiotic-associated diarrhea, irritable bowel syndrome, and inflammatory bowel disease;
- Allergic disorders such as atopic dermatitis (eczema) and allergic rhinitis (hay fever);
- Tooth decay, periodontal disease, and other oral health problems;
- Colic in infants;
- Liver disease;
- The common cold; and
- Prevention of necrotizing enterocolitis in very low birth weight infant.

One marketed probiotic requires a prescription order. According to the manufacturer, VSL#3-DS® is a medical food probiotic that is intended only for the dietary management of ulcerative colitis (UC) or an ileal pouch. The term medical food refers to "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" (as defined by section 5B of the FDA Orphan Drug Act). VSL#3-DS® is a probiotic consisting of 8 strains of live, freeze-dried lactic acid bacteria with each serving containing at least 900 billion lyophilized lactic acid bacteria. Due to the high number of live bacteria, VSL#3-DS® requires a prescription.

Probiotics other than those like prescription only VSL#3-DS®, including regular strength VSL#3, are available over the counter (OTC) without a prescription.

Policy

VSL#3-DS®, available by prescription only as a medical food, may be considered **medically necessary** for the dietary management of an ileal pouch.

VSL#3-DS® is considered experimental/investigational for the dietary management of all other indications including ulcerative colitis because it does not meet TEC criteria #2-5.

Non-prescription probiotics are available over- the -counter (OTC) and are not covered.

Policy Guidelines

Experimental/Investigational

The term "experimental/investigational" describes services or supplies that are in the developmental stage and are in the process of human or animal testing. Services or supplies that do not meet all 5 of the criteria listed below adopted by the BlueCross BlueShield Association Technology Evaluation Center (TEC) are deemed to be experimental/investigational:

1 The technology* must have final approval from the appropriate U.S. government regulatory bodies; and
2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes; and
3. The technology must improve the net health outcome; and
4. The technology must be as beneficial as any established alternatives; and
5. The improvement must be attainable outside the investigational settings.

* Technology includes drugs, devices, processes, systems, or techniques

1. The technology* must have final approval from the appropriate U.S. government regulatory bodies.

Per the FDA, "probiotics" are not defined as a regulatory product category. Products that may be considered "probiotics" may be foods or drugs depending on the intended use of the product. The FDA has not approved any probiotics for preventing or treating any health problem.

2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes.

From UptoDate (2022), clinical research studies have been small in size and lack consistency in probiotic preparations. This variability combined with limitations from methodology fail to produce strong evidence on efficacy. The AGA guidelines state "the lack of consistent harms reporting makes it difficult to assess true harms. The lack of product manufacturing details prohibits true comparisons and decreases the feasibility of obtaining certain products by patients. Future high-quality studies are urgently needed that address these pitfalls."

3. The technology must improve the net health outcome.

Recent updates to *AGA Clinical Practice Guidelines on the Role of Probiotics in the Management of Gastrointestinal Disorders* show a low quality of research evaluating onset of remission of ulcerative colitis from probiotic therapy using the 8-strain combination (L paracasei subsp paracasei, L plantarum, L acidophilus, L delbrueckii subsp bulgaricus, B longum subsp longum, B breve, B longum subsp infantis, and S salivarius subsp thermophilus), did not show evidence of benefit from pooled results. Additionally, the guidelines noted that reviewed research included studies with potential bias. (Su, G. L et al, 2020).

4. The technology must be as beneficial as any established alternatives.

As reported in Up-to-Date's *Probiotics for gastrointestinal diseases* (2022), "No probiotic strategy is currently considered to represent either the standard of care or primary treatment."

5. The improvement must be attainable outside the investigational settings.

Guideline recommendations from the American Gastroenterological Association (AGA) state that probiotics for ulcerative colitis, irritable bowel syndrome, Crohn's disease, and gastroenteritis should only be used as part of a clinical trial. The AGA reports that "research is needed to identify specific patient populations that might benefit most from treatment with probiotics and to define the most effective probiotic formulations." (Su, G. L et al, 2020).

There are limited, small trials evaluating the prescription level dose of VSL#3-DS®. Most studies evaluate the over-the-counter dose of VSL#3®.

According to the NIH National Center for Complementary and Integrative Health, "although some probiotics have shown promise in research studies, strong scientific evidence to support specific uses of probiotics for most health conditions is lacking. Issues that remain unknown are which probiotics are helpful and which are not, how much of the probiotic people would have to take or who would most likely benefit from taking probiotics. Even for the conditions that have been studied the most, researchers are still working toward finding the answers to these questions."

In 2003, Fedorak et al compared the probiotic therapy with VSL#3® versus placebo in the ability to prevent the onset of acute pouchitis during the first year after ileal pouch-anal anastomosis. Forty consecutive patients who underwent ileal pouch-anal anastomosis for ulcerative colitis were randomized to receive either VSL#3® (1 packet containing 900

billion bacteria/day) (n = 20) or an identical placebo (n = 20) immediately after ileostomy closure for 1 year. Two of the 20 patients (10%) treated with VSL#3® had an episode of acute pouchitis compared with 8 of the 20 patients (40%) treated with placebo (log-rank test, z = 2.273; P < 0.05). Treatment with VSL#3® determined a significant improvement in Inflammatory Bowel Disease Questionnaire score, whereas this was not the case with placebo.

The American College of Gastroenterology write in their 2010 Clinical Practice Guidelines for Ulcerative Colitis in Adults, the oral probiotic formulation VSL-3 (containing lactobacilli, bifidobacteria, and Streptococcus salivarius) was shown to be effective in the prevention of pouchitis for up to 1 year after surgery (Gionchetti et al, 2000) and in the prevention of pouchitis relapse (Gionchetti et al, 2003), although benefit has not been as consistently seen in open-label use in other centers.

Tursi and colleagues, in 2010 a double-blind, randomized, placebo-controlled study sponsored by the VSL Pharmaceuticals, assessed the effects of supplementation with VSL#3® in patients with relapsing ulcerative colitis (UC) who were already under treatment with standard pharmaceutical treatment. Seventy-one patients were randomly treated with VSL#3® (3600 billion CFU/day) or with placebo (73 patients). VSL#3® supplementation was found to be safe and able to reduce ulcerative colitis disease activity index (UCDAI) scores in patients with relapsing mild-to moderate UC being treated with standard pharmaceutical treatment. VSL#3® improved rectal bleeding and seemed to reinduce remission in relapsing UC patients after 8 weeks, although the parameters did not reach statistical significance.

A 2011 Cochrane review (Naidoo et al) of probiotics for maintenance of remission in UC concluded "given the relatively small number of patients in the pooled analysis, the small number of events and the high risk and the unclear risk of bias in the included studies, there is insufficient evidence to make conclusions about the efficacy of probiotics for maintenance of remission in UC. There is a lack of well-designed randomized controlled trials in this area and further research is needed."

Jonkers and group published the findings of a systematic review of probiotics in the management of inflammatory bowel disease with studies available through October 2011. "Well designed randomized controlled trials supporting the application of probiotics in the management of inflammatory bowel disease (IBD) is limited. Further well-designed studies based on intention-to-treat analyses by several independent research groups are still warranted to support the promising results for E. Coli Nissle an inactive UC and the VSL#3® in active UC and inactive pouch patients." The authors found no available evidence to support the use of probiotics in Crohn's disease.

Sanders and colleagues write in 2013 that a growing number of meta-analyses vary in their conclusions on the effectiveness of probiotics in treating irritable bowel syndrome, in part, because of inadequate sample size, poor study design and the use of various probiotic strains in the studies that were reviewed. In the treatment of inflammatory bowel disease (IBD), the authors conclude that no consistent effects have been noted in treating or preventing relapse of Crohn's disease. For UC, the probiotic combination of lactobacillus, Bifidobacterium and Streptococcus species or Escherichia coli Nissle in inducing and maintaining remission of disease activity in mild to moderately severe UC have been described. Primary prevention of pouchitis and reducing the likelihood of relapse after successful antibiotic treatment have also been successful.

In a 2013 randomized, double-blind placebo-controlled trial, Gupta and group investigated the effect of probiotics on portal pressure in patients with cirrhosis. Ninety-four cirrhotic patients having large oesophageal varices without history of variceal bleeding were randomized to three treatment groups and given 2 months' treatment with propranolol plus placebo, propranolol plus antibiotics (norfloxacin 400 mg BD) or propranolol plus probiotic (VSL#3®, **900 billion**/day) randomly assigned in 1:1:1 ratio. Adjunctive probiotic (VSL#3®) improved the response rate to propranolol therapy and was found to be safe and well tolerated in patients with cirrhosis. Adjunctive probiotic therapy merits further study for reduction in portal pressure per the authors.

Mardini and Grigorian, in a 2014 meta-analysis of probiotic mix VSL#3®, found five studies treating 441 patients with mild to moderately active UC, but only 3 low risk of bias studies with 319 patients met the inclusion criteria for analysis. A total of 162 patients received VSL#3® and 157 patients received placebo. Ninety-five percent of the patients received concomitant therapies with 5-ASAS and/or immunomodulators. The Ulcerative Colitis Disease Activity Index was used to define response and remission. When added to conventional therapy at a dose of 3.6 x 10 CFU/d, VSL#3® was found to be safe and more effective than conventional therapy alone and achieved high response (53.4% VSL#3® compared to 29.3% in placebo) and higher remission rate (43.8 in VSL#3® versus 24.8% in placebo group).

In 2014, Shen et al performed a meta-analysis of twenty-three randomized controlled trials comparing probiotics to controls in inflammatory bowel disease. A total of 1763 participants met inclusion criteria. Subgroup analysis found VSL#3® significantly increased the remission rates compared with controls in patients with active UC. VSL#3® also significantly reduced the clinical relapse rates for maintaining remission with pouchitis.

In 2015, Fedorak and colleagues, in a multicenter, randomized, double blind, placebo-controlled trial investigated the ability of VSL#3® (900 billion) to prevent Crohn's disease recurrence after ileocolonic resection and re-anastomosis. Within 30 days of surgery patients were randomly assigned to groups given 1 sachet of VSL#3® (900 billion) (n = 59) or matching placebo (n = 60). It was concluded there were no statistical differences in endoscopic recurrence rates at day 90 between patients who received VSL#3® and patients who received placebo. Lower mucosal levels of inflammatory cytokines and a lower rate of recurrence among patients who received early VSL#3® (for the entire 365 days) indicate that this probiotic should be further investigated for prevention of Crohn's disease recurrence.

Updated 2022:
A search of the peer-reviewed literature was performed from November 2019 through January 2022. Findings in the recent literature include practice guidelines from the AGA published in 2020 which state that probiotics for ulcerative colitis, irritable bowel syndrome, Crohn's disease, and gastroenteritis should only be used as part of a clinical trial. As a result, the policy statement has changed. Ulcerative colitis is no longer considered a medically necessary indication and the following statement has been added to the policy: *VSL#3-DS® is considered experimental/investigational for the dietary management of all other indications including ulcerative colitis*.

Updated 2019:
A search of the peer-reviewed literature was performed from October 2017 through November 2019. Findings in the recent literature do not change the conclusions regarding the use of prescribed probiotics, such as VSL#3-DS®, as medical food for the dietary management of an ileal pouch and ulcerative colitis. Therefore, the policy statement remains unchanged.

Update 2017:
A search of the peer-reviewed literature was performed from October 2015 through September 2017. Findings in the recent literature do not change the conclusions on the use of prescribed probiotics as medical food for the dietary management of an ileal pouch and ulcerative colitis. Therefore, the policy statement remains unchanged.

Benefit Applications

When benefits are provided in the member's contract, medical foods are paid as a medical benefit, not under the Pharmacy program.

Benefits **are not provided** for over-the-counter items, such as food supplements or supplies, as determined by CareFirst, that are available for purchase without a prescription unless otherwise a covered service. A prescription from the provider does not guarantee coverage by CareFirst.

NOTE: The District of Columbia Medically Necessary Foods Coverage Act (DC Code § 31–3871) requires coverage for medically necessary foods ordered by a provider to treat certain specific illnesses and diseases. This mandate impacts all health benefit plans issued, renewed, extended, or modified in the District by a health insurer starting January 1, 2023. Members of District of Columbia plans should check their contract for benefits affected by this legislation.

Provider Guidelines

There are no Provider Guidelines for this Medical Policy.

Cross References to Related Policies and Procedures

1.02.002	Amino Acid-Based Elemental Formulas for Treatment of Malabsorption Disorders, Policy
1.02.024A	Over-the-Counter Miscellaneous Supplies and Equipment, Procedure
2.01.026	Medical Foods for Treatment of Inherited Metabolic Disorders, Policy

References

The following were among the resources reviewed and considered in developing this policy. By reviewing and considering the resources, CareFirst does not in any way endorse the contents thereof nor assume any liability or responsibility in connection therewith. The opinions and conclusions of the authors of these resources are their own and may or may not be in agreement with those of CareFirst.

Benlice, C., Shen, B., Steele, S. R. (2019). Prevention and medical treatment of pouchitis in ulcerative colitis. *Current Drug Targets*. doi: 10.2174/1389450120666190723130137.

Bernstein, C.N. (2014). Antibiotics, probiotics and prebiotics in IBD. *Nestlé Nutrition Institute workshop series, 79:83-*100. doi: 10.1159/000360713.

Butterworth A.D., Thomas, A.G., Akobeng, A.K. (2008, July). Probiotics for induction of remission in Crohn's disease. Cochrane Database Systematic Review. #:CD006634.

Cuello-Garcia, C.A., Brozek, J.L., Fiocchi, A., Pawankar, R., Yepes-Nunez, J.J., Terracciano, L., ... Schunemann, H.J. (2015, June). Probiotics for the prevention of allergy: A systematic review and meta-analysis of randomized controlled trials. *Journal of Allergy and Clinical Immunology*, pii: S0091-6749(15)00636-3. doi: 10.1016/j.jaci.2015.04.031.

District of Columbia Medically Necessary Foods Coverage Act (DC Code § 31–3871).

de Andrade Calaca, P. R., Bezerra, R. P., Albuquerque, W. W C., Porto, A. L. F., Cavalcanti, M. T. H. (2017, August). Probiotics as a preventive strategy for surgical infection in colorectal cancer patients: a systematic review and meta-analysis of randomized trials. *Translation Gastroenterology and Heptatology*. 2:67. doi: 10.21037/tgh.2017.08.01.

*Fedorak, R.N., Feagan, B.G., Hotte, N., Leddin, D., Dieleman, L.A., Petrunia, D.M., ... Madsen, L. (2015, May). The probiotic VSL#3 has anti-inflammatory effects and could reduce endoscopic recurrence after surgery for Crohn's disease. Clinical Gastroenterology and Hepatology : The Official Clinical Practice Journal of the American Gastroenterological Association. 13(5): 928-35.e2. doi: 10.1016/j.cgh.2009.07.016.

Ghouri, Y.A., Richards, D.M., Rahimi, E.F., Krill, E.F., Jelinek, K.A., DuPont, A.W. (2014). Systematic review of randomized controlled trials of probiotics, prebiotics, and synbiotics in inflammatory bowel disease. *Clinical and Experimental Gastroenterology*, 7: 473-487.

Gionchetti, P., Calafiore, A., Riso, D, Liguori, G., Calabrese, C., Vitali, G., ... Rizzello, F. (2012). The role of antibiotics and probiotics in pouchitis. *Annals of Gastroenterology,* 25, 100-105.

Gionchetti, P., Rizzello, F., Helwig, U., Venturi, A., Lammers, K.M., Brigidi, P., ... Campieri, M. (2003, May). Prophylaxis of pouchitis onset with probiotic therapy: a double blind, placebo-controlled trial. *Gastroenterology*, 124(5): 1202-9.

*Gionchetti P, Rizzello F, Morselli C, Poggioli G, Tambasco R, Calabrese C, http://www.ncbi.nlm.nih.gov/pubmed/?term=Brigidi%20P%5BAuthor%5D&cauthor=true&cauthor_uid=17934776... Campierei, M. (2007). High-dose probiotics for the treatment of active pouchitis. *Diseases of Colon and Rectum*, http://www.ncbi.nlm.nih.gov/pubmed/1793477650(12):2075-82; discussion 2082-4.

Gionchetti, P., Rizzello, F., Venturi A. Brigidi, P., Matteuzzi, D., Bazzocchi, G.... Campieri, M., (2000). Oral bacteriotherapy as maintenance treatments in patients with chronic pouchitis: a double blind, placebo-controlled trial. *Gastroenterology*, 119:305-9.

*Gupta, N., Kumar, A, Sharma, P., Garg, V., Sharma, B.C., Sarin, S.K. (2013). Effects of the adjunctive probiotic VSL#3 on portal haemodynamics in patients with cirrhosis and large varices: a randomized trial. Liver International, 33(8):1148-57. doi: 10.1111/liv.12172.

Jonkers, D., Penders, J., Muscled, A., Pieria, M. (2012, April). Probiotics in the management of inflammatory bowel disease: a systematic review of intervention studies in adult patients. *Drugs*, 72(6): 802-23. doi: 10.2165/11632710-000000000-00000.

Kornbluth, A., Sachar, D.B. ...The Practice Parameters Committee of the American College of Gastroenterology. (2010). Ulcerative colitis practice guidelines in Adults: American College of Gastroenterology, Practice Parameters Committee. *American Journal of Gastroenterology,* 105: 501-523; doi: 10.1038/ajg.2009.727.

Lau, C.S.; Chamberlain, R.S. (2015, May). Probiotic administration can prevent necrotizing enterocolitis in preterm infants: A meta-analysis. *Journal of Pediatric Surgery*, pii: S0022-3468(15)00362-0. doi: 10.1016/j.jpedsurg.2015.05.008.

Mardini, H.E., Grigorian, A.Y. (2014). Probiotic mix VSL#3 is effective adjunctive therapy for mild to moderately active ulcerative colitis: a meta-analysis. *Inflammatory Bowel Disease*, (9):1562-7. doi: 10.1097/MIB.0000000000000084.

Naidoo, K., Gordon, M., Fagbemi, A.O., Thomas, A.G., Akobeng, A.K. (2011, December). *Cochrane Database Systematic Review*, (12): CD007443. doi: 10.1002/14651858.CD007443

National Center for Complementary and Integrative Health (National Institute of Health). Probiotics (last updated July 2015). https://nccih.nih.gov/health/probiotics/introduction.htm

Nguyen, N., Zhang, B., Holubar, S. D., Pardi, D. S., Singh, S. (2019, May). Treatment and prevention of pouchitis after ileal pouch-anal anastomosis for chronic ulcerative colitis. *The Cochrane Database of Systematic Reviews*. doi: 10.1002/14651858.CD001176.

Orel, R., Trop, T.K. (2014). Intestinal microbiota, probiotics and prebiotics, in inflammatory bowel disease. *World Journal of Gastroenterology*, 20(33): 11501-11504.

*Pelion G, Sciaudone G, Candilio G, Camerlingo A, Marcellinaro R, De Fatico S, ... Selvaggi F. (2013). Early postoperative administration of probiotics versus placebo in elderly patients undergoing elective colorectal surgery: a double blind randomized controlled trial. *BMC Surgery,* 2013; 13 Suppl 2:S57. doi: 10.1186/1471-2482-13-S2-S57

Peng, Y., Li, A., Yu, L., Qin, G. (2015, July). The role of probiotics in prevention and treatment for patients with allergic rhinitis: A systematic review. *American Journal of Rhinology & Allergy*, 29(4): 292-8. doi: 10.2500/ajra.2015.29.4192.

Petrof, E.O. (2009). Probiotics and gastrointestinal disease: Clinical evidence and basic science. *Anti-inflammatory & Anti-allergy Agents in Medicinal Chemistry,* 8(3): 260-269. doi: 10.2174/187152309789151977

Sartor, R. Balfour (2022), Probiotics for gastrointestinal diseases, UpToDate Waltham, MA (2022)

Shen, J., Zuo, Z.X., Mao, A.P. (2014, January). Effect of probiotics on inducing remission and maintaining therapy in ulcerative colitis, Crohn's disease, and pouchitis: meta-analyses of randomized controlled trials. Inflammatory Bowel Disease, 20(1): 21-35. doi: 10.1097/01.MIB.0000437495.30052.

Sood, A., Midha, V., Makharia, G.K.,, Ahuja, V., Singal, D., Goswami, P., Tandon, R.K. (2009, November). The probiotic preparation, VSL#3 induces remission in patients with mild-to-moderately active ulcerative colitis. Clinical gastroenterology and hepatology: the official clinical practice journal of the American Gastroenterological Association. 7(11):1202-9 1209.3.1. doi: 10.1016/j.cgh.2009.07.016

Su, G. L et al (2020). AGA Clinical Practice Guidelines on the Role of Probiotics in the Management of Gastrointestinal Disorders. Gastroenterology, 159(2), 697–705. https://doi.org/10.1053/j.gastro.2020.05.059

Toh, S. L., Boswell-Ruys, C. L., Lee, B. S. B., Simpson, J. M., Clezy, K., R. (2017, September). Probiotics for preventing urinary tract infection in people with neuropathic bladder. *The Cochrane Database Systematic Review*. doi: 10.1002/14651858.CD010723.pub2.

*Tursi, A., Brandimarte, G., Papa, A. Giglio, A., Elisei, W., Giorgetti, G.M., ..., Gasbarrini, A. (2010, October). Treatment of relapsing mild-to-moderate ulcerative colitis with the probiotic VSL#3 as adjunctive to a standard pharmaceutical treatment: A Double blind, randomized, placebo-controlled study. *American Journal of Gastroenterology*, 105(10): 221/-2227.doi: 10.1038/ajg.2010.218

U.S. Food and Drug Administration. Guidance for Industry on Complementary and Alternative Medicine Products and Their Regulation by the Food and Drug Administration. December 2006. Accessed August 13, 2015. http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM145405.pdf

U.S. Food and Drug Administration. Medical Foods Guidance Documents and Regulatory Information. http://www.fda.gov/food/guidanceregulation/guidancedocumentsregulatoryinformation/medicalfoods/default.htm

Zuccutti, G., Meneghin, F. Aceti, A., Barone, G., Callegari, M.L., Di Mauro, A., ... Italian Society of Neonatology. (2015, July). Probiotics for prevention of atopic diseases of atopic diseases in infants: systematic review and meta-analysis. *Allergy*, doi: 10.1111/all.12700.

* References specific to VSL#3-DS.