May 17, 2024

APPEAL OF MEDICATION DENIAL

Appealing party: NAME, DOB: XXXX, Policy Number: XXX, Claim Number: XXX

To whom it may concern:

I write to appeal Wellmark Blue, Blue Cross and Blue Shield's ("BCBS") recent decision denying coverage of 1500 mg/day ORAL VANCOMYCIN HCL (six 250 MG CAPSULEs/day) ("OV") prescribed to treat my ulcerative colitis (PSC-UC) and primary sclerosing cholangitis ("PSC"). BCBS's stated reason for denial of coverage is that the medicine is "non-formulary", which is the same reasoning utilized when the medicine was denied almost exactly one year ago today as well. The following research and clinical data support my appeal and show the effectiveness of OV for my medical condition.

1. **The published medical literature**. The clinical literature shows that oral vancomycin has resulted in sustained clinical and therapeutic responses for multiple years in many PSC-UC patients benefiting both colonic and hepatic symptoms and chemistries. The clinical literature is summarized below in **Attachment A**.

2. **Support for dose escalation**. Two published papers (a case series Alenchery 2023 and a case report Buness 2020) and a Meeting Abstract (Pratt 2011) provide support for higher doses to elicit a full clinical response.

3. **My own medical history**. I was diagnosed with ulcerative colitis and PSC XX years ago and no other medication has been effective in controlling my conditions. I have been taking oral vancomycin and nothing else for treatment of my conditions for the past XX years and its effectiveness cannot be overstated: after years of uncontrolled diarrhea, severe bouts of pruritus, chronic colon inflammation and ulceration, and elevated liver enzymes, immediately upon being started on vancomycin I experienced complete healing of my colon (as demonstrated on colonoscopy); complete normalization of liver lab values; and complete resolution of all symptomatology. Medical records reflecting oral vancomycin's dramatic effect on my health are provided as **Attachment B.**

4. **My request for coverage.** Based on the evidence provided, I request that Blue Cross Blue Shield approve oral vancomycin capsules at the recommended dose of 750 mg/day for treatment of my ulcerative colitis and PSC. This will be a lifelong commitment and treatment path for me until a cure is found.

Sincerely,

ATTACHMENT A

Background on PSC, ulcerative colitis, and vancomycin therapy:

PSC is a progressive, rare cholestatic liver disease that typically progresses to liver failure within 10-15 years. PSC is in 60-90% of cases associated with an inflammatory bowel disease (IBD) that holds unique features, leading to the emerging concept of PSC-IBD as the third form of IBD. (Karlsen 2017, Loftus 2005) PSC-IBD carries unique characteristics when compared to classic forms of IBD with reverse gradient, predominantly right-sided, clinically-less obvious chronic Ulcerative Colitis-like inflammation in 80-90% of patients and the associated backwash ileitis that resembles ileocolonic Crohn's-like inflammation in 10-20% of patients. PSC and the concomitant IBD are associated with many quality-of-life issues including itching, fatigue, pain, fever, and life-threatening infections, which result in significant suffering with no relief available. As PSC progresses, patients can also experience all the suffering of end-stage liver disease including jaundice, fluid retention, confusion, and gastrointestinal bleeding.

The etiology of PSC is poorly understood; one theory is that an abnormal gut microbiome activates innate immunity within the liver, resulting in bile duct-targeted inflammation and biliary fibrosis. In 1998, Cox et al (Cox), reported beneficial effects of treating three paediatric PSC patients with oral vancomycin (OV). Subsequently, multiple published clinical trials, case series, and other reports, have shown that OV treatment for PSC patients can result in significant clinical responses(Shah), allowing patients to avoid colectomies, liver transplants, and hospitalizations and to have a relatively normal QoL(Rahimpour). These benefits are seen in a large proportion of OV-treated PSC patients, especially when treatment is initiated at a relatively early stage of liver disease. There is also considerable benefit in relation to the associated IBD, with clinical and endoscopic remission achieved in most patients even if they have failed conventional IBD therapies. Data underscore not only the potential benefit of OV in patients with PSC, but also its safety and low risk of adverse events (AEs), even if used over an extended period, including a negligible risk of developing vancomycin resistant enterococci (VRE)(Shah). Though not all patients with PSC have a positive response to OV therapy (reportedly used in varying doses, ranging from 250 mg - 3000 mg daily as a maintenance therapy) (Damman) a subset of patients experience dramatic improvements in intestinal and hepatobiliary manifestations. Indeed, a recent large multicentre paediatric cohort study revealed that OV was associated with greater odds of clinical of the gut-related symptoms in patients with PSC-IBD.

The mechanism of action of vancomycin taken orally has been found to be both as an antimicrobial agent and as an immunomodulator. As an antimicrobial agent, it has been extensively and well-studied. OV exerts beneficial antimicrobial effects and may be effective against intestinal pathogens that contribute to intestinal barrier disruption and inflammation in PSC patients. As an immunomodulator, OV therapy results in biochemical improvement in

patients with PSC. (Zigmond 2022, Yang 2022, Nakamoto 2019). Oral vancomycin, which is not absorbed from the gut lumen and is already known to have efficacy in *C. difficile* infections and pouchitis, is now being studied and prescribed by multiple medical institutions in the US, Australia, Canada, and Europe. It has been employed in several published PSC clinical trials and case studies with remarkable success. OV is the only drug known that seems to reverse damage to the two affected organs—the colon and the liver—and, at the same time, stop progression of cholestasis in some patients.

Importantly, ***there is no alternative treatment to OV for PSC patients***. There are *no* FDA-approved drugs for treatment of PSC, nor have any drugs used off-label been proven effective. However, *"From the FDA perspective, once the FDA approves a drug, healthcare providers generally may prescribe the drug for an unapproved use when they judge that it is medically appropriate for their patient."* See https://www.fda.gov/patients/learn-about-expanded-access-and-other-treatment-options/understanding-unapproved-use-approved-drugs-label. There are no FDA-approved medications for PSC. Therefore, patients rely solely on off-label medications.

The clinical literature:

In total, there are 29 published papers—clinical trials, prospective open-label trials, case series, and case reports—on the effectiveness of OV for PSC-UC patients. These papers show that a large subgroup of PSC-UC patients experiences a significant and sustained response to OV therapy. A clear-cut improvement is almost always seen with colitis symptoms, and if the therapy is started early enough in the disease process, with liver manifestations. (Ali 2020). Also shown is that this sustained clinical and therapeutic response allows patients to live normal lives and avoid colectomies, liver transplants, and hospitalizations. These patients also do not suffer from PSC related QoL issues. (Alenchery 2023). A subset of these studies are discussed, in turn, below (and a full list appears at the end of this Attachment).

- In the Ricciuto 2024 retrospective multi-center cohort study 113 PSC-IBD patients received vancomycin (median age 12.7 years, 63% male). The matched cohort included 70 vancomycin-treated and 210 untreated patients. Vancomycin was associated with greater odds of IBD clinical remission.

- In a prospective study, patients on OV had improvement in imaging and IBD, without progression of their PSC. (Ali 2020). None who began treatment in earlier stages PSC progressed to liver transplantation. Many also experienced improvement in their liver biopsies. *Id*. Small-duct PSC patients treated with OV rarely progressed to large-duct inflammation and cirrhosis. *Id.*

- A recently published 2022 study by Shah *et al.* included seven patients with PSC-UC (age range 22 to 53 years) treated with OV (daily dose ranging from 250 mg to 1500 mg) for at least 6 months (range 9-31 months, mean duration of OV treatment, 32.1 months) who underwent periodic vancomycin-resistant enterococci (VRE) testing using rectal swabs. All patients experienced clinical and endoscopic remission of the UC, and all experienced liver biochemical improvement. (Shah 2022). No patient developed VRE or reported any adverse events. Collectively, these data underscore not only the efficacy of OV in patients with PSC-UC, but also its safety.

- *Tan et al.* reported that Oral Vancomycin induces clinical and mucosal remission of colitis in children with primary sclerosing cholangitis-ulcerative colitis (PSC-UC). They stated: "OV has excellent efficacy obtaining clinical, biomarker, mucosal and histological remission of colitis in children with ASC and PSC. This is not a long-term follow-up series, but obtaining mucosal healing is vital for influencing the natural history of IBD and OV in these children with colitis relating to PSC/ASC has an excellent mucosal response." (Tan 2019).

- *Britto et al.* reported on the therapeutic effects of OV in a 7-year-old boy with PSC/UC with clinical colitis resolution within 90 days and full normalization of fecal calprotectin. (Britto 2021).

- In another recent case report *Buness et al.*, the patient has been taking 1,000 mg BID for over 8 years. (Buness 2021). The *Buness et al*. patient experienced full remission of all symptoms for 8 years at the time of publication.

- A paper on an open-label prospective clinical trial at Stanford University published in 2020 set forth the recommended dosing protocol of 50 mg per kilogram per day divided into 3 times per day if weight was < 30 kg, and at a dose of 500 mg 3 times a day if weight >30 kg. (Ali *et al.* 2020). This paper describes 59 patients who were treated with OV.

- *Cox et al*. reported in 1998 that three children with PSC all experienced improvement in liver chemistries and their symptoms of UC. (Cox 1998).

- Review papers set forth trials and case reports up to 2019 (Damman *et al.* 2018 and Shah *et al.* 2019).

- In a Letter to the Editor of Hepatology, 13 prominent physicians summarized the reasons insurance should cover OV for UC-PSC patients. (Ali 2023):

"Although large, controlled trials are not yet completed, two small, controlled trials and evidence from multiple cohort studies are summarized in a systematic review and meta-analysis demonstrating OV has beneficial effects on liver functions in PSC patients. These robust findings are further supported by a recent pediatric/adult cohort study where OV showed benefits in lowering cholestatic enzymes and improving MRCP findings of bile duct dilatation and stenoses. This might translate to fewer liver transplants, fewer hospitalizations for acute cholangitis, and other expensive consequences of not treating this devastating disease.

Additionally, OV has beneficial effects on PSC-associated colitis with improvement of the diarrhea and other symptoms. The medical community desires better treatments at lower costs. For responsive PSC/IBD patients, insurers stand to benefit financially by allowing OV to be substituted for biologic drugs. The beneficial effects of OV on colitis are its most reliable effects. Biologics typically cost 5 times more than OV, and the gain over placebo is small. Some surgeries might also be avoided; our patients have avoided colectomies with OV.

While OV does not work for all PSC patients, no other treatment (besides liver transplantation) has proven effective in even a subgroup of PSC patients. Medical and financial reasons for insurers to cover OV for PSC are compelling as long as the physician and patient can demonstrate that OV benefits the patient."

My request for coverage:

As demonstrated by my historic and current liver chemistries, oral vancomycin is an effective treatment for my PSC and IBD, and has been for 10 years. Published and peer-reviewed medical literature supports therapy with oral vancomycin for PSC/IBD. Oral vancomycin was prescribed to me, NAME, by my physician and is medically necessary for my diagnosed PSC/IBD. Insurer's denial has no support in the published medical literature and is not supported under the policy provisions that cover medications that improve my health.

For all the reasons stated in this appeal, I respectfully request that Insurer reconsider this denial and approve coverage for oral vancomycin for NAME at xxxxx dose.

Sincerely,
XXXXXXX

References

Abarbanel, D. N., et al. (2013). "Immunomodulatory effect of vancomycin on Treg in pediatric inflammatory bowel disease and primary sclerosing cholangitis." J Clin Immunol **33**(2): 397-406.

Ahmed, Taqwa et al. "Besting the Biologics: Vancomycin Monotherapy for Ulcerative Colitis Management in Patients with Primary Sclerosing Cholangitis." *Digestive diseases and sciences*, 10.1007/s10620-023-07826-3. 7 Mar. 2023, doi:10.1007/s10620-023-07826-3

Alenchery, A.J.; Patel, S.; Mahajan, L.; Kurowski, J.A.; Worley, S.; Hupertz, V.; Radhakrishnan, K.; Kabbany, M.N. Single Center Experience of Oral Vancomycin Therapy in Young Patients with Primary Sclerosing Cholangtis: A Case Series. Livers **2023**, 3, 93–104. https://doi.org/10.3390/ livers3010009

Ali, Ahmad H et al. "Letter to the Editor: Insurance should cover vancomycin for primary sclerosing cholangitis." *Hepatology (Baltimore, Md.)*, 10.1097/HEP.0000000000000304. 30 Jan. 2023, doi:10.1097/HEP.0000000000000304

Ali, A. H., et al. (2020). "Open-label prospective therapeutic clinical trials: oral vancomycin in children and adults with primary sclerosing cholangitis." Scand J Gastroenterol **55**(8): 941-950.

Almomen, Hisham S, and Badr Al-Bawardy. "Oral Vancomycin Induced and Maintained Clinical and Endoscopic Remission in Ulcerative Colitis and Primary Sclerosing Cholangitis Post-liver Transplantation." *Inflammatory bowel diseases*, izad040. 8 Mar. 2023, doi:10.1093/ibd/izad040

Austin, Peter C. "Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples." *Statistics in medicine* vol. 28,25 (2009): 3083-107. Doi:10.1002/sim.3697.

Balouch, F ; Burgess, CJ ; Tan, LZ ; Reilly, C ; Clark, J ; Lewindon, PJ: "Paediatric Primary Schlerosing Cholangitis-Ulcerative Colitis. Audit of 2 year Outcome with Oral Vancomycin Treatment; Gastroenterology, 160:6(S44-S44), May 2021, Meeting Abstract

Benito de Valle M, R. M., Lindkvist B (2012). "Factors that reduce health-related quality of life in patients with primary sclerosing cholangitis." Clin Gastroenterol Hepatol: 769-775.

Britto SL, H. K., Tessier ME, Petrosino J, Miloh T, Kellermayer R. (2021). "Microbiome Responses to Vancomycin Treatment in a Child With Primary Sclerosing Cholangitis and Ulcerative Colitis." ACG Case Rep J.

Brost et al. “Orale Therapie mit Vancomycin als Therapieoption bei Primär Sklerosierender Cholangitis.” Z Gastroenterol 2014; 52 - KG125; DOI: 10.1055/s-0034-1386147

Buness, C. W., et al. (2021). “Successful response of primary sclerosing cholangitis and associated ulcerative colitis to oral vancomycin may depend on brand and personalized dose: report in an adolescent.” Clin J Gastroenterol **14**(2): 684-689.

Burak K, A. P., Pasha TM, et al. (2004). “Incidence and risk factors for cholangiocarcinoma in primary sclerosing cholangitis.” Am J Gastroenterol 523-526.

Cheung AC, P. H., Meza-Cardona J, et al (2016). “Factors that Influence Health-Related Quality of Life in Patients with Primary Sclerosing Cholangitis.” Dig Dis Sci 1692-1699.

Cox KL, Cox KM. Oral vancomycin: treatment of primary sclerosing cholangitis in children with inflammatory bowel disease. J Pediatr Gastroenterol Nutr. 1998;27(5):580–3.

Damman, J. L., et al. (2018). “Review article: the evidence that vancomycin is a therapeutic option for primary sclerosing cholangitis.” Aliment Pharmacol Ther **47**(7): 886-895.

Dao, Alexander et al. “Oral Vancomycin Induces and Maintains Remission of Ulcerative Colitis in the Subset of Patients With Associated Primary Sclerosing Cholangitis.” Inflammatory bowel diseases vol. 25,7 (2019): e90-e91. doi:10.1093/ibd/izz027

Davies YK, C. K., Abdullah BA, et al. (2008). “Long-term treatment of primary sclerosing cholangitis in children with oral vancomycin: an immunomodulating antibiotic.” J Pediatr Gastroenterol Nutr 61-67.

Davies, Yinka K et al. “Successful treatment of recurrent primary sclerosing cholangitis after orthotopic liver transplantation with oral vancomycin.” *Case reports in transplantation*. 2013 (2013): 314292. doi:10.1155/2013/314292

de Chambrun, Guillaume Pineton et al. “Oral vancomycin induces sustained deep remission in adult patients with ulcerative colitis and primary sclerosing cholangitis.” *European journal of gastroenterology & hepatology* vol. 30,10 (2018): 1247-1252. doi:10.1097/MEG.0000000000001223

Di Giorgio, Angelo et al. “Use of oral vancomycin in children with autoimmune liver disease: A single centre experience.” World journal of hepatology vol. 13,12 (2021): 2113-2127. doi:10.4254/wjh.v13.i12.2113

Floreani A, D. M. S. (2021). “Treatment of primary sclerosing cholangitis.” Dig Liver Dis (53): 1531-1538.

Gotthardt DN, R. C., Bruhin M, et al (2014). “Pruritus is associated with severely impaired quality of life in patients with primary sclerosing cholangitis.” Eur J Gastroenterol Hepatol 1374-1379.

Gulati R, R. K., Hupertz V, et al. (2013). “Health-related quality of life in children with autoimmune liver disease.” J Pediatr Gastroenterol Nutr: 444-450.

Haapamaki J, T. A., Sintonen H, et al. (2014). “Health-related quality of life among patients with primary sclerosing cholangitis.” Liver Int.

Hasegawa S, Y. M., Kurita Y (2021). "Cholestatic Liver Disease: Current Treatment Strategies and New Therapeutic Agents." Drugs: 1181-1192.Hey, Penelope et al. “Efficacy of oral vancomycin in recurrent primary sclerosing cholangitis following liver transplantation.” BMJ case reports vol. 2017 bcr2017221165. 25 Sep. 2017, doi:10.1136/bcr-2017-221165

Karlsen TH, Folseraas T, Thorburn D, Vesterhus M. Primary sclerosing cholangitis - a comprehensive review. J Hepatol 2017;67:1298-1323.

Lindor, Keith D et al. “ACG Clinical Guideline: Primary Sclerosing Cholangitis.” The American journal of gastroenterology vol. 110,5 (2015): 646-59; quiz 660. doi:10.1038/ajg.2015.112.

Loftus EV, Jr., Harewood GC, Loftus CG, Tremaine WJ, Harmsen WS, Zinsmeister AR, Jewell DA, et al. PSC-IBD: a unique form of inflammatory bowel disease associated with primary sclerosing cholangitis. Gut 2005;54:91-96.

Nakamoto, N., et al. (2019). "Gut pathobionts underlie intestinal barrier dysfunction and liver T helper 17 cell immune response in primary sclerosing cholangitis." Nat Microbiol **4**(3): 492-503.

Pérez Martin CY, et al.. Oral vancomycin in a pediatric patient with primary sclerosing cholangitis and inflammatory bowel disease. Hospital pharmacy. 2023. https://doi.org/10.1016/j.farma.2023.06.015

Pratt, D (Pratt, Daniel) ; Agarwal, S (Agarwal, Sheela) ; Saini, S (Saini, Sanjay) ; Misdraji, J (Misdraji, Joseph) ; Korzenik, JR (Korzenik, Joshua R.): **An Open Label Pilot Trial of Oral Vancomycin in Primary Sclerosing Cholangitis - Results of the VIP Trial.** GASTROENTEROLOGY May 2011, 140;5: S907-S907, Meeting abstract.
Quraishi N, Ferguson J, Mcinnes R, Cheesbrough J, Sharma N, Cooney R, Rimmer P, van Schaik W, Iqbal T, Trivedi P. Oral vancomycin induces remission in PSC-IBD, which is associated with a reduction in bile salt hydrolase and colonic amine oxidase activity. Abstract presented at EASL Congress 2023 Meeting June 21-24, 2023; Vienna, Austria**.**

Rahimpour S, Nasiri-Toosi M, Khalili H, Ebrahimi-Daryani N, Nouri-Taromlou MK, Azizi Z: A triple blinded, randomised, placebo-controlled clinical trial to evaluate the efficacy and safety of

oral vancomycin in primary sclerosing cholangitis: a pilot study. J Gastrointest Liver Dis JGLD 2016, 25:457–464, https://doi.org/10.15403/jgld.2014.1121.254.rah

Rahman AU, Inayat F, Ali S, Zahid E, Charles R. The role of oral vancomycin in inducing remission for biologic-experienced ulcerative colitis with concomitant primary sclerosing cholangitis and liver transplantation. Clin J Gastroenterol. 2021 Feb;14(1):159-164. doi: 10.1007/s12328-020-01272-8. Epub 2020 Nov 1. PMID: 33130984.

Ricciuto, Amanda et al. “Oral vancomycin is associated with improved inflammatory bowel disease clinical outcomes in primary sclerosing cholangitis-associated inflammatory bowel disease (PSC-IBD): A matched analysis from the Paediatric PSC Consortium.” *Alimentary pharmacology & therapeutics*, 10.1111/apt.17936. 10 Mar. 2024, doi:10.1111/apt.17936

Shah, Ayesha et al. “How frequent are vancomycin-resistant enterococci in patients with primary sclerosing cholangitis and ulcerative colitis treated with oral vancomycin?.” *Indian journal of gastroenterology: official journal of the Indian Society of Gastroenterology* vol. 41,5 (2022): 519-524. doi:10.1007/s12664-022-01286-9.

Shah A, Crawford D, Burger D, Martin N, Walker M, Talley NJ, et.al. Effects of Antibiotic Therapy in Primary Sclerosing Cholangitis with and without Inflammatory Bowel Disease: A Systematic Review and Meta-Analysis. Semin Liver Dis. 2019 Nov;39(4):432-441).

Shen, Bo. “Oral vancomycin in the treatment of primary sclerosing cholangitis-associated pouchitis.” Gastroenterology report vol. 9,3 274-275. 5 Feb. 2021, doi:10.1093/gastro/goab004

Sohal, Aalam, and Kris V Kowdley. “Complete Biochemical Remission With Oral Vancomycin in a Patient With Primary Sclerosing Cholangitis and High Serum Immunoglobulin G4 Levels.” *ACG case reports journal* vol. 11,1 e01256. 16 Jan. 2024, doi:10.14309/crj.0000000000001256ABSTRACT

Tabibian JH, A. A., Lindor KD. (2018). "Primary Sclerosing Cholangitis, Part 2: Cancer Risk, Prevention, and Surveillance. ." Gastroenterol Hepatol: 427-432.

Tan LZ, R. C., Steward-Harrison LC, Balouch F, Muir R, Lewindon PJ (2019). "Oral vancomycin induces clinical and mucosal remission of colitis in children with primary sclerosing cholangitis-ulcerative colitis." Gut: 1533-1535.

Vaughn, B. P., et al. (2019). "A pilot study of fecal bile acid and microbiota profiles in inflammatory bowel disease and primary sclerosing cholangitis." Clin Exp Gastroenterol **12**: 9-19.

Yang, Yi et al. “Within-host evolution of a gut pathobiont facilitates liver translocation.” Nature vol. 607,7919 (2022): 563-570. doi:10.1038/s41586-022-04949-x.

Zigmond, Ehud et al. “Bile Duct Colonization With Enterococcus sp. Associates With Disease Progression in Primary Sclerosing Cholangitis.” *Clinical gastroenterology and hepatology: the official clinical practice journal of the American Gastroenterological Association*, S1542-3565(22)00879-5. 16 Sep. 2022, doi:10.1016/j.cgh.2022.09.006.