

## **The Painful Cycle of Chronic Anal Fissure**

### *Does Nitric Oxide Play a Role?*

Chronic anal fissure (CAF) is a tear in the distal anal canal that causes severe pain during, and often after, defecation. Many fissures become deeper and wider over time, with inflammatory and fibrotic manifestations. Upon examination, fibers of the internal anal sphincter (IAS) may be visible at the base of the fissure and there may be noticeable spasm of the anal canal, which causes pain.<sup>1,2</sup>

### **Nitric oxide and the pain associated with CAF**

CAF is characterized by hypertonicity of the IAS and breakdown of the anoderm due to decreased blood flow.<sup>1,3,4</sup> The resulting ischemic environment contributes to the pain of CAF.<sup>2,5</sup> Nitric oxide (NO), the main inhibitory neurotransmitter that mediates relaxation of the IAS, may play a role in this painful cycle.<sup>1</sup> Research has shown that patients with CAF have a low presence of the enzyme nitric oxide synthase and NO in blood vessels of the IAS.<sup>6</sup> This reduced presence of NO may lead to the decreased blood flow in the IAS and high sphincter tone reported in patients with CAF.<sup>6</sup> NO donors have been shown to improve blood flow and reduce pressure in the IAS.<sup>1</sup> This action has been shown to relieve the pain associated with CAF.<sup>2</sup>

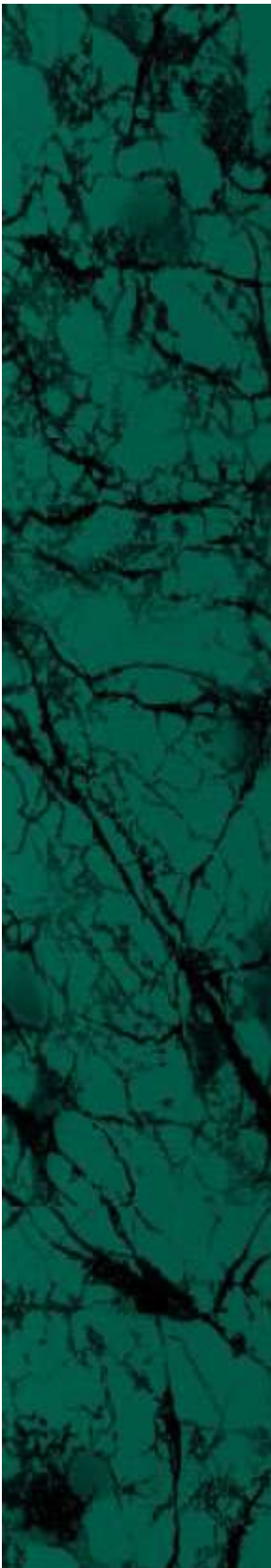
Stephen Gorfine, MD, Clinical Professor of Surgery at Icahn School of Medicine at Mount Sinai in New York City notes that, *"The understanding of nitric oxide's potential role in relaxation of the internal anal sphincter has informed the use of specific nitric oxide donors, such as nitroglycerin, to reduce moderate to severe pain associated with chronic anal fissure. Nitroglycerin applied intra-anally lowers internal anal sphincter pressure and increases anodermal blood flow. Based on evidence derived from controlled clinical trials of nitroglycerin conducted over many years, the American Society of Colon and Rectal Surgeons Practice Parameters support the use of topical nitroglycerin to treat the pain associated with chronic anal fissure during the therapy period."*<sup>7</sup>

### **RECTIV® (nitroglycerin) Ointment 0.4% is the only FDA-approved medication for the treatment of moderate to severe pain associated with CAF<sup>8,9</sup>**

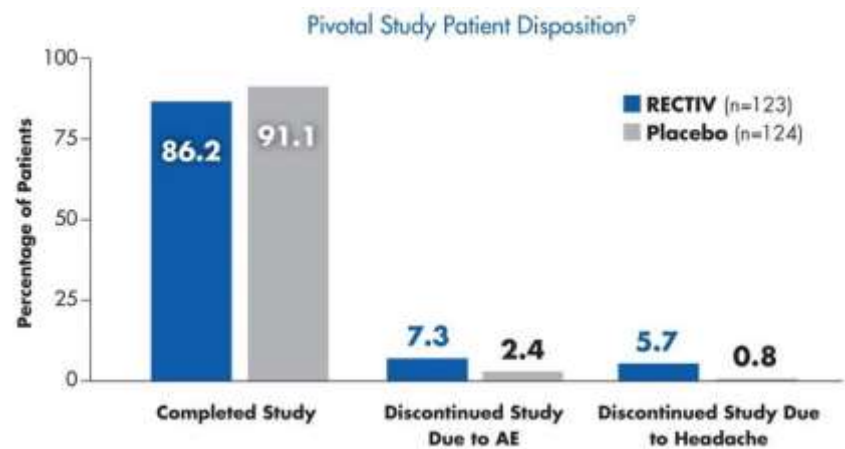
RECTIV features a uniform, standardized formulation that has been clinically tested.<sup>9</sup> Although the exact mechanism of action of nitroglycerin (NTG) in the treatment of pain associated with CAF is unknown, NTG regulates the contractile state in smooth muscle, resulting in vasodilation.<sup>8</sup> When applied topically to the anus, NTG relaxes vascular smooth muscle and reduces sphincter tone and resting intra-anal pressure.<sup>8</sup>

### **On average, patients with moderate to severe pain at baseline reported improvements in pain after 3 weeks of treatment with RECTIV**

In the pivotal phase III, randomized, double-blind, placebo-controlled study of RECTIV, patients with moderate to severe pain due to CAF were randomized to receive RECTIV 0.4% (1.5 mg NTG) or placebo ointment applied to the anal canal every 12 hours.<sup>9</sup> RECTIV significantly lowered pain scores vs placebo (adjusted mean change in average pain score from baseline to days 14 to 18 was -44 mm for RECTIV and -37 mm for placebo; mean placebo-subtracted change=-7.0 mm [95% CI, -13.6 to -0.4 mm; P=0.038]).<sup>8,9</sup> On average, patients with severe pain at baseline reported mild



pain after treatment with RECTIV.<sup>9</sup> These results are consistent with Dr Gorfine’s clinical experience, *“I’ve had success with RECTIV in many patients. Not only is it effective in treating the moderate to severe pain associated with CAF, it doesn’t require compounding, so it’s available at most pharmacies. When I prescribe RECTIV, I know my patients will receive a uniform dose of nitroglycerin.”*



The most common adverse events (AEs) observed in this study for RECTIV and placebo, respectively, were headache (64% vs 41%) and dizziness (5% vs 0%).<sup>8</sup> Headache was not treatment-limiting in most NTG-treated patients. Seven out of 123 patients (5.7%) in the RECTIV group discontinued treatment due to headache; 1 out of 124 patients (0.8%) in the placebo group discontinued treatment due to headache.<sup>9</sup> All patients were instructed to take 650 mg of acetaminophen prior to each administration of study medication for headache prophylaxis.<sup>9</sup>

RECTIV produces dose-related headaches, which may be severe. Tolerance to headache occurs. Headaches may recur after each dose; they are typically short in duration, can be treated with an analgesic, and are reversible upon discontinuation of treatment.<sup>8</sup>

Dr Gorfine explains that with most NTG products, including RECTIV, headaches can occur, *“I explain to my patients that RECTIV increases blood flow to the anal area. That may be why it is useful in relieving the moderate to severe pain associated with chronic anal fissure. That same sort of vasodilation and increased blood flow in the head and brain is what can cause headaches with nitroglycerin. I advise my patients to take an over-the-counter pain medication, such as acetaminophen, to treat these headaches.”*

RECTIV is available for intra-anal use in a standardized, uniform formulation. It does not need to be compounded and is available at most local pharmacies. RECTIV is applied twice a day, for up to 3 weeks.

**Additional Important Safety Information about RECTIV**

RECTIV is contraindicated in patients using phosphodiesterase type 5 (PDE5) inhibitors (eg, sildenafil, vardenafil, and tadalafil), as these are shown to potentiate the hypotensive effects of organic nitrates. RECTIV is also contraindicated in patients with severe anemia, increased intracranial pressure, or known hypersensitivity to nitroglycerin, other nitrates and nitrites, or any components of the ointment. Patients with certain cardiovascular disorders should be closely monitored while taking RECTIV. Venous and arterial dilation as a consequence of nitroglycerin treatment can result in hypotension. Exercise caution in patients with any of the following conditions: blood volume depletion, existing hypotension, cardiomyopathies, congestive heart failure, acute myocardial infarction, or poor cardiac function for other reasons. If patients with any of these conditions are treated with RECTIV, monitor cardiovascular status and clinical condition. The adverse reactions of RECTIV are likely to be more pronounced in the elderly. A number of drug interactions exist with RECTIV, including PDE5 inhibitors,

antihypertensives, aspirin, tissue-type plasminogen activator (t-PA), heparin, ergotamine, and alcohol.

Please see full [Prescribing Information](#) for RECTIV.

For more information about RECTIV, please call 1-800-678-1605, ext. 66297,  
or visit [www.rectiv.com](http://www.rectiv.com).

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Dr. Gorfine is a paid consultant for Aptalis Pharma US, Inc., a wholly-owned indirect subsidiary of Forest Laboratories, Inc.

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