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Oregon State
UNIVERSITY

Drug Use Research & Management Program

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New Dosage Formulation

Month/Year of Review: June 2012

Generic Name: Nitroglycerin ointment 0.4%

PDL Class: N/A

End date of literature search: May 2012

Brand Name (Manufacturer): Rectiv®

Dossier Received: No (Requested)

FDA Approved Indications: Nitroglycerin ointment 0.4% (Rectiv) is a nitrate vasodilator indicated for the treatment of moderate to severe pain associated with chronic anal fissure.¹

Research Questions:

- Does commercially available nitroglycerin ointment 0.4% (Rectiv®) fundamentally change the treatment of and progression of chronic anal fissures?
- Is commercially available nitroglycerin ointment 0.4% (Rectiv®) more effective and safer for the treatment of any covered Oregon Health Plan indication than currently available agents?

Conclusions:

- There is low quality evidence that topical nitroglycerin (NTG) ranging from 0.2% to 0.4% is marginally but significantly better in healing anal fissures compared to placebo.
- There is no evidence demonstrating a difference in efficacy of NTG compared to topical calcium channel blockers or botulinum toxin.
- There is no evidence demonstrating a difference in efficacy between different doses of topical NTG.
- Nitroglycerin ointment 0.4% (Rectiv®) is the first commercially available and FDA approved product for chronic anal fissures and there is insufficient evidence to compare the efficacy to currently available products. Limited, unpublished data demonstrated a significant difference in a patient rated pain score compared to placebo.
- There is no evidence that commercially available nitroglycerin ointment 0.4% is more effective or safer for the treatment of any covered Oregon Health Plan indication.

Recommendations:

- Make nitroglycerin ointment 0.4% non-preferred.
- Require prior authorization for approved OHP diagnoses only (Appendix 1).

Background: Recommendations for initial therapy of anal fissures include conservative measures such as sitz baths, psyllium fiber, bulking agents, and topical anesthetics or anti-inflammatory ointments.² Additional medications are recommended for refractory or chronic anal fissures, including topical nitroglycerin (NTG). Nitroglycerin ointment (Rectiv) is the only FDA-approved prescription product in the United States and has previously been available in Europe and other countries. Currently, locally compounded formulations of topical NTG are used and are generally applied as a 0.2% to 0.4% ointment for anal fissure.³ Rectiv is the first commercially available nitroglycerin ointment that does not have to be compounded. When applied topically to the anus, it increases local blood flow, relaxes anal sphincter tone, and reduces anal pressure.³ After treatment with topical NTG, recurrence of anal fissures occurs in about one-third of the patients over 18 months.³ Other pharmacologic treatments used include calcium channel blockers (CCBs), such as diltiazem and nifedipine, and botulinum toxin (Botox) injected into the anal sphincter.⁴ Topical CCBs also have to be compounded by pharmacies as they are not available in topical form.

A recent 2012 Cochrane assessed the efficacy of medical therapies for anal fissure in an updated systematic review including a total of 5031 participants.⁵ This review demonstrated that in terms of healing anal fissure, there is low quality evidence that topical NTG is marginally but significantly superior to placebo (48.9% vs. 35.5%, $p < 0.0009$; OR 0.35; 95% CI 0.19 to 0.65) and topical NTG causes headache significantly more than those on placebo (OR 4.54; 95% CI 3.01 to 6.85).⁵ All of these studies were in chronic anal fissures only and were of short duration. This review also demonstrated no statistically significant difference in cure rate between NTG and CCBs (OR 0.88; 95% CI 0.54 to 1.42), between topical NTG and the NTG patch (OR 1.07; 95% CI 0.50 to 2.27), or between NTG and botox (OR 0.56; 95% CI 0.20 to 1.57) but in all comparisons, NTG was associated with more adverse events, specifically headache. The risk of headache in the studies combined was 30%.⁵ Three studies evaluated different doses of topical NTG (0.05% to 0.4%) and found that there was no dose response in cure rate (OR 0.91; 95% CI 0.57 to 1.45).

Clinical Efficacy: Nitroglycerin ointment 0.4% was approved based on the reanalysis of the data from a previous Phase 3 clinical unpublished trial that had been unsuccessful in demonstrating effectiveness.⁶ The first analysis of the data used an imputation strategy of baseline-observation-carried-forward (BOCF) and showed no statistically significant difference in pain intensity from baseline between nitroglycerin and placebo ($p=0.118$). It was positioned that the BOCF method was potentially overly conservative in this situation. Two additional methods to impute missing

data were then utilized; the Retrieved Drop-out method and the last-observation-carried-forward (LOCF)/BOCF hybrid method. The LOCF/BOCF method demonstrated a statistically significant difference in the primary efficacy endpoint.⁶

This randomized double-blind, 3-week study took place in adults with moderate to severe pain of at least six weeks in duration due to a chronic anal fissure and compared nitroglycerin ointment to placebo. A total of 247 patients were randomized and 219 completed the trial, resulting in a total attrition of 11.3% (13.8% in the nitroglycerin group vs. 8.9% in the placebo group). The primary efficacy endpoint was the change from baseline in the 24-hour average pain intensity, using the visual analog scale (VAS). There is limited information to assess the quality and risk of bias included in this randomized controlled trial. A statistically significant change from baseline VAS score was seen comparing nitroglycerin ointment to placebo (p=0.038).⁶

Table 1. Primary Outcome Results for Study REC-C-001 using the LOCF/BOCF hybrid analysis

Change from baseline in visual analog scale (VAS) score	Nitroglycerin ointment 0.4% (n=123)	Placebo (n=124)
Change from Baseline Adjusted Means (SE)	-44 (3)	-37 (3.0)
Difference from Placebo (SE)	-7 (3.3); 95% CI (-14 to -0.4)	
p-value	0.038	

Safety: The most common adverse events reported in this study were headache, dizziness, diarrhea, and nausea. There were more discontinuations due to adverse events in the NTG group compared to the placebo group (7.3% vs. 2.4%, RR 3.02; 95% CI 0.78-14.0, p=0.074) and the most common reason within that group was headache, occurring in 64% of patients.^{1,6} It is contraindicated with the use of phosphodiesterase type 5 (PDE5) inhibitors (sildenafil, vardenafil, and tadalafil), as these are shown to potentiate the hypotensive effects of nitrates.

Mechanism of Action: Nitroglycerin forms nitric oxide which regulates the contractile state in smooth muscle and results in vasodilation. Intra-anal application of nitroglycerin reduces sphincter tone and resting intra-anal pressure.¹

Dose and administration: Apply 1 inch of ointment (1.5mg of nitroglycerin) intra-anally every 12 hours for up to 3 weeks.¹

Special Populations: There are no adequate and well-controlled studies in pregnant women, pediatrics, or in the geriatric populations.¹

References:

1. Rectiv Prescribing Information. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021359s000lbl.pdf.
2. Perry WB, Dykes SL, Buie WD, Rafferty JF. Practice parameters for the management of anal fissures (3rd revision). *Dis. Colon Rectum*. 2010;53(8):1110–1115.
3. PL Detail-Document. Rectiv (Nitroglycerin 0.4% Ointment) for Anal Fissure. Pharmacist’s Letter/Prescriber’s Letter. January 2012.
4. Altomare DF, Binda GA, Canuti S, et al. The management of patients with primary chronic anal fissure: a position paper. *Tech Coloproctol*. 2011;15(2):135–141.
5. Nelson RL, Thomas K, Morgan J, Jones A. Non surgical therapy for anal fissure - The Cochrane Collaboration. 2012. Available at: <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003431.pub3/abstract>. Accessed May 8, 2012.
6. Center for Drug Evaluation and Research. Application Number: 21-359. Summary Review. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/021359Orig1s000MedR.pdf.

Appendix 1 : Suggested PA Criteria

Suggested PA

Nitroglycerin Ointment 0.4% (Rectiv)

Goal(s):

- Cover for only OHP covered diagnoses.
- Restrict to indications supported by medical literature.

Length of Authorization: 3 weeks

Approval Criteria		
1. What is the diagnosis?	Record ICD9 code	
2. Is the diagnosis for moderate to severe pain associated with chronic anal fissure?	Yes: Go to #3	No: Pass to RPH; Deny (medical appropriateness).
3. Is the diagnosis an OHP covered diagnosis?	Yes: Approve for 3 weeks	No: Pass to RPH; Deny, (Not covered by the OHP).

P&T Board Action: June 2012

Revision(s):

Initiated: