Rectiv™
(nitroglycerin) Ointment 0.4%

Dear Doctor,

Aptalis Pharma US, Inc. has announced the availability of **RECTIV** (nitroglycerin) Ointment 0.4%, a nitroglycerin formulation approved by the FDA for the treatment of moderate to severe pain associated with chronic anal fissure (CAF). RECTIV does not need to be compounded and is available at most pharmacies, including chain pharmacies.

The dosing for patients with moderate to severe pain from CAF is 1 inch of RECTIV ointment applied intra-anally every 12 hours for up to 3 weeks.*

In a 21-day, randomized, double-blind, placebo-controlled clinical trial of 247 patients, RECTIV significantly reduced moderate to severe pain from CAF vs placebo. Adjusted mean change in average pain visual analog scale (VAS) score from baseline to between days 14 and 18 was 44 mm for RECTIV and 37 mm for placebo (*P*=0.038; 95% CI: -13.6 mm, -0.4 mm).[1,2,†]

†When used BID based on absolute change in 24-hour average pain intensity from baseline to days 14 and 18, as measured by VAS. Mean VAS score at baseline was 72.7 mm for RECTIV and 73.0 mm for placebo; mean VAS score on days 14-18 was 30.7 mm for RECTIV and 37.8 mm for placebo. Based on a hybrid analysis of baseline observation carried forward/last observation carried forward.[2]

The most common adverse events (≥2%) for RECTIV were headache (64%) and dizziness (5%). The incidences of headache and dizziness for placebo were 41% and 0%, respectively.[1] However, headache was not treatment limiting in most patients—nearly 93% of RECTIV patients and nearly 97% of placebo patients completed the trial. All patients were instructed to take a standard dose (650 mg) of acetaminophen before each application of RECTIV or placebo.[2]

RECTIV produces dose-related headaches, which may be severe. Tolerance to headaches occurs. Headaches may recur after each dose of RECTIV; they are typically short in duration, can be treated with an OTC analgesic, and are reversible upon discontinuation of treatment.[1]

*375 mg of ointment is equivalent to 1.5 mg of nitroglycerin.

CI, confidence interval.

Important Safety Information

- RECTIV is contraindicated in patients:
  - Taking phosphodiesterase type 5 (PDE5) inhibitors (eg, sildenafil, vardenafil, and tadalafil), which can potentiate the hypotensive effect of organic nitrates
  - With severe anemia
  - With increased intracranial pressure
  - With known hypersensitivity to nitroglycerin, other nitrates and nitrites, or any components of the ointment
- Patients with cardiovascular disorders should be closely monitored while using RECTIV

- Venous and arterial dilation as a consequence of nitroglycerin treatment can result in hypotension

- Exercise caution when treating 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
- The adverse reactions of RECTIV are likely to be more pronounced in the elderly
- Nitroglycerin produces dose-related headaches, which may be severe
- The following drug interactions may occur in patients taking RECTIV:
  - PDE5 inhibitors: potentiation of hypotensive effects of organic nitrates; concomitant use is contraindicated
  - Antihypertensives: possible additive hypotensive effects
  - Aspirin: increased nitroglycerin levels
  - Tissue-type plasminogen activator (t-PA): decreased thrombolytic effect
  - Heparin: anticoagulant effect of heparin may be reduced. Monitor activated partial thromboplastin time (APTT)
  - Ergotamine: increased bioavailability of ergotamine
  - Alcohol: additive vasodilatory effects to nitroglycerin. Consumption of alcohol should be avoided
- The most common adverse reaction (≥2%) are headache and dizziness
- RECTIV ointment is for intra-anal use, and not for oral, ophthalmic, or intravaginal use

Please see full US Prescribing Information at www.rectiv.com/pdf/rectiv-pi.pdf.

For more information on RECTIV and Aptalis' Patient Assistance Program, please visit www.RECTIV.com/.

Steven Merahn, MD
Chief Medical Officer
Physicians' Desk Reference®

References:

1. Rectiv US Prescribing Information; June 2011.

2. Data on file. Aptalis Pharma US, Inc.

Aptalis Pharma US, Inc.
22 Inverness Center Parkway
Birmingham, Alabama 35242 USA
Tel (800) 472-2634
Fax (205) 991-8426
www.aptalispharma.com 04/12 RE065-0412

RECTIV (nitroglycerin) Ointment 0.4%, for intra-anal use
Rx Only

Initial U.S. Approval: 1955

Brief summary of Prescribing Information. Please consult package insert for full Prescribing Information.

INDICATIONS AND USAGE: RECTIV™ (nitroglycerin) Ointment 0.4% is indicated for the treatment of moderate to severe pain associated with chronic anal fissure.

CONTRAINDICATIONS: PDE5 inhibitor use - Administration of RECTIV is contraindicated in patients who are using a selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5), such as sildenafil, vardenafil, and tadalafil, as these are shown to potentiate the hypotensive effects of organic nitrates [see DRUG INTERACTIONS]. **Severe anemia -** RECTIV is contraindicated in patients with severe anemia. **Increased intracranial pressure -** RECTIV is contraindicated in patients with increased intracranial pressure. **Hypersensitivity -** RECTIV is contraindicated in patients who have shown hypersensitivity to it or to other nitrates or nitrites. Skin reactions consistent with hypersensitivity have been observed with organic nitrates.

WARNINGS AND PRECAUTIONS: Cardiovascular disorders - Venous and arterial dilatation as a consequence of nitroglycerin treatment including RECTIV, can decrease venous blood returning to the heart and reduce arterial vascular resistance and systolic pressure. Exercise caution when treating 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. **Headache -** RECTIV produces dose-related headaches, which may be severe. Tolerance to headaches occurs.

ADVERSE REACTIONS: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The most common adverse reaction of RECTIV (nitroglycerin) Ointment 0.4% applied to the anal canal is headache. Headache may be recurrent following each dose. Headaches are typically of short duration and can be treated with an analgesic, e.g. acetaminophen, and are reversible upon discontinuation of treatment. In Study REC-C-001, a double-blind, placebo-controlled trial in patients with a painful chronic anal fissure, the most frequent (≥ 2%) adverse reactions reported were as follows (Table 1):

Table 1: Incidence of Adverse Reactions (≥ 2%) in Study REC-C-001

	RECTIV N = 123		Placebo N = 124	
System Organ Class Preferred term	**Patients n (%)**	**Events n**	**Patients n (%)**	**Events n**
Nervous system disorders				
Headache	79 (64)	938	51 (41)	225
Dizziness	6 (5)	26	0	0

Hypotension: Transient episodes of light-headedness, occasionally related to blood pressure changes, also may occur. Hypotension (including orthostatic hypotension) occurs infrequently, but in some patients may be severe enough to warrant discontinuation of therapy. *Allergic Reactions:* Flushing, allergic reactions and application site reactions (including drug rash and exfoliative dermatitis) have been reported rarely. *Methemoglobinemia:* In rare cases, therapeutic doses of organic nitrates have caused methemoglobinemia (see OVERDOSAGE).

DRUG INTERACTIONS: PDE5 inhibitors - Phosphodiesterase type 5 (PDE5) inhibitors such as sildenafil, vardenafil, and tadalafil have been shown to potentiate the hypotensive effects of organic nitrates. The time course of the interaction appears to be related to the half-life of the PDE5 inhibitor, however, the dose dependence of this interaction has not been studied. Use of RECTIV within a few days of PDE5 inhibitors is contraindicated. **Antihypertensives -** Patients receiving antihypertensive drugs, beta-adrenergic blockers, and other nitrates should be observed for possible additive hypotensive effects when using RECTIV. Marked orthostatic hypotension has been reported when calcium channel blockers and organic nitrates were used concomitantly. Beta-blockers blunt the reflex tachycardia produced by nitroglycerin without preventing its hypotensive effects. If beta-blockers are used with RECTIV in patients with angina pectoris, additional hypotensive effects may occur. **Aspirin -** Coadministration of aspirin (at doses between 500 mg and 1000 mg) and nitroglycerin has been reported to result in increased nitroglycerin maximum concentrations by as much as 67% and AUC by 73% when administered as a single dose. The pharmacological effects of RECTIV may be enhanced by concomitant administration of aspirin. **Tissue-type Plasminogen Activator (t-PA) -** Intravenous administration of nitroglycerin decreases the thrombolytic effect of tissue-type plasminogen activator (t-PA). Plasma levels of t-PA are reduced when coadministered with nitroglycerin. Therefore, caution should be observed in patients receiving RECTIV during t-PA therapy. **Heparin -** Although an interaction has been reported between intravenous heparin and intravenous nitroglycerin (resulting in a decrease in the anticoagulant effect of heparin), the data are not consistent. If patients are to receive intravenous heparin and RECTIV concurrently, the anticoagulation status of the patient must be checked. **Ergotamine -** Oral administration of nitroglycerin markedly decreases the first-pass metabolism of dihydroergotamine and consequently increases its oral bioavailability. Ergotamine is known to precipitate angina pectoris. Therefore the possibility of ergotism in patients receiving RECTIV should be considered. **Alcohol -** The vasodilating effects of nitroglycerin have been shown to be additive to the effects observed with alcohol.

USE IN SPECIFIC POPULATIONS: Pregnancy - *Pregnancy Category C* - Animal reproduction and teratogenicity studies have not been conducted with RECTIV. Nitroglycerin was not teratogenic when administered by topical or dietary route. There are no adequate and well-controlled studies in pregnant women. RECTIV should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Teratology studies in rats and rabbits were conducted with topically applied nitroglycerin ointment at doses up to 80 mg/kg/day and 240 mg/kg/day, respectively. No toxic effects on dams or fetuses were seen at any dose tested. A teratogenicity study was conducted in rats with nitroglycerin administered in the diet at levels up to 1% content (approximately 430 mg/kg/day) on days 6 to 15 of gestation. In offspring of the high-dose group, an increased but not statistically significant incidence of diaphragmatic hernias was noted together with decreased hyoid bone ossification. The latter finding probably reflects delayed development, thus indicating no clear evidence of a potential teratogenic effect of nitroglycerin. **Nursing Mothers -** It is not known whether nitroglycerin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when RECTIV is administered to a nursing woman. **Pediatric Use -** The safety and effectiveness of RECTIV in pediatric patients under 18 years of age have not been established. **Geriatric Use -** Clinical studies of RECTIV did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Clinical data from the published literature indicate that the elderly demonstrate increased sensitivity to nitrates, which may be therapeutic but also manifest by more frequent or severe hypotension and related dizziness or fainting. Increased sensitivity may reflect the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

OVERDOSAGE: Nitroglycerin toxicity is generally mild. The estimated adult oral lethal dose of nitroglycerin is 200 mg to 1,200 mg. Infants may be more susceptible to toxicity from nitroglycerin. Consultation with a poison center should be considered. Laboratory determinations of serum levels of nitroglycerin and its metabolites are not widely available, and such determinations have, in any event, no established role in the management of nitroglycerin overdose. No data are available to suggest physiological maneuvers (e.g., maneuvers to change the pH of the urine) that might accelerate elimination of nitroglycerin and its active metabolites. Similarly, it is not known which if any of these substances can usefully be removed from the body by hemodialysis. No specific antagonist to the vasodilator effects of nitroglycerin is known, and no intervention has been subject to controlled study as a therapy of nitroglycerin overdose. Because the hypotension associated with nitroglycerin overdose is the result of venodilatation and arterial hypovolemia, prudent therapy in this situation should be directed toward increase in central fluid volume. Passive elevation of the patient's legs may be sufficient, but intravenous infusion of normal saline or similar fluid may also be necessary. The use of epinephrine or other arterial vasoconstrictors in this setting is not recommended. In patients with renal disease or congestive heart failure, therapy resulting in central volume expansion is not without hazard. Treatment of RECTIV overdose in these patients may be subtle and difficult, and invasive monitoring may be required. Methemoglobinemia: Methemoglobinemia has been rarely reported with organic nitrates. The diagnosis should be suspected in patients who exhibit signs of impaired oxygen delivery despite adequate arterial PO_2. Classically, methemoglobinemic blood is described as chocolate brown, without color change on exposure to air. If methemoglobinemia is present, intravenous administration of methylene blue, 1 to 2 mg/kg of body weight, may be required.

PATIENT COUNSELING INFORMATION: See FDA-approved patient labeling (Patient Information and Instructions for Use) in the full prescribing information. **Interaction with PDE5 inhibitors -** Advise patient not to use RECTIV with medications for erectile dysfunction such as Viagra (sildenafil), Levitra (vardenafil), and Cialis (tadalafil). These products have been shown to increase the hypotensive effects of RECTIV and other nitrate drugs. **Hypotension -** Advise patients that treatment with RECTIV may be associated with light-headedness on standing, especially just after rising from a lying or seated position. The effect may be more frequent in patients who have also consumed alcohol, since alcohol use contributes to hypotension. Advise patients to stand up from the supine or sitting position slowly. **Headaches -** Advise patients that headaches sometimes accompany treatment with RECTIV. For patients who get these headaches, the headaches may indicate the activity of the drug. Tolerance to headaches develops. Advise patients that if they experience headache they should not alter the schedule of their RECTIV treatment to avoid the occurrence of headache. An analgesic, such as acetaminophen, may be used to prevent or relieve the headaches. **Dizziness -** Advise patients that dizziness has been reported as a side-effect of treatment with RECTIV. Advise patients not to drive or operate machinery immediately after applying RECTIV.

APTALIS™

Aptalis Pharma US, Inc, 22 Inverness Center Parkway, Birmingham, Alabama 35242 USA, Tel (800) 472-2634, Fax (205) 991-8426, www.aptalispharma.com

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