

# New Zealand Data Sheet

## 1 PRODUCT NAME

RECTOGESIC®

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

0.2% w/w Glyceryl Trinitrate Ointment

## 3 PHARMACEUTICAL FORM

Rectogesic contains the active ingredient Glyceryl trinitrate 0.2% w/w in a smooth light amber ointment formulation for topical application.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

For the treatment of anal fissure and relief of the symptoms associated with anal fissure.

May assist in relief of pain and discomfort associated with haemorrhoids and haemorrhoidectomy.

### 4.2 Dose and method of administration

#### **Adults**

Insert a 1 to 1.5 cm strip of ointment (see measurement on box) into the anal canal, either with the finger or an applicator.

Apply the ointment 3 times daily and do not exceed this dosage.

Close the tube tightly, immediately after each use.

For anal fissure, treatment with Rectogesic should be continued for 2 – 4 weeks, with assessment by a medical practitioner after 2 weeks. For haemorrhoidectomy, treatment with Rectogesic should be continued for a minimum of 2 weeks, with assessment by a medical practitioner after the initial 2 weeks.

#### *Adverse effects*

If headache, fainting or dizziness are observed, treatment should cease for a minimum of 8 hours and then the dosage halved. Simple analgesics such as paracetamol may be helpful for headaches. If headaches are severe and persist, cease administration.

#### *Nitrate-free period*

A daily 'nitrate-free period' of 12 hours is required during treatment with Rectogesic to avoid the development of tolerance. This would normally be overnight.

Where Rectogesic is used concurrently with another nitric oxide donor, the nitrate-free period should correspond with the nitrate-free period already applying to the nitric oxide donor (e.g. this may be during the day for those angina patients who require overnight treatment with glyceryl trinitrate patches).

The frequency of use of Rectogesic may need to be reduced to twice daily when it is used in conjunction with another nitric oxide donor, to reduce the likelihood of adverse systemic effects and to allow an adequate nitrate-free period for the other nitric oxide donor product.

***Use in children***

Safety and effectiveness in children have not been established. This product is intended for Adults Only.

**4.3 Contraindications**

Hypersensitivity to glyceryl trinitrate or any of the excipients in the formulation

Severe anaemia, glaucoma, pregnancy, lactation, hypotension, increased intracranial pressure, idiosyncrasy to glyceryl trinitrate, migraine or recurrent headache, aortic or mitral stenosis, hypertrophic obstructive cardiomyopathy, constrictive pericarditis or pericardial tamponade, postural hypotension, and uncorrected hypovolaemia

Glyceryl trinitrate should not be co-administered with Viagra™ (sildenafil citrate), Cialis (tadalafil), Levitra (vardenafil) which are used to treat erectile dysfunction and/or other Phosphodiesterase Type 5 (PDE5) Inhibitors as this may potentiate the hypotensive effects of organic nitrates.

**4.4 Special warnings and precautions for use**

Glyceryl trinitrate can interfere with the measurement of catecholamines and vanilmandelic acid in the urine, as it increases the excretion of these substances.

Treatment should be stopped if anal bleeding increases.

Patients should be advised to change position slowly when changing from lying or sitting to upright to minimise postural hypotension, especially in patients with low blood volume and under diuretic treatment.

Paradoxical bradycardia and increased angina pectoris may accompany glyceryl trinitrate induced hypotension.

If the physician elects to use glyceryl trinitrate in patients with acute myocardial infarction or congestive heart failure, careful monitoring should be undertaken to avoid hypotension and tachycardia.

***Use in children***

The safety and effectiveness of glyceryl trinitrate in children have not been established.

***Use in the elderly***

No specific information concerning the usage of Rectogesic in the elderly is available.

***Use in renal / hepatic impairment***

No specific information concerning the usage of Rectogesic in renal or hepatic impairment is available

**4.5 Interaction with other medicines and other forms of interaction**

Concomitant use of alcohol may enhance vascular effects.

Concomitant treatment with other vasodilators, calcium channel blockers, ACE inhibitors, and beta-blockers may potentiate the blood pressure lowering effects of Rectogesic.

Acetyl cysteine may potentiate the vasodilatory effects of glyceryl trinitrate.

Concomitant treatment with heparin leads to a decrease in heparin efficacy. Close monitoring of blood coagulation parameters is necessary and the dose of heparin has to be

adapted accordingly. After withdrawal of Rectogesic there may be an abrupt increase in PPT. In this case reduction of heparin dosage may be necessary.

Concurrent administration of glyceryl trinitrate may cause a reduction of the thrombolytic activity of alteplase.

Co-administration of Rectogesic with dihydroergotamine may increase the bioavailability of dihydroergotamine and lead to coronary vasoconstriction.

The possibility that the ingestion of acetylsalicylic acid and NSAIDs might diminish the therapeutic response to Rectogesic cannot be excluded.

#### ***Concomitant use with other nitrates***

Concurrent treatment with Rectogesic and anti-anginal products containing nitrates may interfere with 'nitrate free period' dosage arrangements for the anti-anginal drug. If a patient is already using glyceryl trinitrate or other nitrates for cardiac disease then using Rectogesic could potentially cause tachyphylaxis by eliminating the nitrate free interval. Where another nitric oxide donor anti-anginal drug is used concurrently, Rectogesic should not be used during the nitrate-free dosage arrangements for that product.

## **4.6 Fertility, pregnancy and lactation**

### ***Use in pregnancy (Category B2).***

The safety of RECTOGESIC in pregnancy has not been established. Therefore RECTOGESIC should not be given to pregnant women - see contraindications.

### ***Use in lactation***

It is not known whether glyceryl trinitrate is excreted in human milk. Therefore RECTOGESIC should not be given to lactating women - see contraindications.

## **4.7 Effects on ability to drive and use machines**

As patients may experience faintness and/or dizziness, particularly the elderly, reaction time when driving or operating machinery may be impaired especially at the start of treatment.

## **4.8 Undesirable effects**

Headache is the most common reaction to treatment with glyceryl trinitrate. These are usually mild and usually occur after the first few applications only. In a small number of patients headaches may be severe or persist. If headaches persist the dose should be reduced (see OVERDOSAGE). If the headaches continue to occur or are severe, treatment should be withdrawn. RECTOGESIC may also cause fainting or dizziness, particularly in the elderly.

Incontinence is also a possible adverse reaction, although this has not been reported to date, and should be completely reversible on withdrawal of the drug.

### ***Clinical studies***

In patients treated with Rectogesic 4 mg/g Rectal Ointment, the most common treatment related adverse reaction was dose-related headache which occurred with an incidence of 57%.

Adverse reactions from clinical studies are displayed by system organ class in the table below. Within the system organ class, the adverse reactions are listed by frequency using the following groupings: very common (> 1/10), common (>1/100 <1/10), uncommon (>1/1000 <1/100).

<b>System Organ Class</b>	<b>Frequency</b>	<b>Adverse Reaction</b>
Nervous system disorder	Very common	Headache
	Common	Dizziness
Gastrointestinal disorders	Common	Nausea
	Uncommon	Diarrhoea, anal discomfort, vomiting, rectal bleeding, rectal disorder
Skin and subcutaneous tissue disorders	Uncommon	Pruritus, anal burning and itching
Cardiovascular system disorders	Uncommon	Tachycardia

Adverse reactions to glyceryl trinitrate 2% ointment (used in the prophylaxis of angina pectoris) are generally dose-related and almost all of these reactions are the result of vasodilator activity. Headache, which may be severe, is the most commonly reported side effect. In the Phase III clinical trials with Rectogesic 4 mg/g Rectal Ointment the incidence of mild, moderate and severe headache was 18%, 25% and 20%. Patients with a previous history of migraine or recurrent headache were at a higher risk of developing headache during treatment (see Section 4.3). Headache may be recurrent with each daily dose, especially at higher doses. Headache can be treated with mild analgesics e.g. paracetamol and in general is reversible on discontinuation of treatment.

Transient episodes of light-headedness, occasionally related to blood pressure changes, also may occur. Hypotension occurs infrequently, but in some patients may be severe enough to warrant discontinuation of therapy. Syncope, crescendo angina and rebound hypertension have been reported but are uncommon. Allergic reactions to glyceryl trinitrate are uncommon, and the great majority of those reported have been cases of contact dermatitis or fixed drug eruptions occurring in patients receiving glyceryl trinitrate in ointments or patches. There have been a few reports of genuine anaphylactoid reactions and these reactions can probably occur in patients receiving glyceryl trinitrate by any route. Extremely rarely, ordinary doses of organic nitrates have caused methaemoglobinaemia in normal-seeming patients. Flush has been observed as a rare adverse reaction for other products containing glyceryl trinitrate.

## 4.9 Overdose

Headache, fainting or dizziness are the most common indication of overdose.

When these symptoms are observed, treatment should cease for a minimum of 8 hours and then the dosage halved. Simple analgesics such as paracetamol may be helpful for headaches. If headaches are severe and persist, cease administration.

Accidental overdose of Rectogesic may result in hypotension and reflex tachycardia.

Excessive dosage may give rise to methaemoglobinaemia.

The Poisons Information Centre should be contacted on 0800 764 766 for advice in case of overdose.

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

ATC code C05AE01

The principal pharmacologic action of glyceryl trinitrate is mediated via the release of nitric oxide. When glyceryl trinitrate ointment is applied by the intra-anal route, the internal anal

sphincter becomes relaxed.

Hypertonicity of the internal but not the external anal sphincter is a predisposing factor in the formation of anal fissures. The blood vessels to the anoderm course through the internal anal sphincter (IAS). Therefore hypertonicity of the IAS may thereby decrease blood flow and cause ischaemia to this region.

Distension of the rectum results in the anorector inhibitory reflex and relaxation of the internal anal sphincter. The nerves mediating this reflex lie in the wall of the gut. Release of the neurotransmitter NO from nerves of this type play a significant role in the physiology of the internal anal sphincter. Specifically, NO mediates the anorector inhibitory reflex in man, relaxing the IAS.

The link between IAS hypertonicity and spasm and the presence of an anal fissure has been established. Patients with chronic anal fissure have a significantly higher mean maximum resting anal pressure than controls and anodermal blood flow in chronic anal fissure patients was significantly lower than in controls.

In patients whose fissures healed following a sphincterotomy, a reduction in anal pressure and improvement in anodermal blood flow was demonstrated, providing further evidence for the ischaemic nature of anal fissure. Topical application of a NO donor (glyceryl trinitrate) relaxes the anal sphincter, resulting in a reduction of anal pressure and an improvement in anoderm blood flow.

#### *Clinical trials - effect on pain*

In three Phase III clinical trials Rectogesic 4 mg/g Rectal Ointment has been shown to improve the average daily pain intensity associated with chronic anal fissure compared with placebo, measured using a 100mm visual analogue scale.

In the first study, Rectogesic 4 mg/g Rectal Ointment decreased average daily pain intensity over 21 days by 13.3mm (baseline 39.2mm) compared to 4.3mm (baseline 25.7mm) for placebo ( $p < 0.0063$ ) and over 56 days by 18.8mm compared to 6.9mm ( $p < 0.0001$ ), respectively. This corresponds to a treatment effect (difference between the percentage change for Rectogesic and placebo) of 17.2% over 21 days and 21.1% over 56 days.

In the second study, Rectogesic 4 mg/g Rectal Ointment decreased average daily pain intensity over 21 days by 11.1mm (baseline 33.4mm) compared to 7.7mm (baseline 34.0mm) for placebo ( $p < 0.0388$ ) and over 56 days by 17.2mm compared to 13.8mm ( $p < 0.0039$ ), respectively. This corresponds to a treatment effect of 10.6% over 21 days and 10.9% over 56 days.

In the third study, Rectogesic 4 mg/g Rectal Ointment decreased average daily pain intensity over 21 days by 28.1mm (baseline 55.0mm) compared to 24.9mm (baseline 54.1mm) for placebo ( $p < 0.0489$ ) and over 56 days by 35.2mm compared to 33.8mm ( $p < 0.0447$ ), respectively. This corresponds to a treatment effect of 5.1% over 21 days and 1.5% over 56 days.

#### *Clinical trials - effect on healing*

In all three studies, healing of anal fissures in patients treated with Rectogesic 4 mg/g Rectal Ointment was not statistically different from placebo. Rectogesic is not indicated for healing of chronic anal fissure.

## 5.2 Pharmacokinetic properties

The volume of distribution of glyceryl trinitrate is about 3 L/kg and is cleared from this volume

at extremely rapid rates, with a resulting serum half-life of about 3 minutes. The observed clearance rates (close to 1 L/kg/min) greatly exceed hepatic blood flow. The known sites of extrahepatic metabolism include red blood cells and vascular walls. The initial products in the metabolism of glyceryl trinitrate are inorganic nitrate and the 1,2 and 1,3-dinitroglycerols. The dinitrates are less effective vasodilators than glyceryl trinitrate, but they are longer lived in the serum. Their contribution to the relaxation of the internal anal sphincter is unknown. The dinitrates are further metabolised to non-vasoactive mononitrates and ultimately to glycerol and carbon dioxide. In six healthy subjects, the average bioavailability of glyceryl trinitrate applied to the anal canal as a 0.2% ointment was approximately 50% of the 0.75 mg dose.

### 5.3 Preclinical safety data

There are no preclinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

The other ingredients in RECTOGESIC are alcohol, lanolin, liquid paraffin and yellow soft paraffin.

### 6.2 Incompatibilities

None known.

### 6.3 Shelf life

RECTOGESIC shelf life is 36 months

### 6.4 Special precautions for storage

Store at or below 25°C.

### 6.5 Nature and contents of container

30g aluminium tubes

### 6.6 Special precautions for disposal

No special requirements

## 7 MEDICINE SCHEDULE

Pharmacist Only Medicine

## 8 SPONSOR

Pharmacy Retailing (NZ) Ltd t/a Healthcare Logistics  
54 Carbine Road  
Mt Wellington  
Auckland

## 9 DATE OF FIRST APPROVAL

26 April 2002

## 10 DATE OF REVISION OF THE TEXT

29 December 2016.

## SUMMARY TABLE OF CHANGES

Section changed	Summary of new information