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Prescribing Information

1. NAME OF THE MEDICINAL PRODUCT

Rectogesic Rectal Ointment.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Glyceryl trinitrate: 4 mg/g.

One gram of rectal ointment contains 4 mg Glyceryl trinitrate (GTN). The delivered dose from 375 mg of this formulation is approximately 1.5 mg GTN.

Excipient(s) with known effect:
The ointment also contains 36 mg Propylene Glycol, and 140 mg Lanolin, per gram rectal ointment.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Rectal ointment.
Off-white smooth opaque ointment formulation.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Rectogesic 4 mg/g Rectal Ointment is indicated for relief of pain associated with chronic anal fissure.

In the clinical development of the drug, a modest effect has been shown on improvements in average daily pain intensity (see Section 5.1).

4.2 Posology and method of administration

Route of administration: rectal use

Adults:
A finger covering, such as cling film or a finger cot, may be placed on the finger to be used to apply the ointment. (Finger cots to be obtained separately from local pharmacy or surgical supplies retailer or cling film from local store.) The finger is placed along side a 2.5cm dosing line which is provided on the outside carton in which Rectogesic is supplied, and a strip of ointment the length of the line is expressed onto the end of the finger by gently squeezing the tube. The amount of ointment expressed is approximately 375 mg (1.5 mg GTN). The covered finger is then gently inserted into the anal canal to the distal interphalangeal joint of the finger and applied circumferentially to the anal canal.

The dose delivered from the 4 mg/g ointment is 1.5 mg glyceryl trinitrate. The dose is to be applied intra-anally every twelve hours. Treatment may be continued until the pain abates, up to a maximum of 8 weeks.

Rectogesic should be used following conservative treatment failure for acute symptoms of anal fissure.

Elderly (over 65 years):

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

Patients with Hepatic or Renal Impairment

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

Children and Adolescents:

Rectogesic is not recommended for use in children and adolescents below 18 years of age due to a lack of data on safety and efficacy.

4.3 Contraindications

Hypersensitivity to the active substance "glyceryl trinitrate" or to any of the excipients listed in section 6.1 or to other organic nitrates.

Concomitant treatment with phosphodiesterase type 5 (PDE5) inhibitors e.g. sildenafil citrate, tadalafil, vardenafil and other organic nitrates with nitric oxide (NO) donors, such as other long-acting GTN products, isosorbide dinitrate and amyl or butyl-nitrite.

Postural hypotension, hypotension or uncorrected hypovolaemia as the use of glyceryl trinitrate in such states could produce severe hypotension or shock.

Increased intracranial pressure (e.g. head trauma or cerebral haemorrhage) or inadequate cerebral circulation.

Migraine or recurrent headache.

Aortic or mitral stenosis.

Hypertrophic obstructive cardiomyopathy.

Constrictive pericarditis or pericardial tamponade.

Marked anaemia.

Closed-angle glaucoma.

4.4 Special warnings and precautions for use

The risk/benefit ratio of Rectogesic has to be established on an individual basis. In some patients, following treatment with Rectogesic, severe headache can occur. In some cases re-evaluation of the correct dosing is suggested. In patients where the risk benefit ratio is deemed to be negative, treatment with Rectogesic should be withdrawn under the guidance of a physician and other therapeutic or surgical interventions should be initiated.

Rectogesic should be used with caution in patients who have severe hepatic or renal disease.

Excessive hypotension, especially for prolonged periods of time, must be avoided because of possible deleterious effects on the brain, heart, liver and kidney from poor perfusion and the attendant risk of ischaemia, thrombosis and altered function of these organs. Patients should be advised to change position slowly when changing from lying or sitting to upright to minimize postural hypotension. This advice is particularly important for those patients with low blood volume and under diuretic treatment. Paradoxical bradycardia and increased angina pectoris may accompany glyceryl trinitrate-induced hypotension. The elderly may be more susceptible to the development of postural hypotension, particularly on sudden rising. No specific information concerning the usage of Rectogesic in the elderly is available.

Alcohol may enhance the hypotensive effects of glyceryl trinitrate.

If the physician elects to use glyceryl trinitrate ointment for patients with cardiac disorders, e.g. acute myocardial infarction or congestive heart failure, careful clinical and haemodynamic monitoring must be used to avoid the potential hazards of hypotension and tachycardia.

If bleeding associated with haemorrhoids increases, treatment should be stopped.

This formulation contains propylene glycol and lanolin which may cause skin irritations and skin reactions (e.g. contact dermatitis).

If anal pain persists, differential diagnosis may be required to exclude other causes of the pain.

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

Concomitant treatment with a number of other medicinal products should be handled with caution. Please refer to section 4.5 for specific information.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant treatment with other vasodilators, calcium channel blockers, ACE inhibitors, beta blockers, diuretics, anti-hypertensives, tricyclic anti-depressants and major tranquillisers, as well as the consumption of alcohol, may potentiate the blood pressure lowering effects of Rectogesic. Therefore, concomitant treatment with these medications should be carefully considered before treatment with Rectogesic is initiated.

The hypotensive effect of organic nitrates are potentiated by concurrent administration of phosphodiesterase type 5 (PDE5) inhibitors, e.g. sildenafil, tadalafil and vardenafil (see Section 4.3).

Rectogesic is contraindicated for concomitant treatment with, nitric oxide (NO) donors such as isosorbide dinitrate and amyl or butyl-nitrite (see Section 4.3).

Acetyl cysteine may potentiate the vasodilatory effects of glyceryl trinitrate.

Concomitant treatment of intravenous glyceryl trinitrate with intravenous 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 PTT. In this case reduction of heparin dosage may be necessary.

Concurrent administration of intravenous glyceryl trinitrate and alteplase 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 non-steroidal anti-inflammatory drugs might alter the therapeutic response to Rectogesic cannot be excluded.

4.6 Fertility, Pregnancy and lactation

Fertility
There are no data available on the effect of Rectogesic on fertility in humans. Studies in rats suggest no particular hazard under recommended conditions of use (see Section 5.3).

Pregnancy: There are no adequate data from the use of glyceryl trinitrate in pregnant women. Animal studies are inconclusive with respect to effects on pregnancy embryonal/foetal parturition and postnatal development (see Section 5.3). Rectogesic should not be used during pregnancy.

Lactation: It is not known whether glyceryl trinitrate is excreted in human milk. Due to the potential harmful effects on the breast fed child (see Section 5.3), the use of Rectogesic is not recommended during breast feeding.

4.7 Effects on ability to drive and use machinery

No studies on the effect on the ability to drive and use machines have been performed with Rectogesic. Rectogesic may cause dizziness, light-headedness, blurred vision, headache or tiredness in some patients, especially on first use. Patients should be cautioned about driving or operating machinery while using Rectogesic.

4.8 Undesirable effects

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).

System Organ Class	Frequency	Adverse Reaction
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 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 is reversible on discontinuation of treatment.

Rare cases of orthostatic hypotension-type events associated with symptoms of vertigo and dizziness were reported in clinical trials. There was no discernible dose-related trend in the incidence of these events.

The orthostatic hypotension-type event was of mild intensity in the majority of these patients, and there were no severe orthostatic hypotension-type events reported during the Phase III clinical studies.

Dizziness and vertigo contributed to the discontinuation of glyceryl trinitrate in a few cases.

Post-marketing Experience
Because these reactions are received from spontaneous reporting, the frequency is not known (cannot be estimated from the available data).
Nervous system disorders: Lightheadedness, syncope
Vascular disorders: Hypotension, orthostatic hypotension
Immune system disorders: Hypersensitivity, anaphylactoid reaction
General disorders and administration site conditions: Application site irritation, application site rash, application site pain

Lightheadedness and hypotension (including orthostatic hypotension) in some patients may be severe enough to warrant discontinuation of therapy.

Class effects
Extremely rarely, ordinary doses of organic nitrates have caused methaemoglobinaemia in normal–seeming patients. Flushing, unstable angina and withdrawal hypertension may also occur.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form

http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il

In additionally, you can report to Perrigo via the following address: www.perrigo-pharma.co.il

4.9 Overdose

Accidental overdose of Rectogesic may result in hypotension and reflex tachycardia. No specific antagonist of the vasodilator effects of glyceryl trinitrate is known, and no intervention has been subjected to controlled study as a therapy for glyceryl trinitrate overdose. Because the hypotension associated with glyceryl trinitrate overdose is the result of venodilation and arterial hypovolaemia, prudent therapy in this situation should be directed toward increasing 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. In exceptional cases of severe hypotension or shock, resuscitation measures may be needed.

Excessive dosage may also give rise to methaemoglobinaemia. This should be treated with methylene blue infusion.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Muscle relaxants
ATC Code: C05AE01

The principal pharmacologic action of glyceryl trinitrate is relaxation of vascular smooth muscle 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.

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.

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 Pre-clinical safety data

Repeat Dose Toxicity
No systemic toxicity studies have been conducted with Rectogesic. Published data suggest that high oral doses of glyceryl trinitrate may have toxic effects (methaemoglobinaemia, testicular atrophy and aspermatogenesis) in long term treatment. However, these findings represent no special hazards for humans under the conditions of therapeutic use.

Mutagenicity and carcinogenicity
Data from preclinical studies with GTN indicate genotoxic effects in the repair deficient S. typhimurium strain TA1535 only. Lifetime dietary administration of GTN to rodents led to the conclusion that nitroglycerin has no carcinogenic effects relevant for the therapeutic dose range in humans.

Reproductive Toxicity
Reproductive toxicity studies, in rats and rabbits with intravenous, intraperitoneal, and dermal administration of glyceryl trinitrate did not show any adverse effects on fertility or embryonic development at dosages which did not induce parental toxicity. No teratogenicity had been observed. In rats foetotoxic effects (decreased birth weights) were seen at dosages above 1 mg/kg/d (i.p.) and 28 mg/kg/d (dermal) after in utero exposure during foetal development.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

White soft paraffin
Lanolin anhydrous
Hard paraffin
Propylene glycol
Sorbitan sesquioleate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials

After first opening: 8 weeks

6.4 Special precautions for storage

Do not store above 25°C.
Do not freeze.
Keep the tube tightly closed.

6.5 Nature and contents of container

30 g
Aluminium tubes with white polyethylene non-piercing screw caps.

6.6 Special Precautions for disposal

No special requirements.

7 Manufacturer

PHARBIL Waltrop GmbH, Germany

8 Registration Holder

Perrigo Israel Agencies Ltd., 1 Rakefet St., Shoham, Israel

9 Marketing Authorization Number

140-66-31709

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