Public Assessment Report

Mutual Recognition Procedure

Rectogesic 0.4% Rectal Ointment

UK licence no: PL 16508/0037

PROSTRAKAN LIMITED
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Module 1

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<th>Rectogesic 0.4% Rectal Ointment</th>
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<td>Type of Application</td>
<td>Bibliographic, Article 10.1(a)(ii)</td>
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<td>Glyceryl trinitrate</td>
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<td>Form</td>
<td>Rectal Ointment</td>
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<td>Strength</td>
<td>0.4% w/w</td>
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<td>MA Holder</td>
<td>Prostrakan Limited, 3 Galabank Business Park, Queen Street, Galashields, TD1 1QH, UK</td>
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<td>UK</td>
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Module 2

Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT
Rectogesic 4 mg/g Rectal Ointment.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Glyceryl trinitrate: 4 mg/g.

One gram of rectal ointment contains 40 mg Glyceryl trinitrate in propylene glycol corresponding to 4 mg Glyceryl trinitrate (GTN). The delivered dose from 375 mg of this formulation is approximately 1.5 mg GTN.

The ointment also contains 36 mg Propylene Glycol, and 140 mg Lanolin, per gram rectal ointment.

For a 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 glycercyl 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
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 or idiosyncratic reactions to other organic nitrates.

Concomitant treatment with sildenafil citrate, tadalafil, vardenafil, and 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 reevaluation 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 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 nitrates are potentiated by concurrent administration of phosphodiesterase inhibitors, e.g. sildenafil, tadalafil, vardenafil and theophylline. (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 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 PTT. 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 non-steroidal anti-inflammatory drugs might diminish the therapeutic response to Rectogesic cannot be excluded.

4.6 Pregnancy and lactation
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 Effect 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).

<table>
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<tr>
<th>System Organ Class</th>
<th>Frequency</th>
<th>Adverse Reaction</th>
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<td>Nervous system disorder</td>
<td>Very common</td>
<td>Headache</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Common</td>
<td>Dizziness</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Diarrhoea, anal discomfort, vomiting, rectal bleeding, rectal disorder</td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Uncommon</td>
<td>Pruritus, anal burning and itching</td>
</tr>
<tr>
<td>Cardiovascular system disorders</td>
<td>Uncommon</td>
<td>Tachycardia</td>
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</table>
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
Accidental overdose of Rectogesic may result in hypotension and reflex tachycardia. No specific antagonist of the vasodilator effects of nitroglycerin is known, and no intervention has been subjected to controlled study as a therapy for nitroglycerin overdose. Because the hypotension associated with nitroglycerin 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: pending
ATC Code: pending

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 anodermal 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 and carcinogenic effects. However, an increased carcinogenic risk under the conditions of therapeutic use is considered very unlikely.

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
Propylene glycol
Lanolin
Sorbitan sesquioleate
Hard paraffin
White soft paraffin

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years
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. MARKETING AUTHORISATION HOLDER
Prostrakan Limited,
3 Galabank Business Park,
Queen Street,
Galashields,
TD1 1QH,
UK

8. MARKETING AUTHORISATION NUMBER
PL 16508/0037

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION
August 2004

10. DATE OF (PARTIAL) REVISION OF THE TEXT
21/12/2006
Module 3

Product Information Leaflet
Read all of this leaflet carefully before you start using this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- The information in this leaflet applies only to Rectogesic 4 mg/g Rectal Ointment.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. WHAT Rectogesic IS AND WHAT IT IS USED FOR
2. BEFORE YOU USE Rectogesic
3. HOW to use Rectogesic
4. POSSIBLE side effects
5. Storing Rectogesic
6. Further information

1. WHAT Rectogesic IS AND WHAT IT IS USED FOR

Rectogesic is a rectal ointment which contains the active substance glyceryl trinitrate. Glyceryl trinitrate belongs to a group of medicines called organic nitrates.

The ointment will help to relieve the symptom of pain caused by chronic anal fissures. An anal fissure is a break in the skin lining the anal canal. Topical application of glyceryl trinitrate to the anal canal reduces the anal pressure and increases the blood flow, thereby reducing pain.

2. BEFORE YOU USE Rectogesic

Do not use Rectogesic:
- if you are allergic to glyceryl trinitrate or to similar medicines
- if you are allergic to any of the other ingredients in the product
- if you suffer from low blood pressure
- if you suffer from heart or blood vessel disorders
- if you suffer from closed-angle glaucoma - a condition where pressure inside the eye rises rapidly causing loss of vision
- if you suffer from migraine or recurrent headaches
- if you suffer from increased intracranial pressure or high pressure within your skull (e.g. head trauma or cerebral haemorrhage - bleeding from a ruptured blood vessel in the brain that can be fatal without prompt medical treatment. Cerebral haemorrhage is commonly referred to as a type of stroke) or inadequate cerebral circulation (low volume of blood circulation within your brain)
- if you suffer from anaemia (low iron content in your blood)
- if you are taking any of the following medicines: sildenafil citrate, tadalafl, vardenafl, medicines for angina or heart pain such as glyceryl trinitrate (GTN), isosorbide dinitrate, amyl or butyl nitrite, medicines for high blood pressure or depression (tricyclic anti-depressants), acetyl cysteine or alteplase

Take special care with Rectogesic:
- if you suffer from liver or kidney disease
- if you are to be given heparin, close monitoring of your blood will be required as your dose of heparin may need to be altered. Please discuss with your doctor before stopping Rectogesic
- if you also have haemorrhoids (piles) and notice more bleeding than usual, you should stop using Rectogesic and discuss this with your doctor
- if you get severe headaches when using Rectogesic, please tell your doctor. Your doctor will decide if you need to use a different amount of Rectogesic, or stop using it completely.

Rectogesic may lower your blood pressure. When getting up from a lying or sitting position, you should get up slowly, otherwise you might feel faint. Your blood pressure is more likely to be lowered if you drink alcohol whilst you are using Rectogesic.

Rectogesic is not suitable for children and adolescents under the age of 18 years because it has not been assessed in people in this age group.

Taking Rectogesic with other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines including medicines obtained without a prescription.

The following medicines may increase the blood pressure lowering effect of Rectogesic:
- Medicines for depression (tricyclic anti-depressants)
- Medicines for erectile dysfunction (male impotence) (sildenafil citrate, tadalafl, vardenafl)
- Medicines for high blood pressure
- Diuretics ("water tablets")
- Commonly used tranquillizers
- Medicines used to treat heart problems (isosorbide dinitrate and amyl or butyl nitrite)

Other Medicines
- Acetylsalicylic acid (aspirin) and non-steroidal anti-inflammatory drugs (certain types of painkillers) might lower the therapeutic effect of Rectogesic

Taking Rectogesic with food and drink

Be careful that drinking alcohol as the ointment may affect you more than usual.

Pregnancy and breast-feeding

You should not use Rectogesic during pregnancy or when breast-feeding.

Ask your doctor or pharmacist for advice before taking any medicine when pregnant or breast feeding.

Driving and using machines

No studies on the effect on the ability to drive and use machines have been performed with Rectogesic 4 mg/g Rectal Ointment. If you feel dizzy, sleepy or have blurred vision when you start to use the ointment, do not drive or work machinery until these effects have worn off.

Important information about some of the ingredients of Rectogesic.

This medicinal product contains lanolin (wool fat) which may cause a skin reaction (e.g. contact dermatitis). The product also contains propylene glycol which may cause skin irritation.
3. **HOW TO USE RECTOGESIC**

**Method of Administration**

Rectogesic 4 mg/g Rectal Ointment is for Rectal Use.

Always use Rectogesic exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure. The usual dose is approximately 375 mg of ointment (approximately 1.5 mg glyceryl trinitrate) applied to the anal canal every 12 hours.

A finger covering, such as a cling film or a finger cot, may be placed on the finger to be used to apply the ointment. Finger cots can be obtained from your local pharmacy or surgical supplies retailer or cling film from your local store. The covered finger is placed along side the 2.5 cm dosing line, which is provided on the outside carton, and a strip of ointment the length of the line is expressed onto the end of finger by gently squeezing the tube. Gently insert the ointment into the anal canal using the finger. The finger with the ointment must be inserted to the first finger joint (approximately 1 cm) into the anus.

Apply the ointment every twelve hours as directed by your doctor and do not exceed the dose. Wash hands after use and dispose of the finger cot or plastic wrap (not down the toilet).

Treatment may be continued until the pain goes away, or for up to a maximum 8 weeks. If your anal pain does not get better after using Rectogesic you should talk to your doctor again to check that something else is not causing the pain.

**If you use more Rectogesic than you should**

If you may have used more ointment than you should you may feel dizzy and light-headed. You may also have fast heart beats or palpitations. If you feel these symptoms wipe away any extra ointment and then talk to your doctor or pharmacist immediately.

**If you forget to apply Rectogesic**

Do not use a double dose to make up for forgotten individual doses. Apply the next dose at the usual time.

**If you have any further questions on the use of Rectogesic, ask your doctor or pharmacist.”**

4. **POSSIBLE SIDE EFFECTS**

Like all medicines, Rectogesic can have side effects, although not everybody gets them. Tell your doctor if you notice any of the following:

- **Very Common (occur in more than 1 patient in 10)**
  - Headaches, which may be severe. If you develop a headache as a side effect, wipe off any ointment. If the headaches are unpleasant, you may need to ask your doctor whether you should stop using the medicine.
  - Nausea
  - Uncommon (occur in more than 1 patient in 10 patients but less than 1 in 100 patients)
  - Diarrhoea, anal discomfort, vomiting, rectal bleeding, rectal disorder
  - Allergic skin reactions
  - Itching or burning of the anal canal
  - Fast heart beat or palpitations
  - Flush

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. **HOW TO STORE RECTOGESIC**

Keep out of the reach and sight of children.

Do not use Rectogesic after the expiry date which is stated on the label and carton after “Exp.”

The expiry date refers to the last day of that month.

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

Once opened use up the ointment within 8 weeks.

6. **FURTHER INFORMATION**

**What Rectogesic contains**

The active substance is glyceryl trinitrate. One gram of rectal ointment contains 40 mg glyceryl trinitrate in propylene glycol corresponding to 1 mg glyceryl trinitrate. Approximately 1.5 mg glyceryl trinitrate is contained in the usual 375 mg dose of Rectogesic.

The other ingredients are: propylene glycol, lanolin, sorbitan sesquioleate, hard paraffin and white soft paraffin.

**What Rectogesic looks like and contents of the pack**

Rectogesic is an off-white smooth opaque rectal ointment supplied in 30g aluminium tubes.

**Marketing Authorisation Holder and Manufacturer**

Marketing Authorisation Holder

ProStrakan Limited
Goldbank Business Park
Glasgow
TD1 1QH
UK
Tel. 01896 664000
Fax. 01896 664001

Manufacturer

Penn Pharmaceutical Services Limited
Units 238-24, Trafalmouth Industrial Estate
Tredgar, Gwent NP22 3AA
United Kingdom

This leaflet was last approved:
Module 4

Labelling
Rectogesic®

4 mg/g Rectal Ointment

glyceryl trinitrate 4 mg/g

30 g

Active Ingredient: Glyceryl trinitrate 4 mg/g

One gram of rectal ointment contains 40 mg of glyceryl trinitrate in propylene glycol corresponding to 4 mg of glyceryl trinitrate. The other ingredients are white soft paraffin, lanolin, propylene glycol, hard paraffin and sorbitan sesquioleate.

Use as directed by the medical practitioner.

Read the package leaflet before use.

For rectal use.

Do not store above 25°C.

Do not freeze.

Keep the tube tightly closed; use within 8 weeks of opening.

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.

Marketing Authorisation Holder:
ProStrakan Limited
Galabank Business Park
Galashiels
TD1 1QH
UK

Marketing Authorisation Number:
PL 16508/0037

POM
Module 5

Scientific discussion during initial procedure

I  INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the MHRA has granted a marketing authorisation for Rectogesic 0.4% Rectal Ointment to Cellegy UK Limited for the relief of pain associated with chronic anal fissure.

This application was made under Article 10a of 2001/83 EC, a bibliographic application, for Rectogesic 0.4% Rectal Ointment, a prescription-only medicine.

Article 10a requires that the active constituent have a ‘well established medicinal use, with an acceptable level of safety and with recognised efficacy’. The basic requirement for this is that the active substance has been used as a medicinal product in the EU for not less than one decade. GTN has a very long history of medicinal use for cardiovascular indications. The literature provided refers to numerous clinical trials of such products for the treatment of anal fissure and so indicates a significant extent and scientific interest in the use of this substance for this indication. Therefore, an application under Article 10a can be accepted.

This is a mixed dossier.

Rectogesic® Rectal Ointment contains the active drug substance glyceryl trinitrate (nitroglycerin, NTG or GTN) which is an organic nitrate in an ointment formulation for topical application. The action of GTN is a result of the generation of nitric oxide (NO) on metabolism in the body. NO acts as a neurotransmitter that mediates the relaxation of smooth muscle, and has been postulated to control relaxation of the internal anal sphincter. Therapeutically administered NO, via GTN, is believed to reverse the excessive sphincter tone thought to be a predisposing factor in the formation of anal fissures.

Anal fissure is a crack in the anal mucosa and is a common benign disease affecting both men and women. Anal fissures are associated with intense pain and/or anal bleeding, especially following defecation. There is considerable evidence that increased hypertonicity of the internal anal sphincter is a predisposing factor in the formation of anal fissures and possibly haemorrhoids. The action of nitric oxide (NO) in relaxation can be harnessed therapeutically to reverse the excessive sphincter tone. Reduction of hypertonicity by NTG (acting via NO) has been shown to be clinically useful in the treatment of anal fissures.

Preclinical studies were carried out in accordance with Good Laboratory Practice (GLP), and in accordance with recognised guidelines. No toxicity was demonstrated, and no new toxicological problems for these products were found. The local tolerance study was conducted in accordance with GLP.

Clinical studies on Rectogesic 0.4% Rectal Ointment were carried out in accordance with Good Clinical Practice (GCP). The clinical programme showed that Rectogesic 0.4% Rectal Ointment provides satisfactory clinical benefits.

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product prior to granting its national authorisation.
For manufacturing sites outside the community, the RMS has accepted copies of current GMP Certificates or satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The product was granted marketed authorisations on 24th August 2004. With the UK as Reference Member State in this Mutual Recognition Procedure (MRP), the marketing authorisation holder (Cellegy UK Limited) gained approval for marketing authorisation in Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Luxembourg, The Netherlands, Norway, Poland, Portugal, Slovak Republic, Spain and Sweden.

The licence for Rectogesic 0.4% Rectal Ointment (PL 19075/0003) was subsequently cancelled in the UK on 22nd March 2007 and a Change of Ownership granted to change the licence to Prostrakan Limited (PL 16508/0037). Please note that the documents in this PAR refer to the licence at the time of original assessment (PL 19075/0003).

II. ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Rectogesic 0.4% Rectal Ointment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>Glyceryl trinitrate (nitroglycerine)</td>
</tr>
<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Vasodilators used in cardiac disease (C01DA02)</td>
</tr>
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<td>Pharmaceutical form and strength(s)</td>
<td>Rectal Ointment (0.4% w/w)</td>
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<tr>
<td>Reference Member State</td>
<td>United Kingdom</td>
</tr>
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<td>Member States concerned</td>
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</tr>
<tr>
<td>Name and address of manufacturer responsible for batch release in the EEA</td>
<td>Penn Pharmaceuticals Services Limited, Units 23 and 24, Tafarnaubach Industrial Estate, Tredegar, Gwent, NP22 3AA</td>
</tr>
<tr>
<td>Date of first authorisation</td>
<td>24th August 2004</td>
</tr>
<tr>
<td>Marketing Authorisation Number(s)</td>
<td>PL 16508/0037 (formerly PL 19075/0003)</td>
</tr>
<tr>
<td>Name and address of the authorisation holder</td>
<td>Prostrakan Limited, 3 Galabank Business Park, Queen Street, Galashields, TD1 1QH, UK</td>
</tr>
</tbody>
</table>
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

S. Active substance
General information on the active substance is given below:

**rINN:** Glyceryl trinitrate
**USAN:** Nitroglycerin
**Chemical name:** 1,2,3-Propanetriol trinitrate
**Laboratory code:** SDM 27
**Other names:** GTN, (tri)nitroglycerin, (tri)nitroglycerol, glycerol nitric acid triester, trinitrin
**CAS number:** 55-63-0

**Structure**

![Molecular structure of glyceryl trinitrate](image)

**Molecular formula:** C₃H₅N₃O₉
**Relative molecular mass:** 227.09
**Physical form:** Clear to slightly straw coloured liquid at 25°C

Drug substance is presented as a solution in propylene glycol; the appearance of this is a colourless liquid at 25°C.

The drug substance specification applied by the finished product manufacturer is based on the USP monograph for ‘Diluted Nitroglycerin’. This is satisfactory. The applicant has confirmed that the each batch of drug substance is tested to the full drug substance specification. Certificates of analysis for each batch received by the finished product manufacturer have been provided. All batches received comply with the drug substance specification.

Based on stability data provided, a retest period of 2 years has been proposed and is acceptable.

P Medicinal Product

P.1 Composition

**Composition**
Rectogesic 0.4% Rectal Ointment contains the active substance GTN in propylene glycol (USP) with excipients white soft paraffin (Ph Eur), lanolin (Ph Eur), propylene glycol (Ph Eur), hard paraffin (Ph Eur) and sorbitan sesquioleate (Ph Eur).

**Container/closure system**
The product package proposed for marketing is a pre-printed, open-ended aluminium tubes, with an acrylic polymer sealant on the crimp end, with white LDPE, non-piercing screw-caps.

Documents confirming compliance with the relevant EU food contact legislation has been provided for all packaging components.

Details of the finished product manufacturer’s routine testing procedure for packaging components, and the specifications applied, have been provided and are satisfactory.
P.2 Pharmaceutical development
The stated aim of the pharmaceutical development programme was to develop a product with acceptable appearance, ease of use and manufacture and stability.

No development work with the drug substance has been reported here. It is merely stated that the 10% solution in propylene glycol was chosen for use in this product since it is safe to use and has good stability. This is adequate.

No discussion of the development of the manufacturing process is provided. Since the formulation is fairly straightforward this may be accepted.

Details concerning the development of the excipients, formulation, overages and the container closure system have been provided and are satisfactory.

P.3 Method of preparation of the product
The description of the manufacturing method provided is adequate. A flow-chart summarising this has been supplied. Filling procedures are also outlined; the product is filled by weight and target and acceptance limits are indicated.

Critical steps in the manufacture of the finished product have been identified and adequate control of these described.

Protocols for the prospective validation of manufacturing process have been provided with a commitment by the applicant to provide the results of these validation studies as soon as they are available. Given that batch analytical results are acceptable and the product is manufactured using a straight-forward process, the absence of formal process validation data may be accepted.

P.4 Control of other substance(s) (excipients)
All of the excipients used in the product are compendial, and it is stated that they must conform to the USP/NF specifications. The applicant has confirmed that all batches of excipients used in future manufacture of the finished product will comply with Ph Eur.

Test methods used by the finished product manufacturer are generally those of USP or NF. Since pharmacopoeial methodology is employed, no validation is necessary. The applicant has confirmed that all batches of excipient used comply with their respective Ph Eur monograph.

With the exception of lanolin, none of the excipients used are thought to constitute a TSE risk. Lanolin is obtained from wool from healthy living sheep from Australia or New Zealand and is not, therefore, considered to constitute a TSE risk.

P.5 Control tests on the finished product
Finished Product Specification
The finished product specification contains appropriate controls that will ensure batch to batch reproducibility for a product of this nature. Details of the analytical procedures have been provided and are satisfactory. Validation reports have been provided and these are satisfactory.

Batch Analysis
Batch analytical data have been provided for each strength manufactured by the proposed finished product manufacturer. All results are given and meet the proposed specification.

P.6 Packaging Materials
The product package proposed for marketing is a pre-printed, open-ended aluminium tubes, with an acrylic polymer sealant on the crimp end, with white LDPE, non-piercing screw-caps.

Documents confirming compliance with the relevant EU food contact legislation has been provided for all packaging components.
Details of the finished product manufacturer’s routine testing procedure for packaging components, and the specifications applied, have been provided and are satisfactory.

P.7 Stability tests on the finished product
Stability data has been generated for batches of finished product stored in the packaging proposed for marketing. Studies were conducted in line with ICH recommendations. The results support a shelf life of 36 months, with the storage conditions ‘Do not store above 25°C. Do not freeze.’

Conclusion on quality
The pharmaceutical assessor concluded that a marketing authorisation may be granted for this product.
III.2 PRE-CLINICAL ASPECTS

1. PHARMACODYNAMICS

1.1. Pharmacodynamics for the Proposed Indications

In the proposed indication, the rationale for the use of GTN is based on the ability of nitric oxide (NO), which is formed during the metabolism of GTN, to relax the internal anal sphincter (IAS). The ability of NO to do this has been demonstrated in anaesthetised opossums and in vitro, using tissue from human internal anal sphincter.

The mechanism of action of NO appears to involve its interaction with the heme moiety of guanylate cyclase to increase intracellular levels of cGMP. The subsequent activation of cGMP-dependent protein kinase leads to muscle relaxation.

Repeated administration of GTN in myocardial ischaemia leads to tolerance, with attenuation of the effects being dependent on dose and extent of exposure. Studies conducted to investigate the induction of tolerance in the IAS by GTN have so far not demonstrated tolerance in this tissue.

2. PHARMACOKINETICS

Glyceryl trinitrate is rapidly absorbed and extensively distributed to the tissues. Plasma clearance is very high and is related to systemic blood flow in rats. There is a large first-pass effect, with bioavailability of about 2% following an oral dose. Intra-rectal administration increased bioavailability to 26% in rats.

As well as metabolism in the liver, extensive metabolism of GTN occurs in extra-hepatic tissues, including the erythrocytes.

GTN is metabolised to its dinitrates 1,2-glyceryl dinitrate and 1,3-glyceryl dinitrate, and further to glyceryl mononitrates. The mononitrates are inactive. Nitric oxide is released during these processes. Ultimately glycerol and carbon dioxide are formed.

Glutathione transferase and cytochrome P450 enzymes are reported to be involved in the metabolism of GTN.

GTN has a short half-life (about 4 minutes in rats and dogs). The dinitrates are less pharmacologically active than GTN, but have a longer half-life of about 40 minutes and so may contribute to the activity of the product.

3. TOXICOLOGY

Acute, subchronic and chronic studies have been reported in the literature. Signs of acute toxicity in rats and mice were cyanosis, ataxia and respiratory depression.

Subchronic intravenous studies have been reported in the rat and dog, and 13-week oral studies in mice, rats and dogs. The doses used in the oral studies were increased in all three species due to lack of a toxic effect initially. Subsequently, further rat and dog studies were conducted at higher doses.

Rats were fed 2.5% GTN in their diet for 13 weeks. Dosage of GTN was approximately 1406 and 1416 mg/kg/day in males and females, respectively. Food consumption and weight initially decreased and then increased. Treatment increased erythrocytes, reticulocytes,
haematocrit, haemoglobin concentration and alkaline phosphatase, but no methaemoglobin was found. Pigment deposits were found in the liver and spleen. There was moderate to severe testicular degeneration and/or atrophy with severe to complete aspermatogenesis.

Dogs received 25, 50, 100 or 200 mg GTN/kg/day for 5 days. There was a dose response for both peak methaemoglobin levels and duration of methaemoglobinaemia. At 200 mg/kg/day, recovery was not complete and there were higher levels of methaemoglobin on later days of the study. High methaemoglobin levels corresponded with cyanosis.

Chronic toxicity studies have been conducted in mice, rats and dogs. Mice were fed GTN in their diet for 24 months. Food consumption decreased in the high dose group. An interim sacrifice at 12 months revealed compensated anaemia, increased reticulocytes and the presence of Heinz bodies. Methaemoglobin was found in males. A pigment deposit was found liver spleen and kidney. Similar findings occurred at 24 months.

Rats were fed GTN in their diet for 24 months. Findings included methaemoglobinaemia, reticulocytosis and haemoconcentration. No Heinz bodies were found. Liver enzymes were elevated in males and livers enlarged at the high dose (1% in the diet, corresponding to 363 or 434 mg/kg/day in males and females, respectively). There was a dose-dependent incidence and severity of areas of foci and hepatocellular alteration, with progressive development of hepatocellular carcinoma. There was excessive pigmentation in spleen and renal epithelium in most of the high dose animals.

Dogs received 0, 1, 5 or 25 mg/kg/day in capsules for 12 months. The only finding was a dose-related methaemoglobinaemia.

3.1. Assessor’s Comment
Repeated oral dosing of mice, rats and dogs with GTN resulted in the production of methaemoglobin in all three species. Rats additionally were shown to have testicular atrophy and aspermatogenesis, or to develop hepatocellular carcinoma, depending upon the dose and duration of dosing.

Systemic exposure was not measured in these studies so safety margins can only be stated in terms of the dose given.

In the 13-week study in which testicular degeneration occurred, male rats were receiving an average dose of 1406 mg/kg/day. In the 2-year study in which hepatocellular carcinoma was found, the high dose was 363 or 434 mg/kg/day in males or females, respectively. In man, twice daily application of ointment containing 0.75 mg GTN will result in a daily dose of 0.02 mg/kg/day for a 70 kg person (note that the Pharmaco-toxicological Expert Report states the dosage as 0.03 mg/kg/day, on the basis of application three times a day). Safety margins are, therefore, very large on the basis of the doses given. Differences in bioavailability between the oral and intra-anal routes are likely to reduce the apparent safety margins, which cannot be given accurately without systemic exposure data. However, even if bioavailability were 50-fold higher with intra-anal administration, the safety margins are likely to be reasonably large.
4. REPRODUCTION STUDIES

A third-generation study was conducted in rats that were fed 0, 0.01, 0.1 or 1% GTN in the diet from 6 months before the initial mating of the F₀ generation. The fertility of the F₁ and F₂ generations was severely impaired due to aspermotogenesis in the males. Various litter parameters were reduced in the F₁ and F₂ litters, which were attributed at least in part to the poor nutritional status of the dams. Examination of F₁ litters from a third mating of the F₀ generation showed a single type of visceral anomalies (diaphragmatic hernia) in the high dose group. This occurred in 4/19 high dose litters and may have also been responsible for the reduced litter sizes in the previous F₁ generation litters. Absence and incomplete ossification of the hyoid bone were significantly increased in the high dose group compared with controls, although these findings were generally considered to indicate delayed development rather than teratogenicity.

Studies in pregnant sheep infused with GTN over 30 minutes at 125 to 136 days of gestation (145 day to term) showed increased maternal and fetal heart rate and decreased arterial blood pressure. There were no effects on other fetal parameters, such as arterial pH, partial pressure of carbon dioxide or oxygen or cerebral blood flow.

In humans, no adverse effects on the neonate were reported when 0.5 mg GTN was administered iv to the mother during a planned caesarean section. Levels of GTN in the umbilical cord were much lower than in maternal plasma.

4.1. Assessor’s Comment

The findings on male fertility are in line with those of testicular degeneration and aspermotogenesis reported in the repeated dose studies. The third generation study in rats showed some effects on the fetus at the high dose. There are no adequate data from the use of GTN in pregnant women, and the animal studies are insufficient to determine the potential risk for humans.

5. MUTAGENIC POTENTIAL

GTN gave a positive result in S. typhimurium strain TA 1535 at a concentration of 5 µg/plate. Further investigation suggested this was mainly a C to T transition in either the first or second base of hisG46 (CCC) target codon. This has been shown to occur with other NO-releasing systems, and the present finding was attributed to such an effect of NO. In an in vitro assay in Chinese Hamster Ovary cells, GTN did not induce mutations at 50 or 145 µg/ml, concentrations that killed 65 and 99% of cells, respectively. However, a metabolic activation system was not included in the assay.

A standard in vivo study has not been reported. However, peripheral lymphocytes were obtained from blood samples collected from rats and dogs at 12 months, and bone marrow cells and kidney tissue from rats at the end of the 24 month carcinogenicity study. There were no statistically significant changes in chromosomes as a result of treatment.

6. ONCOGENIC/CARCINOGENIC POTENTIAL

Three groups of rats were given a single intragastric dose of 1.2 g GTN/kg at 6 weeks. One of these groups then received 1% GTN in the diet from 8 weeks to 84 weeks, and a partial hepatectomy at 9 weeks. Another had a partial hepatectomy at 9 weeks whilst the third had no further treatment. A fourth group received 1% GTN in the diet from 8 weeks and a fifth was an untreated control group.
In the two groups receiving GTN in the diet, livers were enlarged. There were pre-neoplastic foci from 14 weeks, focal eosinophilic areas with atypical hepatocytes from 52 weeks, with some mixed hepatocholangiocellular adenomas and carcinomas in the eosinophilic lesions. Hepatocellular carcinomas were present at 78 weeks with an incidence of 50 to 75%. The carcinogenic effect of dietary GTN was not affected by prior administration of a large single dose of GTN or by partial hepatectomy. No \( p53 \) mutations were found but there were \( K-ras \) mutations in codon 12 in 8/18 tumours, mostly those with cholangiocellular elements. These were mainly G to T transversions at the first or second position or G to A transitions at the second position.

6.1. Assessor’s Comment

The hepatocellular carcinomas were evident only in rats fed GTN in their diet for a prolonged period. It has been shown that the overproduction of NO can lead to cytotoxicity. Through a variety of mechanisms, cells exposed to NO undergo DNA damage. The mutations found in the carcinogenicity study were similar to those observed in bacteria with other NO-releasing systems. The formation of the peroxynitrite ion in the reaction of NO with superoxide produced mainly G to T transversions in bacteria, while NO spontaneously released into the solution containing the plasmid produced mainly G to A transitions.

At physiological levels of NO production, DNA damage is more likely to be repaired efficiently. In cases of excessive production of NO for prolonged periods, such as in the carcinogenicity study, the damage may no longer be repaired efficiently. Given the endogenous nature of NO and the extensive clinical experience with the use of GTN-containing products, it is considered that there is unlikely to be a carcinogenic risk to man from use of this product.

7. SPECIAL STUDIES

7.1. Local Tolerance (including Phototoxicity & Photosensitivity)

GTN was a moderate skin sensitisier in guinea pigs, non-irritant to rabbit eye and a mild irritant to rabbit skin. Repeated administration or three topical GTN ointments to rabbit eyes produced a mild conjunctival chemosis. They were reasonably well tolerated.

The finished product has been tested for local tolerance in a 14-day anorectal irritation study in rabbits.

8. THE PHARMACO-TOXICOLOGICAL EXPERT REPORT

This was signed by an appropriately qualified toxicologist. The report provides a brief overview on some of the published literature on GTN.

9. DISCUSSION

This application is based on published literature. GTN has been used for many years for the relief of angina pectoris. The pharmacology of GTN and NO are well documented, and the rationale for the use of GTN in the requested indication is logical. There are some gaps in the published preclinical studies by today’s standards, but the vast clinical experience of its use obviates the need for extensive new preclinical studies to be conducted. High doses of GTN in the rat have been shown to affect male fertility and foetal development. Prolonged administration of high doses of GTN to rats in their diet leads to the development of hepatocellular carcinomas. It is considered that there is unlikely to be a carcinogenic risk to
man from use of this product, given that the NO thought to be responsible for these findings is also an endogenous substance.

10. OVERALL CONCLUSIONS ON PRODUCT SAFETY

There are no preclinical objections to the grant of a marketing authorisation for this product.

III.3 CLINICAL ASPECTS

The initial UK clinical assessment of this application in June 2003 was for two applications (Rectogesic 0.2% and 0.4% Rectal Ointment) and was considered by the UK Committee of Safety of Medicines (CSM) on 31st July 2003. The CSM felt that they could not support the granting of a licence for this product because of safety, efficacy and risk benefit concerns. These were mainly because the risk-benefit was adverse, efficacy and pain relief was considered to be small, and adverse events were common.

In response to this, the applicant provided new data and analyses in December 2003 and withdrew the 0.2% Rectal Ointment application. These data and analyses were also assessed and further advice was given from the UK CSM in March 2004. This advice included necessary amendments to the SPC and PIL to resolve two outstanding points that remained after the company’s responses. The company agreed to incorporate these changes into the SPC and PIL, and the licence for the 0.4% ointment was granted on 24th August 2004.

The enclosed report is a composite of five reports (each presented as an appendix). The first is the original clinical assessment of June 2003 (Appendix 1). Following this is the advice from the CSM meeting in July 2003 (Appendix 2) and the company’s responses to this advice and assessment of these responses (Appendix 3). The minutes from the CSM meeting dated 25th March 2004 (Appendix 4) includes the necessary amendments to the SPC and PIL to resolve the two outstanding points remaining are included as a fourth appendix. Finally, a Type II variation was granted on 5th December 2005 to add new clinical data to Module 5 of the dossier, containing results from a new controlled clinical trial (Study R3), retrospective analysis of two previous trials (Study R1 and Study R2) and combined analysis of three studies (Study R1, Study R2 and Study R3); the variation assessment report is Appendix 5.
APPENDIX 1 – ORIGINAL CLINICAL AND STATISTICAL ASSESSMENT
(DATED JUNE 2003)

LICENCE NO: 19075/0002-3
PROPRIETARY NAME: RECTOGESIC™ OINTMENT
ACTIVE(S): GLYCERYL TRINITRATE 0.2% w/w
COMPANY NAME: CELLEGY UK LIMITED
LEGAL STATUS: POM

1. INTRODUCTION
Rectogesic™ ointment, contains 0.2% or 0.4% w/w glyceryl trinitrate, for pain relief in the treatment of anal fissure.

The current edition of the British National Formulary mentions the unlicenced use of the topical application of a GTN 0.2-0.3% ointment for anal fissure. These preparations are dilutions of GTN 2% ointment, approved in the UK for the prophylaxis of angina.

GTN has a long history as a cardiovascular medicine and qualifies as an abridged application under Article 10.1(a).

The applicant made a previous application, PL 19075/0001, which was rejected at the meeting of CSM on 28th March 2002. This was a bibliographic application which did not present clinical trial data with the product proposed for marketing. Efficacy was considered inadequately proven with uncertainty about the dosing interval, the choice of dose, the problem of nitrate tolerance and conflicting trial results. More long-term efficacy data with respect to relapse rates were requested. The original application also asked for a broader application that the current one, being: "... is indicated to promote the healing and relief of symptoms of chronic anal fissures."

2. REGULATORY STATUS
This is an abridged complex national application. It has been submitted under Article 10.1(a)(ii) of Directive 2001/83/EC as a bibliographical application. In the event of UK approval, the applicant intends to apply for mutual recognition in most of Europe.

The product has been licensed in Australia since 1998, but currently no GTN ointment products are approved in the UK for this indication.

The original application was rejected by CSM at its meeting of 28th March 2002 and withdrawn from the USA on 25th April 2002, as more data were requested.

3. INDICATIONS
3.1 From the SPC, Part IV, page 60,: "... is indicated for relief of pain associated with chronic anal fissures."

3.2 Clinical Assessor's Comment
The risk benefit of this indication is not favourable. The pain relief effect is small and accompanied by an unacceptably high incidence of systemic adverse events, in particular headache, which is often severe, but also dizziness and nausea.
4. CLINICAL PHARMACOLOGY

4.1 Pharmacokinetics

The pharmacokinetics of GTN are established and are reviewed in the clinical expert report on Part IV, page 25. GTN is well absorbed, has a volume of distribution of about 3 L/kg and is 60% protein bound. The half-life is about 1-4 minutes. The active moiety is nitric oxide which forms active nitrosothiols. GTN is metabolised by denitration to metabolites which are a tenth as active as the parent, but they have a longer half-life of about 40 minutes. Further metabolism leads to nitric oxide, glycerol and carbon dioxide. Metabolic enzymes include glutathione S-transferase, cytochrome p450 enzymes and esterases with significant first pass metabolism.

Topical application prolongs the duration of action by delivering drug to the site of action without first pass metabolism. The onset of action of topical ointment is 30-60 minutes and duration of action 3-6 hours.

The recommended dose of Rectogesic is 375 mg of 0.2% or 0.4% cream, two or three times a day. This is equivalent to 1.5 mg - 4.5 mg/day of GTN. As with the sublingual route, where the recommended dose for angina is 300 - 1,000 µg, the rectal route leads to systemic absorption.

Study R4

This phase I study was carried out to determine the pharmacokinetics and bioavailability of single and multiple doses of 0.2% nitroglycerin ointment applied to the anal canal in normal healthy volunteers. It was a three way cross over study in six subjects measuring arterial blood kinetics comparing the ointment with iv dosing. The iv dose was 0.3 mg given by infusion pump over a 30 min period.

Bioavailability was approximately 50% with the ointment applied to the anal mucosa with no significant change in AUC or bioavailability with multiple dosing. The ratio of 1,2-glyceryl dinitrate to 1,3-glyceryl dinitrate was about 4 with the ointment and about 7 when given iv. There was considerable inter-individuality in kinetics, as might be expected with first pass metabolism, Module 5, vol 1, study report, see page 27 onwards. In general, the concentrations of glyceryl trinitrate with the iv infusion were higher than with the ointment, although plasma concentrations were still detectable at 6-8 h in some patients after application of the ointment.

4.2 Pharmacodynamics

The active moiety, nitric oxide, is a potent relaxant of smooth muscle. It is known to be an important neurotransmitter in the internal anal sphincter.

The Clinical Expert Report reviews the evidence that anal fissures are associated with raised intra-anal pressure and hypertonicity of the internal anal sphincter Part IV, page 21.

In vitro, field stimulation of the internal anal sphincter, in the presence of atropine and guanethedine, causes nitric oxide mediated relaxation.

The Clinical Expert Report discusses nitrate tolerance, Part IV, page 31. It is argued that the preclinical data in rats provide evidence of a lack of nitrate tolerance in anorectal smooth muscle, reference 82.
4.3  **Clinical Pharmacology - Clinical Assessor's Comments**

The pharmacodynamics and pharmacokinetics of GTN are well known. The normal volunteer study provides adequate information about systemic absorption.

The Applicant has not been able to identify a dose of glyceryl trinitrate that affects the anal sphincter without significant systemic absorption and systemic pharmacodynamic effects.

5.  **EFFICACY**

5.1  **Controlled Clinical Studies**

Two Phase III clinical trials are presented using 375 mg of 0.2% and 0.4% w/w nitroglycerin ointment applied intra-anally twice or three times a day for patients with chronic anal fissure. They are double-blind, randomised, placebo controlled studies.

The first trial listed below had as the primary objective to determine the dose and dosing interval of nitroglycerin that best promotes complete healing of chronic anal fissure. As there was no statistically significant effect on healing in this trial, but a benefit on a secondary endpoint of pain, a second trial was performed with pain relief as the primary endpoint.

**Study R1**  

This started in 1998 and enrolled 304 patients, mean age 44 years, range 19-81, of whom 55% were male and 81% were Caucasian. It was a multi-centre trial based in the USA. Treatments were placebo or nitroglycerin ointment 0.375 mg, 0.75 mg or 1.5 mg twice or three times a day.

The primary objective was fissure healing. This was assessed by an independent examiner at each two week visit until healing.

Secondary objectives were pain relief, by visual analogue scale, and safety. Pain relief had three scores of average pain, worst pain and defecation pain.

Duration of treatment was 56 days, or until healing.

Allowed concomitant therapy included sitz baths.

**Results**

There was no significant difference from placebo for any treatment compared to placebo for the primary variable of fissure healing (p=0.62).

There was no significant difference from placebo for the two lowest doses for the secondary variable of relief of pain, but significant effects on pain for the 0.2% and 0.4% treatment groups. There was no difference in the relief of pain between the twice or three times a day groups.

The most common side effect was headache, which showed a dose response to the individual dose, rather than the cumulative daily dose, **Part IV, page 34**.

**Study R2**  

This started in 2000 and enrolled 229 patients, mean age 43 years, range 19-83, of whom 58% were male and 88% were Caucasian. It was a multi-centre trial from the USA, Israel, UK and Germany. Patients had chronic anal fissure with pain after at least 50% of bowel movements each week in the last 30 days.
The primary objective was pain relief.

Secondary objectives were time to healing, quality of life and safety. Pain relief measured each evening by visual analogue scale and had three scores of average pain, worst pain and defecation pain. Quality of life was measured by the Gastrointestinal Quality of life Index at baseline, weeks 2 and 4, and at completion. Healing by day 56 was followed for one year to see if relapse occurred.

Duration of treatment was 56 days without regard to healing status.

Allowed concomitant therapy included psyllium, 1 tablespoonful in 8 oz water twice a day, and a sitz bath no more than once a day.

Results
There were 70 patients treated with Rectogesic® 0.2%, 74 with Rectogesic® 0.4% and 75 with placebo. In all, 180 patients completed the 56 day double-blind treatment phase.

Compared to placebo there was a statistically significant decrease in pain intensity over time for the 0.4% group, but not for the 0.2% group. There was no significant treatment effect on healing, p=0.57.

Mean pain intensity is plotted below in Figure 1.

The statistically significant effect on pain was only for mean average pain intensity. There were similar patterns of pain relief in the three treatment groups for worst pain and pain on defecation but these were not significant.
The most common side effect was headache, with one placebo patient, five 0.2% and eight 0.4% patients withdrawing because of headache.

**Combined Analysis of Study R1 and Study R2**
A total of 330 patients were included in the two trials. The dose response to pain relief was maximal at week 2 and had diminished by week 8. Most pain scores for the 0.2% group were not statistically significantly different from placebo except for pain at defecation at weeks 4 and 8.

The spontaneous resolution over 8 weeks with placebo was greater than any treatment effect. At week 1 the percent improvement was 19.5% for placebo which rose to 59% by week 8. The corresponding figures for 0.2% nitroglycerin were 22.4% at week 1 rising to 66% at week 8; and for 0.4%, 24.2% rising to 70%. The results are tabulated and plotted in the clinical expert report on Part IV, page 37.

**5.2 Bibliographic Evidence**
The clinical expert report reviews nine controlled clinical studies of the use of GTN in the treatment of anal fissure Part IV, page 39. These involved 496 patients, of whom 259
received 0.2% GTN, 12 received 0.5% GTN and 12 received an escalating regimen from 0.1-0.6%. Four of the trials were placebo controlled and five had placebo and or comparator. None of the trials used the product proposed for marketing, the largest trial used 2% GTN ointment diluted 1:10 in white soft paraffin to give the lower concentration proposed for marketing, 0.2%.

The largest trial was by Altomare et al. Glyceryl trinitrate for chronic anal fissure - healing or headache? Results of a multi-center randomised, placebo controlled, double-blind trial. Dis Colon Rectum 2000;43:174-9. There were 132 patients recruited in nine Italian centres, of whom 119 patients completed the study. Six patients in the GTN group discontinued because of headache, one because of anal symptoms, one because of herpes genitalis and one was lost to follow up. In the placebo group four dropped out because of anal symptoms.

Of the patients who completed, 59 received 0.2% GTN ointment intra-anally, and 60 placebo, twice daily, for at least four weeks. After treatment the healed rate was 49% for GTN and 52% for placebo. Six patients in each group had marked improvement in symptoms without healing of the fissure. Long term follow up for a median of 12 months of 26 patients who healed with GTN showed that in five patients the fissure recurred and required lateral sphincterotomy.

For patients treated with GTN, the incidence of headache was 34% compared to 8% for those treated with placebo. Orthostatic hypotension occurred only with GTN in four cases, giving an incidence of 6%.

The trial report concluded that "This trial fails to demonstrate any superiority of topical 0.2% glyceryl trinitrate vs. placebo, although the effects of glyceryl trinitrate on anodermal blood flow and sphincter pressure are confirmed. This finding, together with the high incidence of side effects, should discourage the use of this treatment as a substitute for surgery in chronic anal fissure."

The authors discussed the anomaly of these results compared to earlier trials. They suggested the 8% healing rate in the placebo group of the study by Lund and Scholefield is unexpectedly low, whereas their placebo response is much closer to that reported previously by earlier studies with an approximate 50% spontaneous healing rate.

Of the remaining trials, Kennedy et al., 1999, employed a double-blind, randomised, placebo controlled study to investigate 0.2% intra-anal GTN for 43 patients with chronic anal fissures. At the end of treatment, 46% of patients healed with GTN and 16% with placebo. High internal anal sphincter pressures persisted at long term follow up in patients who had responded to GTN treatment.

Lund and Scholefield, Lancet 1997, found healing at 4-8 weeks in 26/38 (68%) of GTN 0.2% ointment patients and 3/39 of placebo. The trial was double-blind, randomised and placebo controlled.

Bacher et al (1997) found a significant effect of GTN in a small number of patients and no effect of lignocaine after 14 days. At four weeks the healing rate was 16/20 (80%) for GTN and 6/15 (40%) for topical anaesthetic gel. Mild headache was observed in the GTN group. The study was not blinded.

In the trial by Oettle et al., 1997, all 12 patients treated by sphincterotomy healed by four weeks with no recurrence within the follow up period of 8-34 months. Ten out of 12 patients
healed with GTN, prepared from a tablet crushed in glycerine, the remaining two were successfully treated by sphincterotomy.

**Carapeti et al., 1999**, studied 72 patients in a double-blind, randomised, placebo controlled study. After eight weeks of treatment, 67% of patients had healed with GTN used at a dose 0.2% three times a day, increasing to a maximum of 0.6% in a subset of patients. The placebo response was 32%. Headache was reported by 72% of GTN and 27% of placebo patients. The paper concluded that: "GTN is a good first line treatment for two thirds of patients with anal fissure. An escalating dose of GTN does not result in earlier healing. Significant recurrence of symptomatic fissures and a high incidence of headaches are limitations of the treatment."

**Brisinda et al., 1999;341:65**, studied 50 patients and found healing of chronic posterior anal fissures at two months in 24/25 patients treated with botulinum toxin and 15/25 patients treated with GTN. The paper concluded that "Although treatment with either topical nitroglycerin or botulinum toxin is effective as an alternative to surgery ........... botulinum toxin is the more effective non-surgical treatment".

**Tander et al., 1999**, studied 65 children aged 2 months to 13 years, median 2½ years, of whom 62 completed the study. Of these, 31 were treated with GTN 0.2% ointment, 14 10% lignocaine and 17 placebo. The healing rate in the three groups was 84%, 21% and 35% respectively. No child reported headache as a side effect. The authors recommended GTN ointment as the treatment of choice for children with anal fissure.

### 5.3 Clinical Assessor's Comment

The pharmacodynamic rationale for treating anal fissure with GTN appears to be sound. The early published clinical trials were encouraging and show a clear benefit, although the numbers treated are small. In contrast, the biggest and latest trial by **Altomare et al.** showed no benefit and concluded that the lack of benefit, together with the high incidence of side effects, "should discourage the use of this treatment as a substitute for surgery in chronic anal fissure".

The paper by **Brisinda et al.** in the NEJM concluded that ".. *botulinum toxin is the more effective non-surgical treatment*". The small trial by **Otelle** showed all 12 patients responded rapidly to sphincterotomy with no recurrence.

A Drugs and Therapeutics Bulletin article written in 1998, reviewed the evidence then available, mainly the **Lund and Scholefield** Lancet 1997 paper. The review advised that if GTN is used, "*a pea sized quantity (around 0.5 g) should be applied twice daily to the anal rim for at least 6 weeks. The ointment should not be wiped off, nor applied to the lower anal canal since this increases absorption and consequently the risk of unwanted side effects.*" The review concluded that: "*In patients with idiopathic anal fissure which has not responded to conservative measures, application of 0.2%-0.3% glyceryl trinitrate (GTN) ointment twice daily to the anal rim for at least 6 weeks may allow the fissure to heal. Patients should be warned of the likelihood of headache and advised to complete the treatment course. ....... A long-term randomised trial comparing topical 0.2% GTN ointment with internal sphincterotomy is essential to establish relative rates of cure and recurrence.*"

The mixture of results obtained by the trials, despite a logical therapeutic rationale, might be explained by dosing variability in the trials. **Altomare et al.** suggest that inadequate duration of action may contribute to treatment failure. The duration of the side effect of headache is short, and the duration of the pharmacodynamic effect on the sphincter may also be short and
inadequate to promote healing in some trials. A further complication is nitrate tolerance to chronic treatment with GTN. The study mentioned above of Kennedy et al. found an initial fall in anal manometric pressure compared to placebo, but this effect disappeared after four weeks of treatment, consistent with the development of nitrate tolerance. Nitrate tolerance was also proposed by Altomare et al. and also found by Watson et al. in their study reported in the Br J Surg 1996;83:771-5, *Topical glyceryl trinitrate in the treatment of chronic anal fissure*.

To address these concerns about the published studies, the present application has two additional clinical trials. The first addressed the initial requested indication, fissure healing, and found no significant effect. The trial did suggest a benefit on pain and the second trial then addressed pain as a primary endpoint. The second trial shows a high spontaneous resolution of pain on placebo, some of which may be regression to the mean.

The applicant claims that the lower dose of 0.2% twice daily shows numerical, but not statistical significant improvements in pain score. They suggest that this dose may be appropriate as a starting dose, or for patients in whom headache is a concern. There is a major concern with this argument. Nitroglycerin shows high inter-individual variation and those patients with headache may be those who obtain greater therapeutic benefit. The applicant has not shown any value of 0.2% nitroglycerin as either a starting dose or as an alternative to 0.4% for those patients with side effects.

### 6. SAFETY

#### 6.1 Adverse events

In the two main clinical trials submitted the following safety concerns are noted:

**Study R1**

There was at least one treatment emergent event in 39% (27/70) of placebo and 55% (129/234) of glyceryl trinitrate treated patients. The most frequent adverse event was headache and 87% (84/97) of headaches occurred in patients receiving nitroglycerin. The incidence of severe headache was 30% in the twice daily nitroglycerin group and 52% in the thrice daily group. The next most frequent events were nausea and dizziness. Nausea occurred in 2.9% of placebo patients and 4.3% of nitroglycerin patients. Dizziness occurred in 0.0% of placebo patients and 3.4% of nitroglycerin patients.

There were 28 nitroglycerin patients (9.2%) and four placebo patients (1.3%) who had severe adverse events. The majority of severe adverse events, 28/46, were headache and considered related to therapy. Twelve nitroglycerin and one placebo patient were withdrawn because of adverse events.

**Study R2**

There was at least one treatment emergent event in 55% of placebo, 66% of 0.2% and 73% of 0.4% glyceryl trinitrate treated patients. The overall incidence of headache was 18% for placebo, 43% for 0.2% and 51% for 0.4% glyceryl trinitrate.

Severe adverse events occurred in 4% of placebo patients and 13% of glyceryl trinitrate treated patients. Of the severe events, 17/24 were headache. One of the severe adverse events in the 0.2% group was exacerbation of migraine. Withdrawals were 6% in the placebo group and 12% of glyceryl trinitrate treated patients. Withdrawal because of headache occurred in 1%, 7% and 10% of the placebo, 0.2% and 0.4% treated patients.

Cardiovascular events occurred in 2.5% of placebo, 2.7% of 0.2% and 7.7% of 0.4% nitroglycerin patients.
Nausea occurred in 0% of placebo, 2.7% of 0.2% and 7.7% of 0.4% nitroglycerin patients.

Dizziness occurred in 0% of placebo, 1.4% of 0.2% and 10% of 0.4% nitroglycerin patients.

In the published trials the following safety concerns are noted:

**Headache**

Headache was more common with nitroglycerin in the published trials, for example 72% for active and 27% for placebo in the trial by Carapeti et al., *Part IV, page 47.* Some trials showed little difference in headache from placebo, whereas others found moderate to severe headache to be common. Overall, the incidence of headache with GTN was about 38%.

**Hypotension**

The clinical expert report only discusses this is general terms, *Part IV, page 47.* Only one trial reported postural hypotension, *Altomare et al,* and this was in four cases.

**Tolerance**

The clinical expert report does not discuss this. It has this as a heading, but the author has confused this with dependence, *Part IV, page 48.*

**Other Adverse Events**

These are discussed briefly in the clinical expert report.

Anal burning and itching were reported in the *Altomare* and *Brisinda* studies only.

### 6.2 Post marketing surveillance

Since marketed in Australia in 1998 as a 0.2% strength, five cases of headache and one of local irritation have been reported, *Part IV, page 49,* with 75,000 tubes of ointment sold.

### 6.3 Safety - Clinical Assessor's Comment

Adverse events were more common in patients treated with nitroglycerin. Most common was headache, which was often severe. Also more common with nitroglycerin was dizziness and nausea. It is possible that postural hypotension may have occurred from vasodilation as this was not excluded.

### 7. EXPERT REPORT

This was written by an appropriately qualified person.

### 8. SUMMARY OF PRODUCT CHARACTERISTICS

8.1 The indication, Section 4.1, should be restricted to patients aged 18 years, or over.

8.2 Posology, Secton 4.2, should be restricted to twice daily as adverse events were more common with thrice daily and efficacy no greater.

8.3 The contraindications, Section 4.2, should include patients with migraine, recurrent headache, or postural hypotension.

8.4 In Section 4.8 the listed side effects should include reflex tachycardia, vomiting, anal burning and itching.
9. PATIENT INFORMATION LEAFLET
9.1 The Patient Information Leaflet should be consistent with the revised SPC.

10. CONCLUSIONS
The early published data presented on efficacy were promising. The later conflicting published results are summarised in an editorial written by Robert Madoff, which accompanies the Altomare et al. paper. This editorial states that: "Topical nitroglycerine therapy remains an enticing but not entirely proven treatment for anal fissure. Trial results are conflicting and more work must be done before this approach becomes standard first-line therapy. The need for more long-term data with respect to relapse rates is especially critical.......the enthusiasm of early reports should be tempered by the natural history of new therapy reporting, one exemplified perfectly by the topical nitroglycerine story".

The applicant has presented two additional trials to address the potential efficacy of nitroglycerin in anal fissure.

These two trials shown there is no significant effect on healing and this is not requested in the indication. This was shown in the first trial, where healing was the primary endpoint, and second trial where it was a secondary endpoint.

This leaves pain relief, which is the requested indication. Some minor benefit was suggested in the first trial, where this was a secondary endpoint, and confirmed in the second trial for 0.4% where one of the three measures of pain that were the primary endpoints, was statistically significant and the other measures showed a similar trend.

Safety is a concern. The incidence of headache, in particular severe headache, is high. Nausea and dizziness are more common with active treatment suggesting sufficient absorption to cause systemic adverse events.

The risk benefit appears adverse as the pain relief is minor compared to placebo, yet adverse events, in particular headache, are common and may be severe. Other treatments are available for pain relief without such systemic adverse events.

11. RECOMMENDATION
It is recommended that marketing authorisation is not granted on grounds of safety and efficacy concerns.

11.1 Efficacy is modest as the pain relief effect is small.

11.2 Adverse events are common. There is particular concern about the incidence of headache, which is often severe, and also dizziness, nausea and postural hypotension.

11.3 The risk benefit is adverse.

11.4 The following changes to the Product Particulars are requested:

11.5 The indication, Section 4.1, should be restricted to patients aged 18 years, or over.

11.6 Posology, Section 4.2, should be restricted to twice daily as adverse events were more common with thrice daily and efficacy no greater.
11.7 The contraindications, Section 4.2, should include patients with migraine, recurrent headache, or postural hypotension.

11.8 In Section 4.8 the listed side effects should include reflex tachycardia, vomiting, anal burning and itching.

11.9 The Patient Information Leaflet should be consistent with the revised SPC.

Clinical Assessor
19th June 2003

Statistical Assessment of Efficacy
This assessment considers the evidence of efficacy for Rectogesic ointment (glyceryl trinitrate 0.2%, 0.4% w/w), proposed for pain relief in the treatment of anal fissure. Two trials have been presented along with a pooled analysis. These are described in detail in the Medical Assessment (from Page 3). Therefore, only comments on methodology are presented below.

Study R1
The primary objective of this trial was to assess the efficacy of nitroglycerin ointment (NTG) on fissure healing. No difference was observed between the three active concentrations and placebo. Therefore, interpretation of the lower order objectives must proceed with caution.

Assessment of pain relief endpoints (average pain, worst pain and defecation pain) was a secondary objective. These were measured using visual analogue scales and were analysed using mixed effects regression models on the ITT population. These models measure the difference between the effects of the treatments over the course of the treatment period, rather than at a specific timepoint, using the treatment-by-time interaction term. This method is considered acceptable for establishing statistical significance. However, care must be taken when interpreting any associated data presentations which display the data by timepoint as, unlike some other types of imputation (e.g. LOCF), the effect of patient withdrawals will not automatically be included in mean levels at each timepoint. Indeed the presentations in the trial report appear predominately to be based on an observed cases population, which is clearly biased and not a suitable population on which is base a judgement on clinical relevance.

Regarding the trial results, more patients randomised to active treatment withdrew from trial therapy compared with placebo, 23.1% versus 12.9%. The majority of withdrawals were due to adverse event (5.1% versus 1.4% respectively) and subject choice (10.3% versus 5.7% respectively). Two patients withdrew due to inadequate response on NTG compared with none on placebo.

There was no evidence of a difference in the effect on pain between twice daily and three times daily dosing. Data were therefore pooled for each concentration and the two groups receiving placebo. This is considered reasonable. The 0.4% NTG group showed highly statistically significant differences to placebo. There was also some evidence of efficacy for the 0.2% concentration, but differences from placebo were not evident for the 0.1% concentration. As described above, the size of the treatment effect is difficult to establish due to patient withdrawals, which are dealt with in the statistical analysis, but not in many of the data presentations. Any future presentations of these trial data should show estimated effect sizes and confidence intervals in addition to p-values and all plots and tabulations should indicate the ‘n’ or standard error associated with each mean. A conservative estimate of
effect might be obtained from an ANCOVA on the Day 56 pain scores, with baseline as covariate, and imputation via LOCF. The estimate would be expected to be conservative because of the combination of improving pain scores in each treatment group and the increased number of withdrawals on active treatment.

Conclusions on Study R1
Despite a larger number of withdrawals on NTG than placebo and concerns over the data analysis and presentation, the trial generates the hypothesis that a concentrations of 0.2% or 0.4% might be efficacious in the treatment of pain relief from anal fissure. However, this needs to be confirmed in at least one further study. For this study to constitute supportive evidence, an ANCOVA analysis is requested, based on Day 56 pain scores and using LOCF to account for patient withdrawals.

The choice of twice-daily rather than three-times daily dosing for the confirmatory trial is based on hypothetical arguments for improved compliance and reduced safety concerns, not on evidence from this trial of a superior risk: benefit.

Study R2
The primary trial objective, relief of pain associated with anal fissures, was assessed in the same manner as for Study R1.

A total of 229 patients were recruited to the three treatment groups. Ten patients have been excluded from the ITT population. This is not considered problematic as the exclusions appear balanced across the three groups. Patient withdrawals appear to be dose-related (see table below).

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Placebo</th>
<th>0.2% NTG ointment</th>
<th>0.4% NTG ointment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomised</td>
<td>78</td>
<td>73</td>
<td>78</td>
</tr>
<tr>
<td>ITT population</td>
<td>75</td>
<td>70</td>
<td>74</td>
</tr>
<tr>
<td>Withdrawals</td>
<td>8 (10.7)</td>
<td>13 (18.6)</td>
<td>18 (24.3)</td>
</tr>
<tr>
<td>Due to AE</td>
<td>2 (2.7)</td>
<td>3 (4.3)</td>
<td>10 (13.5)</td>
</tr>
<tr>
<td>Due to subject choice</td>
<td>3 (4.0)</td>
<td>4 (5.7)</td>
<td>4 (5.4)</td>
</tr>
</tbody>
</table>

The trial report does not give the number of patients withdrawing due to ‘inadequate effect’.

Marginally fewer patients on placebo took concomitant analgesia for pain relief or concomitant treatments to ease defecation.

A statistically significant effect was observed for the 0.4% concentration versus placebo. There was no statistically significant effect observed for the 0.2% concentration. These results are subject to the same caveats as expressed above, i.e. that the clinical significance of these results are difficult to establish (the applicant’s data presentations appear, again, to be based primarily on p-values alone and tabulations of observed case data). Further, the greater number of withdrawals in the active treatment arms may bias the estimate of effect.

The efficacy evaluable population included 93 patients. Analyses based on this population are not considered useful.

Conclusions on Study R2
There are concerns over the number of patient withdrawals on the active treatment arms and the influence of these patients on the statistical analysis. An ANCOVA of the Day 56 pain scores, using LOCF to impute for missing data due to patient withdrawals, should be
provided. This analysis will also assist in the evaluation of the effect size, which, based on
the applicant’s current data presentations, is difficult to establish.
It is considered that this trial does not provide confirmatory evidence of efficacy.

**Pooled analysis**
The pooled analysis was based on similar methods to those described above and provided
evidence of a statistically significant effect for the 0.4% concentration compared with
placebo. However, the most relevant use for this particular pooled analysis is not to establish
statistical significance but to better quantify the estimate of clinical benefit. Unfortunately,
the concerns expressed above clearly apply also to this pooled analysis. Further analyses and
associated data presentations are required.

The applicant attempts to justify the clinical relevance of the statistically significant
effects through time to 50% improvement from baseline. This is a post hoc endpoint and the choice
of 50% appears somewhat arbitrary. Further, it is not clear how patient withdrawals have
been handled in these data presentations.

**Overall Conclusions**
The statistical analyses conducted and data tabulations presented are inadequate and further
investigation is required to confirm the statistical significance and establish the clinical
relevance of the effects of NTG in pain relief associated with anal fissure.

**Points for Clarification**
- The applicant should comment on the validity of the assumptions made for data missing
due to patient withdrawal in the primary analysis.

- The applicant should supply ANCOVA analyses on the Day 56 pain scores using pain at
  baseline as covariate and LOCF to impute data missing due to patient withdrawals.

**Statistical Assessor**
**June 2003**
APPENDIX 2 – DRAFT ADVICE FOLLOWING INITIAL CSM MEETING (JULY 2003)

<table>
<thead>
<tr>
<th>MAIN COMMITTEE</th>
<th>DRAFT ADVICE</th>
</tr>
</thead>
<tbody>
<tr>
<td>DATE OF MEETING</td>
<td>31st July 2003</td>
</tr>
<tr>
<td>REFERENCE NUMBER</td>
<td>PL 19075/0002-3</td>
</tr>
<tr>
<td>COMPANY</td>
<td>Cellergy UK Ltd</td>
</tr>
<tr>
<td>PRODUCT</td>
<td>Rectogesic™</td>
</tr>
<tr>
<td>ACTIVE CONSTITUENT</td>
<td>Glyceryl trinitrate</td>
</tr>
<tr>
<td>THERAPEUTIC CLASS</td>
<td>Smooth muscle relaxant</td>
</tr>
<tr>
<td>KEY WORDS</td>
<td>Anal fissure, nitric oxide, GTN, nitrate, topical</td>
</tr>
</tbody>
</table>

On the evidence before them, the Committee had reason to think that on grounds of safety and efficacy they might be unable to advise the grant of a Marketing Authorisation for this preparation and directed the Secretary to notify the applicant in accordance with paragraph 6(1) of Schedule 2 to the Medicines for Human Use (Marketing Authorisation etc.) Regulation 1994.

The Committee considered that:

1. Efficacy is modest as the pain relief effect is small.

2. Adverse events are common. There is particular concern about the incidence of headache, which is often severe, and also dizziness, nausea and postural hypotension.

3. The risk benefit is adverse.

4. The following changes to the Product Particulars are requested:

4.1 The indication, Section 4.1, should be restricted to patients aged 18 years, or over.

4.2 Posology, Section 4.2, should be restricted to twice daily as adverse events were more common with thrice daily and efficacy no greater.

4.3 The contraindications, Section 4.2, should include patients with migraine, recurrent headache, or postural hypotension.

4.4 In Section 4.8 the listed side effects should include reflex tachycardia, vomiting, anal burning and itching.

4.5 The Patient Information Leaflet should be consistent with the revised SPC.
APPENDIX 3 – COMPANY RESPONSES TO CSM DRAFT ADVICE

PRODUCT: Rectogesic
PRODUCT NUMBER: MA 19075/0003
Active Constituents: Glyceryl trinitrate 0.4% w/w
Proposed Indications: Anal fissure
Therapeutic Class: Smooth muscle relaxant

1. BACKGROUND
1.1 This is an abridged complex national application. It has been submitted under Article 10.1(a)(ii) of Directive 2001/83/EC as a bibliographical application. In the event of UK approval, the applicant intends to apply for mutual recognition in most of Europe.

The product has been licensed in Australia since 1998, but currently no GTN ointment products are approved in the UK for this indication.

1.2 The original application was rejected by CSM at its meeting of 28th March 2002 and withdrawn from the USA on 25th April 2002, as more data were requested.

1.3 A second application for a Marketing Authorisation for this product was received on 25 February 2003, which included data on an additional study.

The Application was considered by the CSM at their meeting on 31 July 2003.

The Committee had reason to think that on grounds relating to safety, quality and efficacy, that they would be unable to advise that the Marketing Authorisation applied for should be granted.

1.4 On 31st July 2003, the Committee provisionally concluded that:

CSM Point 1. Efficacy is modest as the pain relief effect is small.

CSM Point 2. Adverse events are common. There is particular concern about the incidence of headache, which is often severe, and also dizziness, nausea and postural hypotension.

CSM Point 3. The risk benefit is adverse.

CSM Point 4. Points for Clarification
4.1 The applicant should comment on the validity of the assumptions made for data missing due to patient withdrawal in the primary analysis.

4.2 The applicant should supply ANCOVA analyses on the Day 56 pain scores using pain at baseline as covariate and LOCF to impute data missing due to patient withdrawals.

CSM Point 5. The following changes to the Product Particulars are requested:
5.1 The indication, Section 4.1, should be restricted to patients aged 18 years, or over.

5.2 Posology, Section 4.2, should be restricted to twice daily as adverse events were more common with thrice daily and efficacy no greater.
5.3 The contraindications, Section 4.2, should include patients with migraine, recurrent headache, or postural hypotension.

5.4 In Section 4.8 the listed side effects should include reflex tachycardia, vomiting, anal burning and itching.

1.5 On 28 August 2003 the Company wrote to the Committee giving notice that they intended to take the opportunity to seek a Hearing supported by additional data for just the higher concentration of 0.4%. These data have now been received and are placed before the Committee for their consideration.

2. ADDITIONAL DATA
Two volumes of data were received in December 2003.

Although the Company had originally applied for two strengths of 0.2% and 0.4%, they have withdrawn the 0.2% application.

3. CLINICAL ASSESSMENT
CSM Point 1. Efficacy is modest as the pain relief effect is small.

Company Response:
The cardinal symptom of chronic anal fissure is severe, often disabling local pain that may interfere with the patient’s daily activities, including work. Anal fissure pain is due primarily to increased tone and spasm of the internal anal sphincter, and in part to the passage of fecal matter over an open wound. Pain is the complaint that brings the anal fissure patient to the physician’s office, and relief of the pain is what the patient wants and needs most, with healing an important but secondary benefit. Reduction of anal fissure pain and anal fissure healing are not necessarily concordant.

Pain is a significant deterrent to well-being, and any relief is essential. For many physicians pain control ranks relatively low among patient care priorities. For example, a 1994 study found that cancer patients receive inadequate pain treatment, non-cancer participants receive even less adequate treatment, and that minority participants, the elderly and females were more likely than others to receive inadequate pain treatment (quoted in 1). The importance of pain relief is also underscored by the campaign of the European Federation of International Association Study of Pain- Europe Against Pain. They state on their website (http://effic.org.eap.htm#summary August 5, 2003) that “pain, particularly chronic pain, is a major liability in the ledger of quality of life in Europe. The control of pain has been a relatively neglected area of governmental concern in the past, despite the facts that cost-effective methods of pain control are available. The time is right to raise the profile of pain within the European Union (EU), to promote the recognition that pain is not merely a symptom but an important health concern in its own right.”

Although standard treatment with bulk laxatives and sitz baths may provide temporary relief, they do not significantly affect long-term outcome in the patient with a chronic anal fissure. Currently, we believe no drug product has been approved in the UK for treatment of chronic anal fissure. Thus, the only available treatment is surgery. Lateral internal sphincterotomy does reduce anal sphincter tone and relieve anal pain (2, 3), but is associated with a significant risk of anal incontinence (4) in as high as 35% of patients. Medical treatment can also significantly reduce internal anal sphincter tone without significant risk of incontinence.
by application of glyceryl trinitrate (GTN) rectal ointment. GTN is converted in tissue to nitric oxide (NO), a neurotransmitter that relaxes smooth muscle of the internal anal sphincter (5,6) and increases anodermal blood flow (7). These pharmacodynamic effects form a rational basis for the use of GTN to treat the pain of chronic anal fissure.

**Clinical Studies**

Results of two large, double-blind, randomized, placebo-controlled trials with Rectogesic™ rectal ointment, Studies R1 and R2, provide evidence that Rectogesic rectal ointment produces pain relief in participants with a chronic anal fissure significantly greater than provided by standard care. This improvement in pain relief is accomplished without risk of fecal incontinence as may occur following sphincterotomy. Pain relief provided by administration of Rectogesic rectal ointment to subjects with chronic anal fissure was demonstrated initially as results for a secondary endpoint in Study R1 and corroborated as the primary endpoint in Study R2. The effectiveness of Rectogesic in the latter study was established by the results of three measures of efficacy: daily pain intensity (analyzed using a mixed effects regression model); time to 50% improvement in daily pain intensity (8,9) and frequency of sitz bath use (Chi-square statistic and Wilcoxon 2 sample non-parametric test). These results and methods will be discussed below.

### Table 1

<table>
<thead>
<tr>
<th></th>
<th>Study R1</th>
<th>Study R2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Design</strong></td>
<td>Double-blind, randomized, placebo-controlled, parallel groups. Subjects were discontinued when healed.</td>
<td>Double-blind, randomized, placebo-controlled, parallel groups. Subjects were required to remain in study for 56 days even if healed or pain gone.</td>
</tr>
<tr>
<td><strong>Dose</strong></td>
<td>374 mg 0.0% (0.0mg GTN), 0.1% (0.375 mg GTN), 0.2% (0.75mg GTN), 0.4% (1.5mg GTN) ointment</td>
<td>374 mg 0.0% (0.0mg GTN), 0.2% (0.75mg GTN), 0.4% (1.5mg GTN) ointment</td>
</tr>
<tr>
<td><strong>Frequency</strong></td>
<td>bid and tid</td>
<td>bid</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>56 days or until healing, whichever comes first</td>
<td>56 days even though healing occurs or pain is gone</td>
</tr>
<tr>
<td><strong>Standard care</strong></td>
<td>Bulk laxatives, sitz baths allowed <em>ad libitum</em></td>
<td>Daily fiber intake required and provided, one sitz bath/day allowed</td>
</tr>
<tr>
<td><strong>Endpoints</strong></td>
<td>Primary- fissure healing</td>
<td>Primary- decrease in pain intensity</td>
</tr>
<tr>
<td></td>
<td>Secondary- decrease in pain intensity</td>
<td>Secondary- fissure healing</td>
</tr>
<tr>
<td><strong>Effectiveness measures</strong></td>
<td>VAS completed by subject each evening for average pain past 24 hours, pain at last bowel movement, and worst pain during the day</td>
<td>VAS by subject each evening for average pain past 24 hours, pain at last bowel movement, and worst pain during the day</td>
</tr>
</tbody>
</table>

**RESULTS**

Rectogesic 0.4% vs. placebo

Analysis - mixed effects regression model

Healing NS (primary endpoint)  
Pain improvement (secondary endpoint) = rate of change over time between GTN and vehicle  

$P < .0001$

Healing NS (secondary endpoint)

### Analysis - time to 50% improvement

Rectogesic – 7 days  
Placebo- 14 days $P = .005$

### Sitz baths

Sitz bath use not recorded.

Two or more sitz baths during study- Rectogesic 11.8% vs. placebo 23.3% $P = 0.12$

$^1$VAS = 100 mm visual analog scale, “no pain” to “worst pain imaginable”  
NS = not significant

The design, differences and results of the two phase 3 studies that establish the effectiveness of Rectogesic in relieving the pain associated with a chronic anal fissure are summarized in Table 1. Rectogesic 0.2% rectal ointment (0.75mg GTN) was less effective than the 0.4% formulation (1.5mg GTN), and we propose to withdraw the lower strength from further consideration. Therefore only the results for the 0.4% ointment (1.5mg GTN) applied bid are shown and discussed.
Figure 1
Percent Improvement in Mean Average Pain Intensity (mm) by Time Period
Study 1 – Tx (0.4% vs. 0.0%) by Linear Time Interaction p<.0001

Figure 2
Percent Improvement in Mean Average Pain Intensity (mm) by Time Period
Study 2 – Tx (0.4% vs. 0.0%) by Linear Time Interaction p<.005
Methods of analysis
Mixed-effects regression model:
The mixed-effects regression model uses all available data from each subject to compare rates of change in outcome measure. The advantages of the model over traditional analyses are 1) it makes use of all data collected from each subject, thereby increasing statistical power; 2) eliminates bias due to exclusion of collected data from the analysis; 3) does not rely on a single measurement for each subject to characterize response to treatment and 4) subjects leaving the trial early are not artificially assumed to have completed the trial. Relative to traditional “repeated measures” ANOVA, the advantages of the mixed-effects regression model are that 1) it does not assume an overly restrictive correlational structure in which variances and covariances are assumed to be constant over time and 2) it can accommodate missing data and drop-outs. Relative to multivariate growth curve models, the advantage of the mixed-effects regression model is that it does not require any subject with missing data to be excluded from the analysis, a requirement that may produce a situation in which the subjects in the analysis are quite dissimilar to the subjects randomized to the treatment conditions, leading to biased statistical estimates and tests of hypotheses.

The mixed-effects regression model approach was used to evaluate the results from the three categories of pain responses: average 24 hour pain estimate by each subject; worst pain during the day and pain on last daily defecation that one occurs.

Based on this method of analysis, Rectogesic rectal ointment was significantly superior to placebo (p=.0001) in reducing the average pain intensity (Figure 1) in Study R1 and in Study R2 (p=.005, Figure 2). The results of combining the data for average pain intensity changes from the combined studies are shown in Figure 3 and confirm the significant (p=.0001) benefit of Rectogesic rectal ointment in reducing pain. Although average pain was the primary endpoint, significant treatment by time effects for Rectogesic rectal ointment were also apparent for the secondary categories worst pain (p<.0008) and pain at defecation (p<.03) in Study R1. Significant overall linear-time interactions for the comparison between...
Rectogesic rectal ointment and placebo were also observed in Study R2 for worst pain (\(p < 0.005\)) and pain at defecation (\(p < 0.04\)) in spite of a higher placebo response in this study.

Time to 50% improvement:
Survival curves were constructed and time to 50% improvement for 50% of the subjects determined. This method provides the clinician with a reasonable assessment of the drug’s ability to decrease pain intensity. The evidence to justify the 50% criterion is provided below in Robustness of Time to 50% Improvement, by examining several alternative criteria. The time to 50% improvement in Study R1 was 7 days with Rectogesic vs. 14 days with placebo (\(p = 0.005\)); in Study R2 time to 50% improvement was 7 days with Rectogesic vs. 21 days with placebo (\(p = 0.02\)) (Fig 4) and with the combined studies was 7 days with Rectogesic vs. 21 with placebo (\(p = 0.008\)).

**Figure 4**

**Survival Estimates**

*Time to 50% reduction in pain*

*Sample: Study 2*

Robustness of time to 50% improvement
The clinical significance of the pain relief produced by Rectogesic ointment is clearly demonstrated by determining the time to 50% improvement in pain intensity, an endpoint frequently used in pain studies. In clinical terms, 50% of subjects who use Rectogesic obtained 50% improvement in pain intensity in 7 days compared to 21 days for the placebo group. In Study R2, these benefits of pain relief are demonstrated even in subjects receiving standard daily doses of fiber (bulk laxative) and permitted to take one sitz bath a day.

To determine the robustness of the results for time to 50% improvement, we, examined results of inter-group comparisons for improvement of 20%, 30%,
Table 2: Statistical Significance of 20-80% Improvement

<table>
<thead>
<tr>
<th>% improvement</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>&lt;.08</td>
</tr>
<tr>
<td>30</td>
<td>&lt;.07</td>
</tr>
<tr>
<td>40</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>50</td>
<td>&lt;.02</td>
</tr>
<tr>
<td>60</td>
<td>&lt;.007</td>
</tr>
<tr>
<td>70</td>
<td>&lt;.03</td>
</tr>
<tr>
<td>80</td>
<td>&lt;.09</td>
</tr>
</tbody>
</table>

40%, 50%, 60%, 70% and 80%. Results of these analyses are displayed graphically as survival curves in APPENDIX 1. Statistical tests of equality of the two time-to-improvement distributions (placebo vs. Rectogesic) had the one-tailed probability values recorded in Table 2.

Note that the original report listed a two-tailed probability for time to 50% improvement (p<.04), but the hypotheses are clearly one-sided (i.e., Rectogesic > Placebo). These probability values and the corresponding figures provide strong evidence that the Rectogesic effect is robust and not the result of a fortuitous or “data-conditioned” choice of degree of improvement (i.e. 50%). Indeed, the time to 70% improvement is also significant (p<.03), providing further evidence of the clinical effectiveness of Rectogesic in decreasing the pain associated with chronic anal fissure.

Sitz baths
We also examined differences in proportions of subjects who took two or more sitz baths during the course of treatment, and compared these proportions between Rectogesic ointment 0.4% and placebo. The proportions of subjects who took two or more sitz baths during the course of treatment were 23.3% (17/73) for the placebo group vs only 11.8% (8/68) for the GTN group. The associated one-tailed probability is p=.12. Although not statistically significant, the percentage of subjects using two or more sitz baths during the course of treatment was reduced by 50% with Rectogesic, certainly a clinically significant effect. Note that the study was powered to detect an effect on pain and not on use of sitz baths. A study to detect such a binary effect with $\alpha$ set at 0.05 would have had to have been considerably larger than that conducted.

Standard Care
The effect of adding standard care (subjects were given and requested to consume psyllium bid and allowed to take one sitz bath each day) to all subjects in Study R2 may be observed in Figures 5 and 6. The effect of Rectogesic on average pain relief in both studies was similar (Figure 5) whereas the placebo response was better in Study R2 than in Study R1 (Figure 6). The addition of standard care is most likely the reason for the improved effect of placebo in Study R2 compared to Study R1. These observations also show however, that Rectogesic has a salutary effect beyond that achieved with standard care and placebo.
Published Studies

Altomare DF et al:
The study by Altomare et al (10) has been cited by the clinical assessor as a large controlled study that provides evidences of the ineffectiveness of GTN for healing and relieving the pain associated with a chronic anal fissure. The Altomare et al study has several significant flaws. Pain relief with GTN was reported to be significantly different than pretreatment, but not different than the placebo; however pain was evaluated for only the first week of treatment, an inadequate duration of observation. In assessing the relevance of the Altomare et al study, it is essential to understand that the dose of GTN is not the percentage in the dosage form, but rather the amount of active ingredient applied. In the Rectogesic studies, a measuring device was used to apply 375mg 0.4% Rectogesic ointment (1.5mg GTN) bid. The dose in the Altomare et al study was reported to be 200mg 0.2% GTN ointment (0.4mg GTN) bid. This dose is well below that used in other published studies and similar to that provided by the 0.375mg GTN low dose used in Study R1 that was also ineffective in relieving pain. In addition, the Altomare et al study followed subjects for only four weeks compared to eight weeks of treatment in the two Rectogesic studies. Anal pressure reductions were observed in a few subjects administered GTN, but also in subjects treated with placebo, raising questions...
about the validity of the measurements. Further, a green colouring agent was added to the ointment without data to provide evidence it did not affect the bioavailability of GTN. Thus, the Altomare et al study was flawed and should be considered irrelevant as it used a much lower dose than that which we showed to be effective in the Rectogesic studies and followed the subjects for only a short period.

**Nelson, RL editorial and rebuttals:**
Since submission of the application for Rectogesic in February 2003 and assessment of the application by the CSM, a report by Nelson (11) appeared in which the author concluded that the effectiveness of GTN on healing anal fissure was minimal. Nelson’s discussion related only to healing; he made no mention of pain.

Following publication of the Nelson’s report, several letters were written to the editor disagreeing with some of Nelson’s conclusions, including one by Lund et al (12) that provided a rebuttal of the Altomare et al study similar to ours. In addition a response from colorectal surgeon Lindsey (13) states, “Professor Nelson’s view comments on the treatment of chronic anal fissure seem unreasonably pessimistic. Recent developments in medical management have transformed the approach to this difficult problem.” Lindsey also indicates that long-term incontinence is a problem and medical therapy should be used as first-line treatment for anal fissures. In another response, O’Brien (14) points out that the only reference given by Nelson is his personally written article commenting on non-surgical approaches to treatment of anal fissure that is still in press.

**Effective Dose of GTN**
The majority of the published studies submitted as supporting information in the MAA do not indicate the quantity of 0.2% GTN administered. The exception to this is the study by Altomare et al (10) discussed above, in which 200 mg GTN ointment was administered, equivalent to 0.4 mg GTN, and found to be ineffective for pain relief. Another more recent study by Scholefield et al (31) specified that approximately 220 mg ointment was applied. Three different concentrations GTN ointment used were 0.1% (0.22mg GTN), 0.2% (0.44mg GTN) and 0.4% (0.88mg GTN). None of the three doses were statistically better than placebo in relieving overall pain and pain on defecation determined only at each clinic visit. As we have made clear in section 4.2, significant statistical power is lost by determining pain intensity only at two week intervals rather than daily. Interestingly, when a subgroup analysis was done with subjects whose fissures were confirmed to be chronic based on specific physical findings, the 0.22mg GTN and 0.88mg GTN, but not the 0.44mg GTN dose were associated with statistically significant healing compared to placebo. Unfortunately the results of the pain intensity measurements and analyses were not recorded.

The other published controlled trials included in the MAA, e.g. Lund and Scholefield (32), Carapeti et al (33), Kennedy et al (34), Oettle et al (35), employed 0.2% GTN ointment either bid or tid, but did not specify in the publication the quantity administered. JN Lund has informed Cellegy (personal communication) that they estimate 0.5g ointment was applied in the Lund and Scholefield (32) study, i.e. 1mg GTN applied bid. This is consistent with the recommendations in Drugs and Therapeutics Bulletin (19) which recommended that a pea-sized quantity (about 0.5g) should be applied twice daily to the anal rim for at least 6 weeks. The patient Information Leaflet available at the Prodigy Guidance for Anal Fissure also recommends a pea-sized amount. From the published studies that provide evidence of pain relief, it is likely that at least 1mg GTN was applied bid or tid, i.e. a daily dose of 2 to 3 mg GTN. The recommended dose of Rectogesic 0.4% ointment is 375mg, i.e. 1.5mg GTN every 12 hours, a daily dose of 3mg.
Summary of efficacy

Three different methods (mixed effect regression model analysis of all available VAS scores, time to 50% improvement and sitz bath usage) for evaluating chronic anal pain intensity response to Rectogesic clearly provide strong evidence of the effectiveness of this treatment. The dose of 375 mg Rectogesic 0.4% ointment delivers 1.5 mg GTN which when applied twice daily in the two double-blind placebo controlled studies provided pain relief.

The evidence from published studies and from the recommendations of different groups also indicates that a dose of about 1 mg GTN, two or three times a day is effective in healing and providing pain relief in patients with chronic anal fissure.

Clinical Assessor's Comment:

There is no doubt that severe pain is important. The issue is how much pain relief Rectogesic allows. No new efficacy data have been submitted.

As discussed in the last assessment, Pink Sheets Part IV, page 3, the primary objective of the first study, Study R1, was fissure healing. There was no significant effect on healing, but a significant effect on pain for the 0.4% group when compared to placebo. As pain was not the primary variable, this can be viewed as an exploratory study and supportive evidence only for pain relief.

This benefit in pain relief influenced the design of the second study, Study R2, where pain relief was made the primary objective. There was a significant difference in pain relief with the 0.4% group compared to placebo, although the difference was not as marked as in the first exploratory trial. The effect of 0.2% was not significant compared to placebo and there was no significant effect on healing with either strength. The statistically significant effect on pain with 0.4% was only for mean average pain intensity. There were similar patterns of pain relief for worst pain and pain on defecation, but these were not significant. Eight patients withdrew from the second trial because of headache with the 0.4% preparation, compared to one patient on placebo.

The biggest effect on mean average pain intensity was about 3-4 weeks after treatment, see Figure 2 above. Most patients had pain relief over 8 weeks, whether they were on active treatment or not.

The Company have performed a further analysis, as suggested at the pre-submission meeting. For this they looked at the time difference between 0.4% and placebo for a 50% reduction in pain for 50% of patients. The results for the time to a 50% improvement suggest that many patients will have a significant shortening in the duration of pain, Figure 4 above. This analysis is most relevant to the second study, where pain was the primary variable, but the analysis was restricted to just one of the three pain variables. For average pain intensity the time to 50% improvement was 7 days with Rectogesic and 21 days with placebo. This difference of 14 days for the second study was more impressive than the difference of 7 days for 50% improvement for the first study even though Figure 1 above suggests that the effect in the first study was greater than the effect in the second study, Figure 2.

As discussed in the statistical comment, below, the choice of 50% is to some extent retrospective and favourable, but the Company has provided additional time points for comparison. There seems little doubt that although most cases resolve spontaneously, significant attenuation of symptoms occurs sooner with the active treatment.
MHRA Statistical Assessor’s Comment:
The two studies presented as evidence of efficacy are summarised in Table 1 of the applicant’s response. The first study (Study R1) is considered exploratory as there were no differences between NTG and placebo on the primary endpoint (effect on fissure healing). There were statistically significant effects on the secondary endpoints assessing pain; average pain intensity, pain on defecation and worst pain intensity. The second study (Study R2) was designed to confirm the effects on pain observed in Study R1. The primary objective of this study was pain relief, measured by average pain, pain on defecation and worst pain. Fissure healing was a secondary endpoint. A statistically significant effect in favour of NTG was demonstrated only for average pain, though effects on the other assessments of pain trended in the same direction. No effect was observed on fissure healing. An analysis pooling data from these two studies was also presented. In this analysis, all assessments of pain reached statistical significance.

Effects on pain were assessed using a mixed-effects regression model. This is considered appropriate for these data (see Point 4). The levels of statistical significance derived from this model are interpretable and provide evidence of statistically significant differences between NTG and placebo for average pain in both studies. Whether this provides confirmatory evidence of efficacy is questionable. It must be considered that only one pivotal study has been provided. It should also be considered that average pain was one of three assessments of pain, resulting in concerns over multiplicity. On balance, this assessor considers that there is adequate evidence to confirm a statistically significant difference between NTG 0.4% and placebo with regards average pain. Effects on pain on defecation and worst pain have not been established robustly and no effect has been demonstrated on fissure healing.

Although the mixed effects model provides information on statistical significance, it does not provide a readily interpretable estimate of clinical benefit. Analyses of average pain scores at Day 56, which would be readily interpretable, show no evidence of a benefit for NTG over placebo (see Point 4). The applicant attempts to quantify the clinical benefit in Figure 4 and Table 2 in which time to event analyses based on data from Study R2 are presented. Using data from Study R2 is considered preferable to using data from Study R1 or from the pooled dataset as Study R2 was the pivotal study, in which the assessments of pain were the primary objective. Figure 4 should be interpreted with caution as the choice of time to 50% reduction is post hoc. Table 2 should be interpreted with caution as the p-values presented are 1-sided, which is inappropriate, as stated in ICH E9. Table 2 is, therefore, repeated below including 2-sided p-values and median differences for other levels of pain reduction. It is appropriate to consider this range of pain reduction given the above-mentioned concerns of selection bias.

<table>
<thead>
<tr>
<th>% improvement</th>
<th>Two-sided p-value*</th>
<th>Approximate difference in medians (days)**</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>&lt; 0.16</td>
<td>0</td>
</tr>
<tr>
<td>30</td>
<td>&lt; 0.14</td>
<td>-1</td>
</tr>
<tr>
<td>40</td>
<td>&lt; 0.1</td>
<td>8</td>
</tr>
<tr>
<td>50</td>
<td>&lt; 0.04</td>
<td>14</td>
</tr>
<tr>
<td>60</td>
<td>&lt; 0.014</td>
<td>7</td>
</tr>
<tr>
<td>70</td>
<td>&lt; 0.06</td>
<td>7</td>
</tr>
<tr>
<td>80</td>
<td>&lt; 0.18</td>
<td>7</td>
</tr>
</tbody>
</table>

* Taken from table 2 but doubled to correspond to the more appropriate 2-sided test. ** Estimated from Appendix 1. Positive values favour NTG 0.4%. Pain scores were assessed on a daily basis.
Although the applicant retrospectively selected time to 50% improvement, which is arguably the most favourable, all analyses requiring improvement of 40% or more indicate a trend in favour of NTG. The levels of statistical significance observed are not crucial to the consideration of efficacy as this has been established already in the primary analysis, which has greater statistical power. Of greater interest are the estimates of effect size. If it can be considered that a more timely reduction in pain of at least 40% is a clinically relevant outcome, then the above table indicates that the time to achieve this relevant response is approximately 1 week shorter on NTG than on placebo. Although the estimate of a time to 50% reduction is 14 rather than 7 days, claiming a 2-week reduction based on this retrospective analysis of this single study would not be a reliable conclusion.

The applicant’s response also presents data on Sitz bath usage, for which there is a trend toward greater use on placebo, but no further analyses are presented for fissure healing, pain on defecation or worst pain.

The applicant concludes that three methods ‘clearly provide strong evidence of the effectiveness of this treatment’. In fact, only one of these methods gave statistically significant results from a pre-specified analysis. The other methods should be used solely for judging clinical relevance and should be interpreted with caution given the concerns over selection bias.

In summary, notwithstanding the less robust evidence for pain on defecation and worst pain, there is sufficient statistical evidence to conclude that NTG 0.4% is effective on average pain. Retrospectively, the applicant has attempted to quantify the magnitude of this effect using time to event analyses. Clinical judgement should consider whether differences in median time to improvement are an appropriate way to assess clinical relevance and, if so, whether the above results confirm a clinically relevant effect.

Point resolved.

CSM Point 2. Adverse events are common. There is particular concern about the incidence of headache, which is often severe, and also dizziness, nausea and postural hypotension.

Company Response:
The side effects of treatment with GTN with any dosage form, by any route or for any indication are well established from over a century of use. These side effects are secondary to the pharmacologic effects of the compound and its metabolites; they include headache, dizziness, postural hypotension, and nausea, and are usually dose related.

**Headaches**
Throbbing frontal headache of relatively short duration is the most common side effect of GTN administration and appropriate warnings and precautions are included in the literature for approved GTN products. The onset of a nitric oxide- induced headache is typically within 30 minutes of administration of GTN.

During the Rectogesic trials, no prospective attempt was made to collect data to establish a temporal relationship between administration of GTN and onset of headache. During the trials, a mild analgesic (paracetamol) was allowed for rescue but was restricted to eight doses over the course of the trial to minimize any potential confounding although paracetamol has little effect on anal fissure pain. Headache was the most frequently reported adverse event in the two Rectogesic studies. The incidence and severity of headache are recorded in Table 3.
Table 3: Incidence and Severity of Headaches in Rectogesic Studies

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Subjects reporting headaches</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>148</td>
<td>27</td>
<td>18</td>
</tr>
<tr>
<td>All subjects</td>
<td>385</td>
<td>155</td>
<td>40</td>
</tr>
<tr>
<td>0.2%</td>
<td>151</td>
<td>62</td>
<td>41.1</td>
</tr>
<tr>
<td>0.4%</td>
<td>158</td>
<td>79</td>
<td>50</td>
</tr>
<tr>
<td>- mild</td>
<td>32</td>
<td>158</td>
<td>20.3</td>
</tr>
<tr>
<td>- moderate</td>
<td>26</td>
<td>158</td>
<td>16.5</td>
</tr>
<tr>
<td>- severe</td>
<td>21</td>
<td>158</td>
<td>13.3</td>
</tr>
</tbody>
</table>

Dropouts in NTG 00-02-01 due to headache were unrelated to the intensity of anal fissure pain, and neither the incidence of headache, nor headache severity was significantly related to rate of change in anal fissure pain (cf discussion in 4.1). Eight of the 14 NTG-treated subjects who were withdrawn from the study due to headache did not receive analgesics prior to withdrawal. Headaches had responded to paracetamol or other analgesic therapy in the other 6 subjects, but recurred in most subjects after the analgesic was stopped, as required by the protocol. In clinical use, mild analgesics, especially if taken 30 minutes or so before application of GTN will ameliorate the potential for/ and intensity of any GTN-induced headache pain. Mahapatra et al (15), for example, report that the headaches of patients receiving 5-20 mg glyceryl trinitrate patches plus sublingual tablet supplementation were satisfactorily managed with analgesics.

Headaches are much more likely to occur following administration of GTN to patients with a history of migraine, cluster or tension headaches (16). In the Rectogesic studies, among those subjects who received GTN and developed severe headaches, 61.1% had histories of headaches and 18.8% did not. For those on placebo, none who had histories of headaches developed a severe headache. For mild and moderate headaches a previous history of headache did not predict headache response to Rectogesic. We believe that the risk of developing a severe headache in association with use of Rectogesic will be significantly reduced by modification of the SPC and the Patient Information Leaflets to indicate that a history of migraine or severe recurrent headaches contraindicates use of Rectogesic rectal ointment.

The side effect profiles for marketed glyceryl trinitrate products are similar to that for Rectogesic rectal ointment. For example, in a follow-up study of patients using transdermal patches delivering 0.2, 0.4 or 0.6mg GTN/hour, the incidence of headaches was 53% (17). Mahapatra et al (15) reported that in patients treated with 5-20mg glyceryl trinitrate patches plus rescue sublingual tablets for angina pectoris, the incidence of headaches was 68%. Even with a low dose patch delivering 0.1mg/hour for management of dysmenorrhea, the incidence of headaches was 26% during three days of treatment (18). If, as we recommend in the PIL and SPC, patients with migraine or recurrent headaches do not use Rectogesic ointment, the incidence of mild and moderate headaches in subjects receiving 1.5mg GTN bid is 42/116 (36.2%), not dissimilar to that for use of GTN for dysmenorrhea (18), another benign, but painful disorder.

**Dizziness and Nausea**

The incidence of dizziness and nausea in Study R2 was 10% and 7.7% respectively, similar or less than patients using GTN patches that are associated with dizziness incidences of 8% (17) and 21% (15) and nausea of 15% (15) in other studies. Patients using Rectogesic will be instructed to rise slowly from the supine or sitting positions.
Blood pressure
There were no time-or-dose-related trends in diastolic, systolic blood pressure or pulse rate. However, a few subjects in the Phase 3 studies experienced vasodilatation or hypotension, known pharmacologic effects of GTN. Postural hypotension was not specifically evaluated during the studies; however the effect of GTN on sitting blood pressure was assessed 10-20 minutes after administration of Rectogesic and placebo ointments. To evaluate this potential effect of Rectogesic ointment, the proportion of subjects with clinically significant decreases (≥ 20 mm Hg) in diastolic blood pressure were determined, based on blood pressure measurements obtained immediately before and 10-20 minutes after administration of study medication at each clinic visit. Our results are shown in Table 4.

Table 4: Number (%) of Subjects With ≥20 mmHg Decreases in Sitting Diastolic Blood Pressure 10-20 minutes After Dose (All Subjects in completed Phase 3 Studies)

<table>
<thead>
<tr>
<th>GTN Ointment</th>
<th>Placebo (N=148)</th>
<th>0.1% (N=76)</th>
<th>0.2% (N=151)</th>
<th>0.4% (N=158)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td>0 (0.0)</td>
<td>3 (3.9)</td>
<td>2 (1.3)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Day 14</td>
<td>3 (2.0)</td>
<td>5 (6.6)</td>
<td>3 (2.0)</td>
<td>5 (3.2)</td>
</tr>
<tr>
<td>Day 28</td>
<td>4 (2.7)</td>
<td>6 (7.9)</td>
<td>4 (2.6)</td>
<td>4 (2.5)</td>
</tr>
<tr>
<td>Day 42</td>
<td>3 (2.0)</td>
<td>6 (7.9)</td>
<td>4 (2.6)</td>
<td>3 (1.9)</td>
</tr>
<tr>
<td>Day 56</td>
<td>4 (2.7)</td>
<td>5 (6.6)</td>
<td>0 (0.0)</td>
<td>3 (1.9)</td>
</tr>
<tr>
<td>Any</td>
<td>9 (6.1)</td>
<td>12 (15.8)</td>
<td>6 (4.0)</td>
<td>12 (7.6)</td>
</tr>
</tbody>
</table>

Overall, 9 placebo subjects (6%) and 30 Rectogesic subjects (8%) had significant decreases in diastolic blood pressure at least once within 10-20 minutes of a dose of study drug. The highest incidence of blood pressure decrease is seen with the lowest dose of GTN, so there were no dose-related trends. The incidence of blood pressure decreases was lowest on Day 1; aside from that there were no time-related trends. Patients using Rectogesic will be instructed to rise slowly from the supine or sitting positions.

Incontinence
Flatus and fecal incontinence have been reported in up to 35% of patients undergoing internal lateral sphincterotomy (1). Rectogesic does not result in incontinence.

Post marketing information
Cellegy is marketing Rectogesic® glyceryl trinitrate rectal ointment 0.2% in Australia. More than one hundred thousand tubes have been sold, and only eight reports of headache have been received.

Clinical Assessor's Comment:
In the second trial, which provides the main evidence of efficacy, there were significant increases in adverse events, as discussed in the original assessment report, Pink Sheets Part IV, page 8. Severe adverse events occurred in 4% of placebo patients and 13% of GTN treated patients; of the severe events 17/24 were headache. The main adverse events are shown in the table below:

Table - Adverse events in trial NTG 00-02-01

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Placebo</th>
<th>NTG 0.4%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>18%</td>
<td>51%</td>
</tr>
<tr>
<td>Withdrawal because of headache</td>
<td>1%</td>
<td>10%</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>2.5%</td>
<td>7.7%</td>
</tr>
<tr>
<td>Nausea</td>
<td>0%</td>
<td>7.7%</td>
</tr>
</tbody>
</table>
There is no doubt that headache is common with Rectogesic and may be severe. Some of the patients took paracetamol for this, which was allowed by the protocol. Up to eight doses of paracetamol per patient were allowed during the trial to try to reduce complicating the assessment of efficacy by an analgesic. It is not clear if the reduction in anal pain is counterbalanced by an increase in headache and other adverse effects.

**Point not resolved.**

**CSM Point 3.** The risk benefit is adverse.

**Company Response:**
A clinically significant reduction in chronic fissure pain was observed in study Study R2 using a mixed effect regression analysis, time to 50% improvement in pain intensity and sitz bath data. These results corroborate the significant reduction in pain intensity observed as a secondary endpoint in Study R1 and were obtained without producing incontinence. Headache pain did not affect anal fissure pain reduction. The incidence of the well-known side effects of glyceryl trinitrate - headache, dizziness, postural hypotension and nausea that occurred during the study were not significantly different from those reported for currently marketed products, and do not outweigh the importance of significantly relieving the patient’s anal fissure pain with Rectogesic. The small number of subjects who dropped out due to headache did so only after their fissure pain had been significantly relieved. Thus, Rectogesic provides a satisfactory risk/benefit ratio. Side effects of glyceryl trinitrate will be highlighted in the appropriate sections of the Patient Information Leaflet and Summary of Product Characteristics leaflets as they are for the currently marketed glyceryl trinitrate products.

**Clinical Assessor's Comment:**
It is not clear is that the reduction in time to significant relief in mean average pain intensity is outweighed by the increase in adverse events, particularly headache. The amendments to the SPC that exclude patients with migraine, recurrent headache, or postural hypotension may help reduce exposure of patients at particular risk, but the incidence of adverse events requiring simple analgesia remains high. Simple analgesia may provide pain relief of anal fissure without the high incidence of adverse events seen with GTN.

An editorial in the BMJ, Nelson RJ. Treatment of anal fissure. BMJ 2003;327:354-5, reviewed the published trials with nitroglycerin. This stated that "Overall nitroglycerin ointment was more effective than placebo, but in sensitivity analyses that excluded studies with placebo cure rates below than 10% - more than two standard deviations below the mean - statistical evidence of efficacy disappeared. In addition, with nitroglycerin ointment, the most investigated medical treatment, headache was common, occurring in almost 40% of subjects in the combined analyses and severe enough often to stop treatment". This view is expanded further in a Cochrane Review, Issue 1, 2004, by the same author, a view is contested by the Company, see page 27.

**Point not resolved.**
CSM Point 4. Points for Clarification

4.1 The applicant should comment on the validity of the assumptions made for data missing due to patient withdrawal in the primary analysis.

4.2 The applicant should supply ANCOVA analyses on the Day 56 pain scores using pain at baseline as covariate and LOCF to impute data missing due to patient withdrawals.

Company Response:

The applicant provided the analyses requested, but argues they are not sensible.

An important feature of generalized mixed-effects regression models is their treatment of missing data. Since there are no restrictions on the number of observations per individual, in such analyses, subjects who are missing measurements are not excluded from the analysis, nor is it necessary to impute values for their missing observation(s). The assumption of the model is that the data available for a given subject are representative and can be used to assess that subject's response with regards to the average trend lines for the whole sample. Thus, the model estimates the subject's trend across time based on data available for the subject, augmented by the time-trend estimated for the sample as a whole, including effects of all covariates in the model.

As Laird (26) points out, random-effects models for longitudinal data using maximum likelihood estimation provide valid inferences in the presence of ignorable non-response. Ignorable non-response means that the probability of non-response is dependent on observed covariates and previous values of the dependent variable from the subjects with missing data. The notion here is that if subject attrition is related to previous performance, in addition to other observable subject characteristics, then the model provides valid statistical inferences for the model parameters. Since many instances of missing data are related to previous performance or other subject characteristics, the random-effects approach provides a powerful method for dealing with longitudinal datasets in the presence of missing data.

In longitudinal studies, ignorable non-response falls under Rubin's (27) "missing at random" (MAR) assumption, in which the missingness depends only on observed data, and has also been termed "random dropout" by Diggle and Kenward (28). It is important to distinguish MAR data from what Little (29) refers to as "covariate-dependent" dropout, in which the missing data can be explained by model covariates (the independent variables in a model), but does not depend on observed values of the dependent variable. Covariate-dependent drop-out is sometimes viewed as a special case of Rubin's (27) "missing completely at random" (MCAR) assumption, and has also been called "completely random drop-out" by Diggle and Kenward (28). The essential distinction between MAR and covariate-dependent missing data, is then that in addition to allowing dependency between the missing data and the model covariates, MAR allows the missing data to be related to observed values of the dependent variable. This distinction is important because longitudinal statistical procedures like Generalized Estimating Equations (GEE) (30) assume that the data are covariate-dependent, while full likelihood-based procedures like the random-effects models allow for MAR data. Thus, if the missing levels of the dependent variable are thought to be related to observed previous levels of the dependent variable (e.g., subjects with very bad or very good scores drop-out), then likelihood-based random-effects analysis may be valid, however GEE analysis, in general, is not.

With respect to the proposed study, the MAR assumption is quite reasonable. One of the key concerns is drop-out due to headache. Headaches increase with increasing dosage of GTN ointment. Since treatment is in the model, the effect of treatment on drop-out due to headache
is ignorable for the generalized mixed-effects regression model proposed in this study. Analysis of Study R2 VAS scale-scores provided evidence that little or no remaining anal fissure pain was present in GTN-treated participants who dropped out of the study due to headache. This finding indicates that dropout due to headache was unrelated to the intensity of anal fissure pain, and if anything, patients dropped out of the study due to headache only after their anal fissure pain had remitted. However, 14 patients in the Rectogesic arm of study CP125 00-02-01 experienced headaches and left the study early. Random intercept and slope models were fitted to compare 1) linear time trends for patients with and without headache and 2) the effect of headache severity on average 24 hour pain intensity. The analyses indicate that neither incidence of headache nor headache severity is significantly related to rate in change of anal fissure pain. Patients with headache had lower average pain score compared to those without headache over time (Figure 7). Among participants who dropped out of the study, there was no association between severity of headache and anal fissure pain (Figure 8).

Figure 7

![Average Pain Over Time for Subjects With and Without Headache](image1)

Data: Study 2 (0.4% Ointment)

Figure 8

![Average Pain Over Time for Subjects Who Discontinued Study for Various Levels of Headache Severity](image2)

Data: Study 2 (0.4% Ointment)
In light of these results we feel that the assumption of ignorable non-response (i.e., MAR) that is implicit in the generalized mixed-effects regression model is well justified. It should be noted that these assumptions are, in fact, far more general than the very restrictive assumptions which underlie the last observation carried forward (LOCF) end-point analysis suggested by the Committee on Safety of Medicines.

**MHRA Statistical Assessor’s Comment:**
The explanation given in 4.1 is technically correct. Question 4.1 was asked as more patients withdrew from the trial (due primarily to adverse events) on NTG 0.4% than on placebo and the impact of this on the trial results was unclear. In particular, it was unclear whether the weight given to a patient withdrawn from the trial was equal to that given to a patient who completed the trial. Question 4.2 was asked in order that a more easily interpretable estimate of effect size was available than that from the mixed-effect model. The weaknesses of the LOCF approach are well understood, but the method does provide a conservative estimate of effect on a scale that is readily interpretable. The applicant argues that pain scores at Day 56 are not relevant as many patients, both on NTG and placebo, are pain free at this time. They argue that the aim of treatment is to alleviate pain more speedily. Readily interpretable estimates of effect size are therefore available from the time to event analyses presented, though an analysis of time to 100% pain relief would have been of particular interest.

**Point resolved.**

**CSM Point 5.** The following changes to the Product Particulars are requested:

5.1 The indication, Section 4.1, should be restricted to patients aged 18 years, or over.  
**Point resolved.**

5.2 Posology, Section 4.2, should be restricted to twice daily as adverse events were more common with thrice daily and efficacy no greater.  
**Point resolved.**

5.3 The contraindications, Section 4.2, should include patients with migraine, recurrent headache, or postural hypotension.  
**Point resolved.**

5.4 In Section 4.8 the listed side effects should include reflex tachycardia, vomiting, anal burning and itching.  
**Point resolved.**

The Patient Information Leaflet should be consistent with the revised SPC.  
**Point resolved.**
6. CLINICAL/STATISTICAL SUMMARY CONCLUSIONS

<table>
<thead>
<tr>
<th>CSM letter point:</th>
<th>Resolved/ not resolved</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CSM Point 1.</strong></td>
<td>Resolved</td>
</tr>
<tr>
<td><strong>CSM Point 1.</strong> Efficacy is modest as the pain relief effect is small.</td>
<td></td>
</tr>
<tr>
<td><strong>CSM Point 2.</strong></td>
<td>Not resolved</td>
</tr>
<tr>
<td><strong>CSM Point 2.</strong> Adverse events are common. There is particular concern about the incidence of headache, which is often severe, and also dizziness, nausea and postural hypotension.</td>
<td></td>
</tr>
<tr>
<td><strong>CSM Point 3.</strong></td>
<td>Not resolved</td>
</tr>
<tr>
<td><strong>CSM Point 3.</strong> The risk benefit is adverse.</td>
<td></td>
</tr>
<tr>
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<td></td>
</tr>
</tbody>
</table>
APPENDIX 4 – MINUTES OF CSM MEETING (DATED 25 MARCH 2004)

DISCUSSION BY CSM, 25th MARCH 2004

The findings from CPS were presented. There were some minor pharmaceutical issues, which were considered resolvable. There was concern that withdrawal of the supply of the measuring device would need to be addressed by the applicant and adequate advice given to the prescriber and patient so that the results of the trial were reproducible in practice.

The Committee agreed that the new analysis of benefit, in terms of the percentage of patients who had a reduction in pain, particularly around weeks three to four, was useful. Even allowing for multiplicity, it appeared that there was clear evidence of significant clinical benefit for pain reduction. Although there was an effect on pain, there was no effect on healing.

The adverse event profile was a concern, particularly headache. However, it was considered that patients who had adverse events could stop the treatment, provided that the adverse event profile was clear in the SPC and PIL. The advice in the PIL that headache normally wears off and responds to analgesics was thought inappropriate. It was considered that additional advice would be required in the PIL on what constitutes intra-anal administration.

It was considered that an oral hearing was not necessary.

RECOMMENDATION BY CSM

Recommended approval provided that:

Pharmaceutical Points for clarification:

1. The Company should clarify how dose reproducibility will be addressed now that the supply of the measuring device has been withdrawn. They should provide adequate evidence that the advice in the SPC and PIL will allow dosing to be dispensed within the degree of accuracy required, consistent with dosing in the clinical trials.

2. The Company should clarify if a patient will be issued with a finger cot or plastic wrap. If not, the SPC and PIL should include additional information on how to obtain a suitable supply.

Part H: An appropriately licensed company must be nominated to perform import and batch release operations in the EEA prior to granting of the Marketing Authorisation.

Part H:

4. It should be confirmed that batches of all excipients used in future manufacture will comply with the Ph Eur.
SPC Points
6. As the Company has shown no effect on healing, Section 4.2 should be amended. Please delete "Since healing of chronic anal fissures occur over time, treatment should be continued until two weeks after the pain abates, healing occurs or for up to 8 weeks." and replace with "Treatment may be continued until the pain abates, up to a maximum of 8 weeks."

7. Section 4.2, Children, should be amended to "Children: Rectogesic 0.4% Rectal Ointment should not be used in children as safety and effectiveness in children under 18 years have not been established".

8. In Section 4.8 the advice for headache should be amended: "and which responded to mild analgesics" should be deleted.

PIL Points
9. The PIL should delete the reference to fissure healing in Section 1.

10. Under section 3, please change: "When changing from a lying ..." to: "When getting up from a lying or sitting position, you should get up slowly, otherwise you might feel faint."

11. The PIL contraindicated medicine list should include "medicines for angina, or heart pain, such as glyceryl trinitrate, GTN, isosorhde dinitrate ...".

Delete: "Treatment should be continued every twelve hours until 2 weeks after the pain has gone away, healing occurs or for up to 8 weeks." and replace with "Treatment may be continued until the pain goes away, or up to a maximum of 8 weeks."

13. Under Section 3, if you use more than you should, please add: "...you should wipe away any extra ointment and then talk to your ....".

14. The PIL advice on the side effect of headache should be deleted and replaced by: "Headaches. These are common and may be severe. If you develop a headache as a side effect, wipe off any remaining ointment. If the headaches are unpleasant, you may need to stop taking the medicine."

Delete the sentence: "These are all mild side effects of RECTOGESIC™."

Label
15. A full size mock-up of the carton label should be submitted.
APPENDIX 5 – VARIATION ASSESSMENT REPORT (DATED 5 DECEMBER 2005)

Our Reference: PL 19075/0003 - 0011
Product: Rectogesic 0.4% Rectal Ointment
Active Ingredient(s): Glyceryl trinitrate 10% in propylene glycol

Type of Procedure: National
Submission Type: Variation
Submission Category: Type II
Submission Complexity: Standard

Reason:
To update Module 5 with the following:
a) results from a new controlled clinical trial Study R3;
b) retrospective reanalysis of two previously submitted studies Study R1 and Study R2;
c) combined analysis of the three studies Study R1, Study R2 and Study R3.

Sections 2.5 (Clinical Overview) and 2.7 (Clinical Summary) of Module 2 have been updated to reflect the proposed changes to Module 5.

There are no proposed changes to the Summary of Product Characteristics (‘SPC’) or Patient Information Leaflet (‘PIL’).

Supporting Evidence
The Applicant submits the following materials:
a) Module 2.5 (Clinical Overview);
b) Module 2.7 (Clinical Summary);
c) Module 5.3.5.1 (Study R3);
d) Module 5.3.5.3 (Reanalysis Report of Studies R1 and R2);
e) Module 5.3.5.3 (Combined Analysis Report of Studies R1, R2 and R3).

Executive Summary
The Applicant submits a national Type II medical variation to include in Module 5 results of a new controlled clinical trial of Rectogesic 0.4% ointment in the relief of pain from chronic anal fissure in adults over the age of 18 years (Study R3). In addition, the Applicant wishes to include:
• a retrospective reanalysis of two previously submitted studies (Studies R1 and R2);
• a combined analysis of the three studies R1, R2 and R3.

Study R3 was a prospective, randomised, double blind, placebo controlled trial of Rectogesic 0.4% in patients with chronic anal fissure. Pain intensity was assessed using a standard visual analogue scale, and the primary endpoint was rate of change of 24 hour average pain over the first 21 days of treatment. Notwithstanding some concerns regarding the analysis, this study demonstrated a statistically significant effect on rate of change of 24 hour average pain over the first 21 days, and for the 56 days duration of the study. However, the benefit observed was modest and the clinical significance is open to debate.
In 2004, following consideration by the Committee of Safety of Medicines, this product received an initial authorisation based on data from studies R1 and R2. Considering the revised data presented, it is concluded that the overall evidence on efficacy is not substantially different from the situation in 2004.

Study R3 does not raise any new safety issues, but confirms that this product is associated with a high incidence of headache. This is not unexpected, and is in line with other glyceryl trinitrate containing products.

In summary, the benefit/risk ratio for the symptomatic treatment of chronic anal fissure in adults is not significantly different from that in 2004 when the initial authorisation was granted. On this basis, the variation is approved.

Background
Introduction
Rectogesic is a topical formulation of glyceryl trinitrate (‘GTN’) approved for the relief of pain associated with chronic anal fissure in adults; this product is not approved for use in persons under the age of 18 years. GTN is a nitric oxide (‘NO’) donor, which in turn causes smooth muscle relaxation. Topical application of GTN is believed to relax the internal anal sphincter, reducing anal pressure and increasing anodermal blood flow.

Regulatory Background
An initial bibliographical application for a Marketing Authorisation (‘MA’) for this product was rejected by the Committee of Safety of Medicines (‘CSM’) on 28 March 2002 on grounds of insufficient efficacy data.

A second application for grant of a MA was subsequently made based on two Phase III studies R1 and R2. Initially the CSM felt unable to approve a MA but, following a Hearing, a UK national MA was granted on 25 March 2004.

This product is now the subject of an outgoing mutual recognition procedure (‘MRP’). However, in light of the proposed changes to Modules 2.5, 2.7 and 5 above, the MRP has been suspended pending the outcome of this national variation.

Studies R1 and R2 have already been assessed by the MHRA and considered by the CSM. By way of background information, a brief summary of each is set out below:

Study R1
This was a randomised, double-blind, placebo-controlled trial of Rectogesic in patients with chronic anal fissure. The study duration was 56 consecutive days or until the fissure had healed, whichever was the lesser time. The primary endpoint was fissure healing, as judged by an independent observer. Pain and safety were assessed as secondary endpoints, the pain parameters being the rate of change of the following over the 56 day study period:

a) 24 hour average pain;
b) worst pain;
c) defecation pain.

These pain scores were assessed using a simple visual analogue scale (‘VAS’).

Patients were randomised to receive either placebo or GTN ointment 0.1%, 0.2% or 0.4% either two or three times per day.
The primary endpoint was not achieved in that there was no significant effect on fissure healing. However, the study did report a significant reduction in pain in the patients taking Rectogesic 0.4%, although there was no significant difference between the twice or three times a day regimens.

**Assessor’s Comment:**
As pain relief was only a secondary endpoint, and the primary endpoint was not met, this study can only be considered supportive and not pivotal.

**Study R2**
This was also a randomised, double-blind, placebo-controlled trial of Rectogesic in patients with chronic anal fissure, with a study duration of 56 days. The primary endpoint was rate of change of 24 hour average pain over the 56 day study period assessed by VAS. The secondary endpoints were:
- rate of change of defecation pain over the 56 day study period;
- time to healing of fissure;
- safety;
- gastrointestinal quality of life.

There were 3 patient groups: placebo, GTN 0.2% and GTN 0.4% twice a day. The primary endpoint was achieved and the study report concluded that Rectogesic 0.4% twice daily significantly improved 24 hour average pain over the 56 day study period. As with study R1, there was no significant effect on fissure healing.

**Assessor’s Comment:**
Based on:
- a) Study R1
- b) Study R2
Rectogesic was granted a UK national MA for the symptomatic treatment of chronic anal fissure in adults over the age of 18 years.

Regarding safety, both studies showed a high incidence of headache in the GTN treated groups. This is reflected in section 4.8 of the current SPC, which states that dose-related headache occurred in 50% of clinical trial patients.

**Clinical Assessment**

**Study R3**

**Background**
The clinical study report states that this study was commissioned at the request of the US Food and Drug Administration (‘FDA’). The FDA considered Study R1 was only supportive as pain relief was not a primary endpoint. The study report continues ‘...The FDA also determined that Study R2 was supportive, but not sufficient, because the use of a quadratic term to transform the non-linear data into analyzable linear data, although appropriate, was not prespecified in detail in the protocol...’ The study protocol for Study R3 was agreed with the FDA by way of a Special Protocol Assessment.

**Study design**

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1 Study Report Section 1.2 Rationale for the Study, p 20.
This was a prospective, randomised, double blind, placebo controlled trial of Rectogesic 0.4% in patients with chronic anal fissure. Patients were randomised to receive either placebo or Rectogesic 0.4% twice daily for the total study duration of 56 days.

Assessor’s Comment:
The dose regimen for Rectogesic 0.4% follows the present approved SPC.

Study endpoints were as follows:

<table>
<thead>
<tr>
<th>ENDPOINT</th>
<th>PRIMARY</th>
<th>SECONDARY</th>
<th>TERTIARY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>Rate of change of 24 hour average pain intensity* over a 21 day treatment period.</td>
<td>Time to 50% improvement in the 3 day moving average of 24 hour average pain intensity.*</td>
<td>Rate of change of the 24 hour average pain intensity* over a 56 day treatment period.</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>Rate of change of the pain intensity* during the last bowel movement of the day (if any) over a 21 day treatment period.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Effect on complete healing of chronic anal fissures over a 56 day treatment period.**</td>
</tr>
</tbody>
</table>

*Assessed by VAS.
**As determined by an independent observer.

It should be noted that the primary endpoint for this study is the rate of change of 24 hour average pain intensity over a 21 day period, as opposed to the 56 day period used to define the primary endpoint in Study R2. The Applicant states that this was based on the results of the previous studies, where the observed rate of change of pain intensity was linear with time over the first 21 days, becoming non-linear over the 56 day study period (hence the need to introduce a quadratic expression into the analysis model).

Inclusion and exclusion criteria were:

| Inclusion criteria | 1. Had a single anal fissure. 2. Gave voluntary consent to participate in the study following a full explanation of the nature and purpose of the study, by signing the IRB/IEC-approved informed consent document before any screening evaluations. 3. Were male or female aged 18 to 75 years. 4. Had a history of anal pain, especially upon defecation, at least three days a week for at least 30 days before enrollment, with a |
sentinel pile confirmed by visual anal examination; pain (VAS for 24-hour average pain intensity = 35 mm) for each of the two days before beginning treatment; and a historical categorical pain score (mild, moderate or severe) on defecation of moderate or severe on at least one of the two days before treatment.
5. Were willing to forego the use of non-prescription/over-the-counter (OTC) or prescription medication for the treatment of anal fissures for the duration of the study.
6. Were willing to limit sitz baths, if necessary, to no more than one per day.
7. Were willing to provide urine for pregnancy test and practice an approved method of birth control for the duration of the study, if female and of childbearing potential.
8. Were willing to provide blood and urine samples for clinical laboratory tests before and after treatment.

<table>
<thead>
<tr>
<th>Exclusion criteria</th>
<th>1. Had more than one anal fissure.</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Had a fistula-in-ano.</td>
<td>3. Had fissures associated with anal surgery within 30 days of study enrollment.</td>
</tr>
<tr>
<td>4. Had participated in any experimental drug, biologic, or device study within the preceding 30 days.</td>
<td>5. Were unsuitable for participation in this study, in the opinion of the investigator, for any reason (e.g., recent, severe psychiatric illness).</td>
</tr>
<tr>
<td>6. Had a positive test result for an illicit drug, unless the drug was prescribed by his/her physician (e.g., benzodiazepines for anxiety, opiates for pain).</td>
<td>7. Were known to be allergic to NTG, lanolin, white petrolatum, paraffin wax, sorbitan sesquioleate, or propylene glycol.</td>
</tr>
<tr>
<td>8. Had hypotension or uncorrected hypovolemia; increased intracranial pressure (e.g., head trauma or cerebral hemorrhage) or inadequate cerebral circulation; aortic or mitral stenosis, hypertrophic obstructive cardiomyopathy, constrictive pericarditis, or pericardial tamponade; marked anemia; or closed-angle glaucoma.</td>
<td>9. Were receiving NTG or any other NO donors by any route of administration for any indication.</td>
</tr>
<tr>
<td>10. Were pregnant or nursing females.</td>
<td>11. Had an anal abscess.</td>
</tr>
<tr>
<td>12. Had inflammatory bowel disease.</td>
<td>13. Had or was receiving pelvic radiation.</td>
</tr>
<tr>
<td>14. Had fixed anal stenosis.</td>
<td>15. Were immunocompromised (e.g., receiving cancer chemotherapy or steroids).</td>
</tr>
</tbody>
</table>

Although the inclusion criteria specified that patients should not take any other non-prescription/OTC medication for anal fissure, the protocol did allow patients to take paracetamol as follows:
- for headache occurring within 30 minutes of applying the treatment;
- at a dose of 1,000 mg for European patients and 650 mg for US patients;
- limited to a maximum of 8 doses during the first 21 days of the study;
- no limit imposed after 21 days.
In addition, patients were asked to keep a specific record of start/stops times of headache, severity and number of doses of paracetamol taken.

Safety was assessed by recording adverse events (‘AE’), laboratory tests, physical examination (including vital signs) and electrocardiogram (‘ECG’).

In summary the study protocol was as follows:

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Screening</th>
<th>Treatment Day (±2 Days)</th>
<th>Follow-up</th>
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<td></td>
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<td>ECG</td>
<td>X</td>
<td></td>
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</tr>
<tr>
<td>Anal exam</td>
<td>X</td>
<td>X X X X X</td>
<td>X</td>
</tr>
<tr>
<td>Clinical laboratory</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine pregnancy test</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Randomization</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vital signs</td>
<td>X X X X X X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug Screening</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dispense/return study drug</td>
<td>X</td>
<td>X X X X X</td>
<td>X</td>
</tr>
<tr>
<td>Adverse events</td>
<td>X X X X X X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diary/VASg,h</td>
<td>X i X X X X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global assessment</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Telephone follow-upk</td>
<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a On Day 1, subjects initiated treatment at home but did not have a scheduled study-site visit.
b History of anal pain, especially upon defecation, at least 3 days a week for at least 30 days before enrolment; a single fissure, including a sentinel pile, was confirmed by visual anal examination.
c Healing was defined as complete re-epithelialization.
d Hematology, chemistry, and urine panels.
e Females of childbearing potential only; must be read and negative before subject was enrolled.
f Medication tube was weighed at each visit and usage since last visit calculated.
g Diary was to be completed every day at bedtime starting on Day 1 and returned on each subsequent visit. The following were to be recorded in the diary: VAS for 24-hour average pain and pain on defecation; times of study medication application; number of sitz baths; number of doses of fibre used; headache start time, stop time, and severity; time and number of acetaminophen or paracetamol tablets used; and concomitant medications.
h Subjects withdrawing from the study before the close-out visit on Day 56 were asked to continue to record the 24-hour average pain intensity and pain intensity during the last bowel movement of the day through Day 56.
i On Day 0, baseline VAS for 24-hour average pain intensity was recorded in the diary and was ≥ 35 mm on Screening Days −1 and −2; and historical categorical pain score on defecation was moderate or severe on Screening Days −1 and/or −2.
j Supplementary pain assessment was made at a few US and Russian study sites by a cohort of 20 subjects on the 2 consecutive days following the visit on Day 7.
k Subjects were to be contacted by telephone every 3 months for 12 months for information on any subsequent treatments received for anal fissure. The results of the follow-up phase of the study will be submitted in a separate report.

Patient disposition
The disposition of study patients is outlined below:
In the placebo arm 92 subjects completed the study to Day 56 (92.0%), and in the Rectogesic arm 78 completed to Day 56 (83.9%). Of the 8 patients who withdrew from the placebo arm, all did so after Day 21 and only 2 because of AEs. In the Rectogesic arm 9 patients withdrew before Day 21, of which 5 were due to AEs, and a further 6 patients withdrew between Day 21 and Day 56, of which 2 were because of AEs.

A higher number of patients withdrew from the Rectogesic arm compared to placebo at both the 21 day and 56 day endpoints:

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Placebo</th>
<th>Rectogesic 0.4% Ointment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 21</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>Day 56</td>
<td>8</td>
<td>15</td>
</tr>
</tbody>
</table>

**Assessor’s Comment:**
There was a marked imbalance between placebo and Rectogesic arms in respect of patient withdrawals. The issue of missing data is discussed in detail in the statistical assessment below.
The predominant reason for withdrawing from the Rectogesic arm was AE (total of 7 patients; 46.7%). Further, the most common AE causing patient withdrawal from the Rectogesic arm was headache, and this is discussed in detail below.

Concomitant medications
The study report lists the most commonly taken concomitant medications (defined as taken by ≥ 5% of subject in a treatment group):

<table>
<thead>
<tr>
<th>Medication</th>
<th>Placebo (N=98)</th>
<th>Rectogesic 0.4% Ointment (N=89)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetylsalicylic acid</td>
<td>9 (9.2)</td>
<td>6 (6.7)</td>
</tr>
<tr>
<td>Diazepam</td>
<td>6 (6.1)</td>
<td>6 (6.7)</td>
</tr>
<tr>
<td>Paracetamol</td>
<td>26 (26.5)</td>
<td>36 (40.4)</td>
</tr>
</tbody>
</table>

The study protocol allowed patients to take a limited number of doses of paracetamol for headache occurring within 30 minutes of applying study medication. In this respect, paracetamol was taken by 24 patients in the placebo arm and 34 patients in the Rectogesic arm.

Assessor’s Comment:
A majority of patients took paracetamol for headache. However, compared to the placebo arm, there were a higher number of patients taking paracetamol in the Rectogesic arm (40.4% versus 26.5%). This was almost certainly due to the higher incidence of headache in the Rectogesic arm, but it should be noted that the Rectogesic patients overall were more likely to have taken paracetamol than those on placebo.

This study also recorded the number of Sitz baths taken:

<table>
<thead>
<tr>
<th>Time Perioda</th>
<th>Statistics</th>
<th>Placebo (N=98)</th>
<th>Rectogesic 0.4% Ointment (N=89)</th>
<th>P-valueb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days 1 through 21</td>
<td>N</td>
<td>98</td>
<td>89</td>
<td>0.2031</td>
</tr>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>5.2 (7.74)</td>
<td>4.4 (7.37)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>0.5</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Min – Max</td>
<td>0 – 21</td>
<td>0 – 26</td>
<td></td>
</tr>
<tr>
<td>Days 1 through 56</td>
<td>N</td>
<td>98</td>
<td>89</td>
<td>0.4986</td>
</tr>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>12.0 (19.77)</td>
<td>10.3 (17.83)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>1.0</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Min – Max</td>
<td>0 – 56</td>
<td>0 – 64</td>
<td></td>
</tr>
</tbody>
</table>

a Summary statistics were calculated by using the total number of sitz baths recorded for each subject during the indicated time period.
b P-values were calculated by using a Wilcoxon rank-sum test.

The study report concludes ‘...Although the difference was not statistically significant, Cellegesic-treated [Rectogesic-treated] subjects took fewer sitz baths than controls, a further indication of better pain relief...’

Assessor’s Comment:
On the basis that:

2 An established symptomatic treatment for anal fissure.
3 Study Report Section 3.4 Concomitant Treatments, p 46.
Patient demographics
The demographic data are summarised in Annex I. The study report states:

‘...Both treatment groups had more females than males (62.2% in placebo, 66.3% in Cellegesic), and most subjects were Caucasian (95.9% in placebo, 94.4% in Cellegesic). Demographic characteristics were generally similar between the treatment groups, although the placebo group had more subjects in the middle age range (46-64 years) than the Cellegesic group (58.2% versus 42.7%). The placebo group also had a slightly larger proportion of current alcohol and tobacco users (25.5% versus 18.0% for both substances)…’

Assessor’s Comment:
These differences are unlikely to be of major clinical significance.

Efficacy
The results of the change in pain intensity, as assessed by VAS, are as follows (expressed in mm):

<table>
<thead>
<tr>
<th>Time Period</th>
<th>Statistics</th>
<th>Placebo (N=98)</th>
<th>Rectogesic 0.4% Ointment (N=89)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>N</td>
<td>98</td>
<td>89</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>54.1 (14.52)</td>
<td>55.0 (15.32)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>49.0</td>
<td>50.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Min – Max</td>
<td>35 – 98</td>
<td>36 – 100</td>
<td></td>
</tr>
<tr>
<td>Days 1 – 21</td>
<td>N</td>
<td>98</td>
<td>89</td>
<td>&lt;0.0309</td>
</tr>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>-24.9 (18.58)</td>
<td>-28.1 (18.46)</td>
<td>&lt;0.0498</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>-25.6</td>
<td>-31.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Min – Max</td>
<td>-77 – 19</td>
<td>-77 – 14</td>
<td></td>
</tr>
<tr>
<td>Days 1 – 56</td>
<td>N</td>
<td>98</td>
<td>89</td>
<td>&lt;0.0447</td>
</tr>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>-33.8 (18.03)</td>
<td>-35.2 (18.92)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>-34.4</td>
<td>-37.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Min – Max</td>
<td>-88 – 13</td>
<td>-73 – 20</td>
<td></td>
</tr>
<tr>
<td>Day 7</td>
<td>N</td>
<td>93</td>
<td>85</td>
<td>&lt;0.3144</td>
</tr>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>-25.3 (19.58)</td>
<td>-28.0 (18.97)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>-23.0</td>
<td>-30.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Min – Max</td>
<td>-74 – 23</td>
<td>-78 – 23</td>
<td></td>
</tr>
<tr>
<td>Day 8</td>
<td>N</td>
<td>96</td>
<td>84</td>
<td>&lt;0.0379</td>
</tr>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>-23.5 (21.40)</td>
<td>-29.5 (19.19)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>-25.8</td>
<td>-30.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Min – Max</td>
<td>-73 – 35</td>
<td>-80 – 7</td>
<td></td>
</tr>
<tr>
<td>Day 9</td>
<td>N</td>
<td>98</td>
<td>84</td>
<td>&lt;0.1242</td>
</tr>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>-26.1 (21.94)</td>
<td>-30.7 (21.62)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>-30.3</td>
<td>-32.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Min – Max</td>
<td>-85 – 34</td>
<td>-89 – 20</td>
<td></td>
</tr>
<tr>
<td>Day 10</td>
<td>N</td>
<td>98</td>
<td>84</td>
<td>&lt;0.1862</td>
</tr>
<tr>
<td>Day</td>
<td>N</td>
<td>Mean (SD)</td>
<td>Median</td>
<td>Min – Max</td>
</tr>
<tr>
<td>------</td>
<td>-----</td>
<td>------------</td>
<td>--------</td>
<td>-----------</td>
</tr>
<tr>
<td>11</td>
<td>98</td>
<td>-27.0 (21.78)</td>
<td>-29.8</td>
<td>-81 – 35</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-30.7 (20.03)</td>
<td>-29.5</td>
<td>-89 – 4</td>
</tr>
<tr>
<td>12</td>
<td>98</td>
<td>-27.5 (22.64)</td>
<td>-31.0</td>
<td>-89 – 43</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-32.4 (20.77)</td>
<td>-31.8</td>
<td>-89 – 10</td>
</tr>
<tr>
<td>13</td>
<td>98</td>
<td>-28.9 (21.62)</td>
<td>-32.0</td>
<td>-91 – 25</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-33.2 (21.09)</td>
<td>-34.0</td>
<td>-89 – 18</td>
</tr>
<tr>
<td>14</td>
<td>98</td>
<td>-27.7 (22.54)</td>
<td>-30.8</td>
<td>-85 – 34</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-34.7 (20.55)</td>
<td>-35.8</td>
<td>-78 – 19</td>
</tr>
<tr>
<td>15</td>
<td>98</td>
<td>-27.0 (23.67)</td>
<td>-29.0</td>
<td>-93 – 43</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-34.8 (20.51)</td>
<td>-36.5</td>
<td>-77 – 27</td>
</tr>
<tr>
<td>16</td>
<td>98</td>
<td>-28.5 (23.01)</td>
<td>-29.0</td>
<td>-91 – 35</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-33.6 (21.32)</td>
<td>-36.5</td>
<td>-76 – 18</td>
</tr>
<tr>
<td>17</td>
<td>98</td>
<td>-28.9 (22.23)</td>
<td>-31.0</td>
<td>-94 – 29</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-36.3 (20.93)</td>
<td>-37.5</td>
<td>-82 – 24</td>
</tr>
<tr>
<td>18</td>
<td>98</td>
<td>-30.1 (22.90)</td>
<td>-32.0</td>
<td>-95 – 26</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-36.1 (21.41)</td>
<td>-39.3</td>
<td>-89 – 20</td>
</tr>
<tr>
<td>19</td>
<td>98</td>
<td>-29.6 (22.48)</td>
<td>-33.0</td>
<td>-93 – 25</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-35.0 (22.56)</td>
<td>-36.3</td>
<td>-83 – 51</td>
</tr>
<tr>
<td>20</td>
<td>98</td>
<td>-31.2 (22.20)</td>
<td>-33.3</td>
<td>-93 – 35</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-36.2 (25.43)</td>
<td>-39.5</td>
<td>-89 – 60</td>
</tr>
<tr>
<td>21</td>
<td>94</td>
<td>-31.2 (21.84)</td>
<td>-34.0</td>
<td>-93 – 25</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-35.3 (22.44)</td>
<td>-36.5</td>
<td>-81 – 29</td>
</tr>
</tbody>
</table>

* P-values were determined by using a mixed-effects regression model.
* NA = Not applicable.
* Analysis using all available data from each subject up until the time of the exit visit or early withdrawal.
* Analysis using LOCF for subjects clinically identified as withdrawing due to NTG-related headache.

The mean baseline pain intensity scores were comparable between placebo and Rectogesic arms (54.1 mm versus 55.0 mm).

Over the first 21 days of the study mean change in pain intensity compared to baseline decreased by 24.9 mm in the placebo arm and 28.1 mm in the Rectogesic arm, a difference between treatment groups of 3.2 mm that was statistically significant.
After 56 days, there was a reduction of 33.8 mm in the placebo arm and 35.2 mm for patients receiving Rectogesic, a difference of only 1.4 mm that was statistically significant.

The 24 hour average VAS pain intensity data are also presented as percent improvement:

<table>
<thead>
<tr>
<th>Time Period</th>
<th>Statistics</th>
<th>Placebo (N=98)</th>
<th>Rectogesic 0.4% Ointment (N=89)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days 1 – 21</td>
<td>Mean (SD)</td>
<td>50.2 (29.31)</td>
<td>53.5 (28.59)</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>53.8</td>
<td>52.4</td>
</tr>
<tr>
<td></td>
<td>Min – Max</td>
<td>0 – 99</td>
<td>0 – 100</td>
</tr>
<tr>
<td>Days 1 – 56</td>
<td>Mean (SD)</td>
<td>65.2 (26.89)</td>
<td>66.2 (27.72)</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>75.9</td>
<td>72.4</td>
</tr>
<tr>
<td></td>
<td>Min – Max</td>
<td>2 – 100</td>
<td>0 – 100</td>
</tr>
</tbody>
</table>

The study report states ‘...Both treatment groups improved in 24-hour average pain score during the study, but the Cellegesic [Rectogesic] treatment group had a numerically greater percent improvement than the placebo group over all time intervals beginning with the period Days 7 to 9...’

Assessor’s Comment:
These results demonstrate that placebo exerts a significance effect on pain intensity of chronic anal fissure in adults, and highlights the importance of properly controlled trials in this field.

The primary endpoint namely effect of Rectogesic on rate of change of 24 hour average pain intensity over the first 21 days of treatment, based on change of VAS score in millimetres, reached statistical significance. This is supported by a smaller, but still statistically significant effect of Rectogesic on pain intensity over the entire 56 days of the study (a tertiary endpoint). However, although the changes are statistically significant, it is somewhat debatable whether a mean change in VAS of -24.9 mm for placebo compared to -28.1 mm for Rectogesic (after 21 days treatment), i.e. a difference of only 3.2 mm, is clinically significant. The VAS results at 56 days were also statistically significant, but the difference between mean scores of only 1.4 mm is again of questionable clinical significance.

Where the change in pain intensity is presented as a percentage improvement, the results are not statistically significant.

The secondary endpoint was time to 50% improvement in average 24 hour average pain intensity (as assessed by VAS). This data were presented as follows:
In respect of the secondary endpoint the study report states ‘...The secondary endpoint, time to 50% reduction in pain did not differ significantly in this study, but the effect was in the hypothesized direction, and as much as a 7-day difference in time to 50% improvement was noted during the first 21 days…’

**Assessor’s Comment:**
It must be noted that, despite the study report commentary, the secondary endpoint of CP125 03-02-01 did not achieve statistical significance.

**Safety**
A total of 79 patients in the placebo arm reported at least one AE (80.6%), and 81 in the Rectogesic arm (90.0%). Regardless of relationship to study drug, the adverse events reported were (expressed as number (%)):

<table>
<thead>
<tr>
<th>Body System</th>
<th>Placebo (N=98)</th>
<th>Rectogesic Ointment 0.4% (N=90)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Adverse Event(s)</td>
<td>79 (80.6)</td>
<td>81 (90.0)</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>1 (1.0)</td>
<td>5 (5.6)</td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td>3 (3.1)</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>1 (1.0)</td>
<td>2 (2.2)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>11 (11.2)</td>
<td>16 (17.8)</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>5 (5.1)</td>
<td>5 (5.6)</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>12 (12.2)</td>
<td>6 (6.7)</td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td>1 (1.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Investigations</td>
<td>3 (3.1)</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>1 (1.0)</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>4 (4.1)</td>
<td>6 (6.7)</td>
</tr>
<tr>
<td>Nervous system disorders (including headache)</td>
<td>67 (68.4)</td>
<td>78 (86.7)</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>0 (0.0)</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>0 (0.0)</td>
<td>2 (2.2)</td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td>2 (2.0)</td>
<td>1 (1.1)</td>
</tr>
</tbody>
</table>
No deaths were reported during the study period.

Three subjects reported serious adverse events, but none of these were thought to be causally related to Rectogesic.

A total of 9 patients discontinued the study because of one or more AEs. These are summarised below in tabular form:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Age (yrs)</th>
<th>Sex</th>
<th>Adverse Event Resulting in Discontinuation (Primary Term)</th>
<th>Onset (Study Day)</th>
<th>Severity</th>
<th>Relationship to Study Drug</th>
<th>Duration (Days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>54</td>
<td>F</td>
<td>Vertigo Proctalgia</td>
<td>36 42</td>
<td>Mild</td>
<td>Probably related</td>
<td>10</td>
</tr>
<tr>
<td>Placebo</td>
<td>50</td>
<td>F</td>
<td>Pruritus NOS, Burning sensation NOS</td>
<td>7 7</td>
<td>Moderate</td>
<td>Probably related</td>
<td>Ongoing</td>
</tr>
<tr>
<td>Rectogesic</td>
<td>42</td>
<td>M</td>
<td>Headache</td>
<td>1</td>
<td>Severe</td>
<td>Not NTG related</td>
<td>1</td>
</tr>
<tr>
<td>Rectogesic</td>
<td>54</td>
<td>F</td>
<td>Headache, Dizziness, Bradycardia NOS, Extrasystoles NOS</td>
<td>1 1 8</td>
<td>Severe</td>
<td>NTG related</td>
<td>9 8</td>
</tr>
<tr>
<td>Rectogesic</td>
<td>52</td>
<td>F</td>
<td>Headache</td>
<td>1</td>
<td>Severe</td>
<td>NTG related</td>
<td>7</td>
</tr>
<tr>
<td>Rectogesic</td>
<td>34</td>
<td>F</td>
<td>Pruritus NOS, Burning sensation NOS</td>
<td>31 31</td>
<td>Moderate</td>
<td>Probably related</td>
<td>Ongoing</td>
</tr>
<tr>
<td>Rectogesic</td>
<td>52</td>
<td>F</td>
<td>Headache, Tachycardia NOS</td>
<td>1</td>
<td>Severe</td>
<td>NTG related</td>
<td>7</td>
</tr>
</tbody>
</table>

*Only a headache that occurred within ≤ 30 minutes of Cellegesic NTG ointment 0.4% administration was to be considered an GTN-related AE. Headache was either GTN related or Not GTN related. Relationship of other AEs was either Related, Probably related, Possibly related, or Not related.

b NOS = Not otherwise specified.

c Based upon clinical review of the data for Subject 037-358, this subject was classified as not having discontinued due to GTN-related headache for the purpose of LOCF in the primary efficacy analysis

Assessor’s Comment:
It should be noted that:

a) seven patients on Rectogesic discontinued because of AEs compared to two on placebo;
b) of these seven, five experienced severe headache;
c) in three patients on Rectogesic severe headache was the sole AE leading to discontinuation.
Headaches are a recognised adverse effect of GTN, and this is reflected in the present SPC for this product. As a consequence, the study report provides a specific analysis of the incidence of headache. The overall incidence of headache reported in the safety population is listed below:

<table>
<thead>
<tr>
<th>Category</th>
<th>Statistics</th>
<th>Placebo (N=98)</th>
<th>Rectogesic Ointment 0.4% (N=90)</th>
<th>P-value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects Reporting Headache&lt;sup&gt;b&lt;/sup&gt;</td>
<td>n (%)</td>
<td>66 (67.3)</td>
<td>77 (85.6)</td>
<td>0.0035</td>
</tr>
<tr>
<td>Subjects Reporting Headache with Maximum Severity&lt;sup&gt;c,d&lt;/sup&gt;</td>
<td>Mild n (%)</td>
<td>17 (25.8)</td>
<td>12 (15.6)</td>
<td>0.1315</td>
</tr>
<tr>
<td></td>
<td>Moderate n (%)</td>
<td>37 (56.1)</td>
<td>36 (46.8)</td>
<td>0.2670</td>
</tr>
<tr>
<td></td>
<td>Severe n (%)</td>
<td>11 (16.7)</td>
<td>29 (37.7)</td>
<td>0.0053</td>
</tr>
<tr>
<td>Subjects Treated with Concomitant Medication for Headache&lt;sup&gt;c&lt;/sup&gt;</td>
<td>n (%)</td>
<td>32 (48.5)</td>
<td>39 (50.6)</td>
<td>0.7963</td>
</tr>
<tr>
<td>Average Duration of Headache (hours)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>N</td>
<td>65</td>
<td>77</td>
<td>0.1034</td>
</tr>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>19.5 (55.54)</td>
<td>9.0 (8.98)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>7.0</td>
<td>5.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Min – Max</td>
<td>0 – 372</td>
<td>0 – 48</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> P-value for average duration of headache was computed by using a t-test; all other p-values were computed by using a Chi-square test.

<sup>b</sup> Percents are based on the number of subjects in the safety population.

<sup>c</sup> Percents are based on the number of subjects reporting headaches.

<sup>d</sup> One placebo subject had missing severity data.

<sup>e</sup> For each subject, the longest duration of any headache was used.

However, the study design defined GTN-related headache as that occurring within 30 minutes of applying study medication. Based on this definition, the incidence of GTN-related headache was as follows:

<table>
<thead>
<tr>
<th>Category</th>
<th>Statistics</th>
<th>Placebo (N=98)</th>
<th>Rectogesic Ointment 0.4% (N=90)</th>
<th>P-value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects Reporting GTN-Related Headache</td>
<td>n (%)</td>
<td>29 (29.6)</td>
<td>64 (71.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Subjects Reporting GTN-Related Headache with Maximum Severity&lt;sup:b&lt;/sup&gt;</td>
<td>Mild n (%)</td>
<td>8 (27.6)</td>
<td>10 (15.6)</td>
<td>0.1762</td>
</tr>
<tr>
<td></td>
<td>Moderate n (%)</td>
<td>17 (58.6)</td>
<td>31 (48.4)</td>
<td>0.3627</td>
</tr>
<tr>
<td></td>
<td>Severe n (%)</td>
<td>1 (3.4)</td>
<td>22 (34.4)</td>
<td>0.0014</td>
</tr>
<tr>
<td></td>
<td>Missing n (%)</td>
<td>3 (10.3)</td>
<td>1 (1.6)</td>
<td>0.0531</td>
</tr>
<tr>
<td>Subjects Treated with Concomitant Medication for GTN-Related Headache</td>
<td>n (%)</td>
<td>11 (37.9)</td>
<td>31 (48.4)</td>
<td>0.3456</td>
</tr>
<tr>
<td>Average Duration of GTN-Related Headache (hours)</td>
<td>N</td>
<td>25</td>
<td>63</td>
<td>0.0501</td>
</tr>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>4.3 (4.77)</td>
<td>8.0 (8.86)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>2.0</td>
<td>5.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Min – Max</td>
<td>0 – 15</td>
<td>0 – 48</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> P-value for average duration of headache was computed by using a t-test; all other p-values were computed by using a Chi-square test.

<sup>b</sup> A subject with multiple headaches was counted under the severity category of the most severe headache.

**Assessor’s Comment:**

<sup>d</sup> Study Report Section 3.6.3 Headaches, p 68.
A feature of GTN-induced headache is rapid onset following administration and, in the case of sublingual GTN used to treat angina, can be used as an indicator that the patient is taking their medication correctly. It is therefore reasonable to define GTN-related headache as that occurring within 30 minutes of applying study medication.

Overall, patients in the Rectogesic arm reported a higher incidence of headache within 30 minutes of applying study medication, particularly in those reporting severe headache (3.4% on placebo versus 34.4% on Rectogesic).

A range of laboratories parameters were measured, including haematological indices, renal and liver function, and blood glucose. During the study there were no significant abnormalities associated with Rectogesic.

Assessor’s Comment:
Nitrates have the potential to cause methaemoglobinemia, a parameter that was not measured in this study. However, this is a comparatively rare adverse drug reaction that is more likely to occur in individuals with methaemoglobin reductase deficiency. Further, section 4.8 of the approved SPC for Rectogesic does include methaemoglobinemia as a potential adverse drug reaction.

The change in vital signs (from Day 0) on Days 21 and 56 were as follows:

<table>
<thead>
<tr>
<th>Time Point</th>
<th>Vital Sign (unit)</th>
<th>Statistics</th>
<th>Placebo (N=98)</th>
<th>Rectogesic 0.4% Ointment (N=90)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 21</td>
<td>Systolic BP (mmHg)</td>
<td>N</td>
<td>95</td>
<td>82</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean (SD)</td>
<td>-1.8 (10.55)</td>
<td>-1.4 (11.15)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Min – Max</td>
<td>-60 – 20</td>
<td>-38 – 20</td>
</tr>
<tr>
<td></td>
<td>Diastolic BP (mmHg)</td>
<td>N</td>
<td>95</td>
<td>82</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean (SD)</td>
<td>-0.5 (8.18)</td>
<td>-0.4 (8.62)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Min – Max</td>
<td>-23 – 20</td>
<td>-30 – 20</td>
</tr>
<tr>
<td></td>
<td>Pulse (beats per min)</td>
<td>N</td>
<td>95</td>
<td>82</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean (SD)</td>
<td>-1.0 (6.50)</td>
<td>-0.5 (6.73)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Min – Max</td>
<td>-24 – 25</td>
<td>-19 – 20</td>
</tr>
<tr>
<td></td>
<td>Temperature (°C)</td>
<td>N</td>
<td>95</td>
<td>82</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean (SD)</td>
<td>0.01 (0.290)</td>
<td>0.03 (0.322)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Min – Max</td>
<td>-1.1 – 0.7</td>
<td>-0.8 – 0.8</td>
</tr>
<tr>
<td>Day 56</td>
<td>Systolic BP (mmHg)</td>
<td>N</td>
<td>97</td>
<td>88</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean (SD)</td>
<td>1.0 (10.56)</td>
<td>-2.2 (13.99)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Min – Max</td>
<td>-35 – 25</td>
<td>-58 – 50</td>
</tr>
<tr>
<td></td>
<td>Diastolic BP (mmHg)</td>
<td>N</td>
<td>97</td>
<td>88</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean (SD)</td>
<td>1.8 (8.32)</td>
<td>0.0 (8.85)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Min – Max</td>
<td>-33 – 20</td>
<td>-20 – 30</td>
</tr>
<tr>
<td></td>
<td>Pulse (beats per min)</td>
<td>N</td>
<td>97</td>
<td>88</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean (SD)</td>
<td>0.0 (7.85)</td>
<td>-1.4 (9.00)</td>
</tr>
<tr>
<td></td>
<td>Temperature (°C)</td>
<td>N</td>
<td>97</td>
<td>88</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean (SD)</td>
<td>-0.02 (0.301)</td>
<td>-0.01 (0.308)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Min – Max</td>
<td>-1.3 – 0.9</td>
<td>-0.9 – 1.1</td>
</tr>
</tbody>
</table>

Assessor’s Comment:
GTN is a potent vasodilator and may therefore cause hypotension leading to dizziness, syncope and rebound hypertension. Although the data on vital signs shows no significant changes during the course of the study, it is somewhat limited. In particular, it is not stated when, in respect of time of application of study medication, the vital signs were measured. It
is likely they were recorded some time after the last application, and would not therefore reflect the acute onset of GTN induced hypotension.

A more insightful indicator of significant hypotension might be symptoms of dizziness, faintness or syncope. One patient on Rectogesic who discontinued the study did report dizziness, and another in this category reported mild vertigo (see table above). Otherwise, the detailed listings of AEs in the study report\(^5\) do not record any symptoms of significant hypotension.

Finally, one patient on Rectogesic, who discontinued the study, developed significant ECG changes of bradycardia and extrasystoles; this was the same patient who reported dizziness. The study report states that the screening ECG was normal, and that the ECG abnormalities that developed during the study were ‘possibly related’ to Rectogesic.

**Assessor’s Comment:**
It is possible that this subject had underlying ischaemic heart disease, and that GTN-induced hypotension unmasked this condition. This is a recognised problem with GTN and is adequately reflected in section 4.4 of the current approved SPC for Rectogesic, which states:

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

Regarding safety, the study report concludes:

‘...Cellegesic* NTG** ointment 0.4% was safe and well tolerated in these subjects. Significantly more subjects receiving Cellegesic NTG ointment 0.4% reported any headaches than subjects receiving placebo, and significantly more Cellegesic subjects reported severe headaches. Significantly more Cellegesic subjects used concomitant medication to treat their NTG-related headaches. Although the average duration of headaches was shorter in the Cellegesic NTG ointment 0.4% group, this difference was not statistically significant. Four subjects receiving Cellegesic NTG ointment 0.4% discontinued due to NTG-related headaches, and one subject receiving Cellegesic NTG ointment 0.4% discontinued due to non NTG-related headache. However, the majority of subjects who experienced NTG-related headaches were able to complete the study. No other safety concerns were identified...’

* Cellegesic is the product name for Rectogesic in the US.
** NTG is nitroglycerin, an alternative name for GTN.

**Conclusion on Study R3**
Regarding efficacy, this study just met its primary endpoint by demonstrating a significantly higher reduction in rate of change of 24 hour average pain intensity for Rectogesic treated patients compared to controls over the first 21 days, albeit based on change in VAS expressed in millimetres. However, the difference in mean change in VAS between Rectogesic and control patients was only 3.2 mm at 21 days and 1.4 mm at 56 days, the clinical significance of which is open to debate.

Where the pain scores were expressed as percentage improvement, the difference between placebo and Rectogesic arms was not statistically significant at either 21 or 56 days. Further, the secondary endpoint of time to 50% improvement was not significantly different between placebo and Rectogesic.

Considering:

a) although the primary endpoint was statistically significant, there are concerns regarding the analysis, in particular the issue of missing data;
b) the benefit observed does not necessarily translate into a clinically significant effect;
c) there were no statistically significant benefits in terms of percentage improvement of pain intensity or time to 50% improvement;
d) Rectogesic had no effect on anal fissure healing;

it is concluded that Study R3 considered alone does not represent persuasive evidence of clinical efficacy of Rectogesic 0.4% ointment in the relief of pain associated with chronic anal fissure.

This study does not raise any new or unforeseen safety issues. The most prevalent adverse drug reaction remains headache, which was often reported as severe, and caused or contributed to withdrawal from the study in 5 patients randomised to the Rectogesic arm (5.1%). Headache is a widely recognised adverse event associated with nitrates including GTN, and arises from its inherent action as a NO donor and vasodilator. However, experience with the long-term use of nitrates to treat angina suggests that a degree of tolerance to headache develops with time. Unfortunately, this study does not provide any data of whether tolerance to headache does occur with this product.

Reanalysis Report of Studies R1 and R2

**Introduction**

Studies R1 and R2 assessed pain intensity over a 56 day period, although in the case of R1 this was not a primary endpoint. The objectives of this reanalysis were as follows:

<table>
<thead>
<tr>
<th>Primary objective</th>
<th>To determine the effect of Rectogesic ointment versus placebo on the rate of change of 24 hour average pain over the first 21 days of treatment, i.e. the primary endpoint used in Study R3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary objective</td>
<td>To determine the effect of Rectogesic ointment versus placebo on time to 50% improvement in the 3 day moving average of 24 hour average pain intensity.</td>
</tr>
</tbody>
</table>
| Tertiary objectives | To determine the effect of Rectogesic ointment versus placebo on:
  a) the rate of change of 24 hour average pain over the whole 56 day study period;
  b) the rate of change of pain intensity during the last bowel movement of the day (if any) over the first 21 days;
  c) the rate of change of pain intensity during the last bowel movement of the day (if any) over the 56 day study period;
  d) complete healing of fissure over 56 days; |
Assessor’s Comment:
The primary objective mirrors the primary endpoint of Study R3. However, it is important to note that the secondary objective of this reanalysis, to determine time to 50% improvement, was based on a 3 day moving average of 24 hour pain intensity as opposed to single 24 hour average scores in Study R3. The Applicant’s expert states this was in order to ‘...produce a more stable estimate of 50% improvement...’

Results
There was a marked difference in mean baseline pain scores between the placebo and Rectogesic arms (25.7 mm for placebo versus 39.2 mm for Rectogesic) of Study R1. For Study R2 the mean baseline pain scores were comparable (34.0 mm versus 33.4 mm).

Assessor’s Comment:
The consequences of this imbalance in Study R1 are discussed in the statistical report below.

The Applicant reports that at 21 days there were statistically significant differences in 24 hour average pain scores between placebo and Rectogesic 0.4% arms for both Study R1 and Study R2. The differences in 24 hour average pain scores were also statistically significant at the end of the study (Day 56).

Conclusion
The reanalysis shows a statistically significant effect on pain intensity at the retrospectively defined 21 day endpoint, as well as the established 56 day endpoint.

There was no significant effect on anal fissure healing.

Combined Analysis Report of Studies R1, R2 and R3
Introduction
This analysis was performed with the following objectives:

<table>
<thead>
<tr>
<th>Primary objective</th>
<th>To determine the effect of Rectogesic ointment versus placebo on the rate of change of 24 hour average pain over the first 21 days of treatment.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary objective</td>
<td>To determine the effect of Rectogesic ointment versus placebo on time to 50% improvement in the 3 day moving average of 24 hour average pain intensity.</td>
</tr>
</tbody>
</table>

Assessor’s Comment:
As with the reanalysis of Studies R1 and R2, the secondary objective of this combined analysis was based on a 3 day moving average for 24 hour pain intensity as opposed to single 24 hour average scores.

Results
The Applicant again reports statistically significant differences in average 24 hour pain scores between placebo and Rectogesic 0.4% arms at both 21 and 56 days. The combined results, given as percent improvement in average pain intensity, are as follows:

<table>
<thead>
<tr>
<th>Time point</th>
<th>Placebo</th>
<th>Rectogesic 0.4% ointment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 21</td>
<td>-15.4</td>
<td>-19.3</td>
</tr>
<tr>
<td>Day 56</td>
<td>-22.4</td>
<td>-25.8</td>
</tr>
</tbody>
</table>

Assessor’s Comment:
This shows a mean difference between placebo and Rectogesic of 3.9 mm at 21 days, and 3.4 mm at 56 days.

The reanalysis also presents percent improvement in average pain score for patients with a sentinel pile, using data from studies R2 and R3.

Assessor’s Comment:
This subgroup analysis of patients with a sentinel pile is of little weight as it was not a predefined objective of the reanalysis.

Conclusion
Overall, the combined analysis shows statistically significant differences between placebo and Rectogesic in 24 hour average pain scores after 21 and 56 days treatment. The mean pain
scores are broadly comparable with the reanalysis of Study R2, which represented the pivotal
study in respect of the initial grant of a MA in 2004.

**Statistical Assessment**

**Statistical Assessment of Efficacy**

Rectogesic 0.4% Rectal Ointment is currently indicated in the UK for the relief of intense
pain associated with a chronic anal fissure. Rectogesic was approved on the basis of two
phase 3 pivotal studies (studies R1 and R2).

The main statistical concerns with the original application were over the increased number of
withdrawals on active treatment compared to placebo and the method used for handling
missing data. In response to these points, appropriate sensitivity analyses were presented by
the MAH and the points considered resolved. For the approved posology, some benefit using
secondary endpoints assessing pain was suggested in Study R1. In Study R2 one of the three
measures of pain used as primary endpoints, showed a statistically significant difference
between Rectogesic 0.4% and placebo, the other measures showed a similar trend.

This is a variation to assess the results from a third pivotal study (Study R3), a re-analysis of
the previously submitted studies and two combined analyses of all three pivotal studies.

**Study R3**

**Design, analysis and objectives of the study**

As with studies R1 and R2, study R3 was a randomised, double-blinded, placebo controlled
study. Patients were randomised to be treated with either Rectogesic 0.4% or a matching
placebo for the treatment of chronic anal fissure. The primary endpoint was the rate of
change in the 24-hour average pain intensity over the first 21-day treatment period. This
endpoint over the first 56 days of treatment was assessed as a tertiary objective. Subjects
were required to stay in the study for 56 days, even if the anal fissure had previously healed
or the pain gone.

The primary endpoint was analysed using a generalized mixed-effects regression model using
the ITT population. Comparisons of rate of change in pain between Rectogesic and placebo
treatment groups were analysed using the linear component of the treatment-by-week
interaction. The MAH states that in previous studies, the rate of pain decrease was linear over
the first 21 days but not linear over the first 56 days. Therefore for those analyses carried out
up to day 56, a quadratic term was added to the model. Centre was included in the model and
those with fewer than 6 subjects were combined randomly with another centre.

For the primary analysis, all available data from subjects who dropped out for any reason
other than headache were used and no imputation carried out for their missing data. The last
observation was carried forward (LOCF) for all patients who discontinued due to headache.

<table>
<thead>
<tr>
<th>Statistical assessors comment: There are some methodological concerns with the analysis used by the MAH.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not imputing data for those patients who dropout of the study for reasons other than headache makes the assumption that their missing data is ignorable (i.e. those patients who discontinue from the study prematurely have similar properties to those who continue in the study). This does not seem appropriate as it is often reasonable to suspect that patients who withdraw from a study systematically differ from those who continue, whether they have dropped out for a headache or for many other reasons. Therefore ideally the MAH should</td>
</tr>
</tbody>
</table>
have also analysed the primary endpoint and the corresponding day 1-56 endpoint, using an alternative approach assuming all missing data were non-ignorable.

From the results of this study, the primary endpoint seems to have a non-linear relationship over time, whether the first 21 or 56 days of treatment are considered. Diagnostic checks of the model assumptions should have been included in the submission for the primary analysis.

Combining centres consisting of less than 6 subjects randomly with other centres is questionable. Differing effects of treatment can be seen across geographical regions. Therefore, if different effects were seen across centres these effects could be diluted by randomly pooling centres. Information on how many centres were pooled, and its effect on the final analyses should have been discussed by the MAH. The MAH should have analysed the data using an appropriate pooling of centres, for example by region.

Disposition and results
A total of 193 patients were randomised into this trial, 100 placebo treated patients and 93 Rectogesic 0.4% treated patients. Of these, all placebo and 84 Rectogesic treated patients (5 patients withdrew due to adverse events) were still in the study on day 21; of those 92 placebo and 78 Rectogesic treated patients completed the study until day 56 (2 patients withdrew due to adverse events in each treatment group).

Of the 100 subjects randomised to the placebo group, 2 were lacking drug exposure information and had no efficacy assessments. Of the 93 subjects randomised to the Rectogesic group, 3 were lacking drug exposure information, and 4 had no efficacy assessments. Therefore 98 placebo treated patients and 89 Rectogesic treated patients were included in the ITT population. A figure of the patient’s disposition is given in the medical assessors report.

Patient’s demographics and baseline anal exam assessment were similar across treatment groups.

The results of the analysis of change from baseline in 24-hour average pain intensity are shown in the table below.

<table>
<thead>
<tr>
<th>Time Period</th>
<th>Statistics</th>
<th>Placebo (N=99)</th>
<th>Rectogesic Ointment 0.4% (N=89)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>N</td>
<td>99</td>
<td>89</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>54.1 (14.52)</td>
<td>55.0 (15.32)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>49.0</td>
<td>50.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Min – Max</td>
<td>35 – 98</td>
<td>36 – 100</td>
<td></td>
</tr>
<tr>
<td>Days 1 – 21</td>
<td>N</td>
<td>98</td>
<td>89</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>-24.9 (18.58)</td>
<td>-28.1 (18.46)</td>
<td>&lt;0.0109</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>-23.6</td>
<td>-31.8</td>
<td>&lt;0.0493</td>
</tr>
<tr>
<td></td>
<td>Min – Max</td>
<td>-77 – 19</td>
<td>-77 – 14</td>
<td></td>
</tr>
<tr>
<td>Days 1 – 56</td>
<td>N</td>
<td>98</td>
<td>89</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>-33.8 (18.03)</td>
<td>-35.2 (18.97)</td>
<td>&lt;0.0447</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>-34.4</td>
<td>-37.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Min – Max</td>
<td>-85 – 13</td>
<td>-73 – 20</td>
<td></td>
</tr>
</tbody>
</table>
The figure below shows the percentage change from baseline in 24-hour average pain intensity, the full line indicates the Rectogesic 0.4% treatment group and the dashed line the placebo treatment group.

![Graph showing percentage change in pain intensity](image)

**Figure 3.** Percent Improvement in Average Pain Intensity (mm) Due to Anal Fissure by Time Period, ITT Population

Statistical assessors comment: Using an LOCF approach to account for missing data for patients who withdrew due to headache, a statistically significant difference between Rectogesic and placebo for the analysis for up to day 21 was seen. No analyses were carried out using this LOCF approach for missing data for analysis up to day 56. However, a statistically significant difference was seen between Rectogesic and placebo for this endpoint, not appropriately accounting for missing data. As stated previously, the MAH should also have carried out these analyses using a technique to account for missing data which assumes it is non-ignorable.

In addition further information on the patient’s disposition, including the time patients withdrew from the study should have been included by the MAH. This would have helped
assess the impact of missing data, which is a concern here as there is an imbalance of withdrawals across treatment groups.

Clinical judgement will be required if it is considered that enough confidence has been established in the estimated effect sizes.

**Re-analysis and combined analyses of the data**

The MAH carried out extra analyses for this variation to assess the rate of change in the 24-hour average pain intensity over a 21-day treatment period. They also carried out a combined analysis using this endpoint to estimate the overall effect of Rectogesic compared to placebo. The extra analyses all used patients who were treated with Rectogesic 0.4% or placebo approximately every 12 hours.

A re-analysis of the data from studies R1 and R2 was carried out using the average daily pain rating up until day 21 rather than day 56 as used in the original submission.

In addition two combined analyses were carried out using:
- all patients included in the ITT population for all three pivotal studies.
- the subset of patients included in the ITT population from studies R2 and R3 who had sentinel pile documented at baseline. Sentinel pile was not recorded in study R1 and so this study was not included in this analysis.

The re-analyses are considered appropriate as they help to estimate the overall treatment effect for the first 21 days. They should be considered in conjunction with the average pain intensity score over the 56 day treatment period. As with all combined analyses they are useful as they can give a more precise estimate of treatment effect, if carried out appropriately. It should not be considered in isolation, but in combination with the results from each study alone.

For both the re-analysis and combined analyses of the data, the MAH claims that as the reason for discontinuation being headache or not was not recorded for studies R1 or R2 that it was “impossible” to use LOCF in the analysis. Therefore, LOCF was not used in any of these analyses. The mixed-effects regression model previously described, was used for both the re-analysis and combined analyses of the data.

Statistical assessors comment: The MAH claimed that as information on whether the reason for a discontinuation was a headache had not been collected in studies R1 or R2 then it was “impossible” to use LOCF in the analysis. This is clearly untrue, as when a patient withdraws from a study for an adverse event, all information on the adverse event should have been recorded. In addition an LOCF approach for all patients discontinuing could have been carried out. Sensitivity analyses which use techniques to account for missing data for both the re-analysis and combined analyses should have been carried out, assuming any missing data were non-ignorable.

**Overview of the combined analyses**

The three pivotal studies used for the combined analyses have slightly different designs which are summarised in the table below.
<table>
<thead>
<tr>
<th>Study R1</th>
<th>Study R2</th>
<th>Study R3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary endpoints</strong></td>
<td>Fissure healing</td>
<td>Rate of change of the 24-hour average pain intensity over a 56-day period</td>
</tr>
<tr>
<td><strong>Secondary endpoints</strong></td>
<td>Rate of change of the 24-hour average pain intensity, worst pain and defecation pain over a 56-day period and safety</td>
<td>Rate of change of defecation pain over a 56-day period and safety</td>
</tr>
<tr>
<td><strong>Tertiary endpoints</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Inclusion criteria**
- Chronic anal fissure(s); pain and/or bleeding for at least 30 days prior to enrollment
- A single anal fissure and pain after at least 50% of bowel movements each week for 30 days prior to enrollment
- A single anal fissure and sentinel pile; pain especially on defecation ≥3 days a week for 30 days prior to enrollment; 24-hour average VAS pain score ≥5 mm for each of 2 days before study treatment, and defecation pain of moderate or severe intensity on at least 1 of the 2 days

**Treatment regimens**
- Study R1: 3 NTG concentrations (0.1%, 0.2%, and 0.4%) or placebo; 2 dosing frequencies (b.i.d. and t.i.d.)
- Study R2: 2 NTG concentrations (0.2%, and 0.4%) or placebo; 1 dosing frequency (b.i.d.)
- Study R3: 1 NTG concentration (0.4%) or placebo; 1 dosing frequency (b.i.d.)

**Duration of treatment**
- Study R1: 56 days or until fissure healing
- Study R2: 56 days without regard to healing status
- Study R3: 56 days without regard to healing status

**Concomitant anorectal treatments**
- Subject was allowed to use dietary fiber supplement or stool softeners and sitz baths.
- Standard therapy (psyllium, 1 tablespoonful in 8 oz of water b.i.d., and sitz baths, no more than 1 per day if needed)
- If a dietary fiber supplement or stool softener was used during the week before enrollment, the subject was allowed to continue their use at the same dose; no more than 1 sitz bath per day was allowed.

**KEY:** NTG = nitroglycerin; b.i.d. = approximately every 12 hours; t.i.d. = approximately every 8 hours.
The primary endpoint for the combined analyses was the 24-hour average pain intensity score which was recorded in all three pivotal studies. The statistical analysis used was identical to the generalised mixed model approach described for study R3.

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Placebo Mean (SD) N</th>
<th>Rectogesic Mean (SD) N</th>
<th>Difference between means</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>42.3 (22.53) 204</td>
<td>44.2 (22.38) 198</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Results from the re-analysis and combined analyses
The combined analyses using the patients in the ITT population across all three studies consisted of 201 subjects treated with Rectogesic 0.4% and 206 patients treated with placebo.

Results for change from baseline in 21 and 56-day measurements of 24-hour average pain intensity (mm) are given in the table below.
The figures below show the mean percentage improvement in 24-hours average pain intensity over time, firstly for the combined analysis and secondly for the individual studies.

**Figure 2.7.3-1: Mean Percent Improvement in 24-Hour Average Pain Intensity (mm) by Time Period – Combined Analysis**

![Graph showing mean percent improvement in 24-hour average pain intensity over time.](image)

<table>
<thead>
<tr>
<th>Study</th>
<th>Combined</th>
<th>Study R3</th>
<th>Study R1</th>
<th>Study R2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-15.4 (19.33)</td>
<td>-24.9 (18.58)</td>
<td>-4.3 (12.52)</td>
<td>-7.7 (16.69)</td>
</tr>
<tr>
<td></td>
<td>203</td>
<td>98</td>
<td>32</td>
<td>73</td>
</tr>
<tr>
<td></td>
<td>194</td>
<td>89</td>
<td>37</td>
<td>68</td>
</tr>
<tr>
<td>Day 1-21</td>
<td>3.9 (0.0007*)</td>
<td>3.2 (0.0489*)</td>
<td>9 (0.0063**)</td>
<td>3.4 (0.0388**)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>Combined</th>
<th>Study R3</th>
<th>Study R1</th>
<th>Study R2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-22.4 (20.8)</td>
<td>-33.8 (18.03)</td>
<td>-6.9 (14.22)</td>
<td>-13.8 (18.14)</td>
</tr>
<tr>
<td></td>
<td>203</td>
<td>98</td>
<td>32</td>
<td>73</td>
</tr>
<tr>
<td></td>
<td>-25.8 (21.96)</td>
<td>-35.2 (18.92)</td>
<td>-18.8 (22.15)</td>
<td>-17.2 (20.88)</td>
</tr>
<tr>
<td></td>
<td>194</td>
<td>89</td>
<td>37</td>
<td>68</td>
</tr>
<tr>
<td>Day 1-56</td>
<td>3.4 (0.0001*)</td>
<td>1.4 (0.0447**)</td>
<td>11.9 (0.0001**)</td>
<td>3.4 (0.0039**)</td>
</tr>
</tbody>
</table>

*Analysis using the generalised mixed model approach using LOCF for those discontinuing for headache

**Analysis using the generalised mixed model approach with no imputation for missing data

The combined analysis includes all ITT subjects who applied Celegesic NTG ointment 0.4% bid or placebo bid in studies R1, R2, and R3. One subject in the Celegesic NTG ointment 0.4% group (from Study R1) did not have any pain data and was excluded from this figure.
One subject in the Cellegesic NTG ointment 0.4% group (from Study R1) did not have any pain data and was excluded from this figure.

**Figure 2.7.3-9: Mean Percent Improvement in 24-Hour Average Pain Intensity (mm) by Time Period – Study R1**

![Graph showing mean percent improvement in 24-hour average pain intensity by time period for Study R1.]

**Figure 2.7.3-11: Mean Percent Improvement in 24-Hour Average Pain Intensity (mm) by Time Period – Study R2**

![Graph showing mean percent improvement in 24-hour average pain intensity by time period for Study R2.]

21 days: p < 0.0005 and 60 days: p < 0.0001.
Figure 2.7.3-7: Mean Percent Improvement in 24-Hour Average Pain Intensity (mm) by Time Period – Study R3

Note: Plotted mean values and P-values above use all available data. For the 21-day test: p<0.0498 if LOCF is used for subjects who withdrew due to NTG-related headache and p<0.0309 if all post study discontinuation data are excluded.

Statistical assessors comment: No table of patient disposition was presented for the combined analysis and it is not clear which patients have been used in which analysis. It is difficult to interpret the results from the re-analyses and combined analysis of the studies without fully understanding the impact any missing data may have. A summary of the patient’s withdrawal profile, split by treatment group and study should have been included by the MAH together with sensitivity analyses of the data for both the combined analyses and re-analysis which assumed any missing data were non-ignorable.

Furthermore, when presenting the figures of treatment effect over time it would have been useful to have the numbers of patients included at each timepoint. If the figures were based on a completers analysis, then fewer patients would have been used to estimate the curve at later, rather than earlier, timepoints. This could cause a bias in the treatment effect seen.

Notwithstanding these points:

There is a large variation in placebo effect across the studies, which the MAH should have discussed further as it is a signal of potential heterogeneity across studies.

The treatment effect seen is largest in Study R1, for which there was a large baseline imbalance. This could account for the larger treatment effect seen in this study compared to the significantly smaller treatment effects seen in the other two studies. However, the results from Study R1 have a relatively small impact on the combined treatment effect seen as it was the smallest study. The treatment effect seen in the new study of 3.2mm for the day 1-21 endpoint and 1.4mm for the day 1-56 endpoint, are smaller than those seen previously.

Although statistical significance has been shown for the re-analysis of the studies alone and the combined analysis, clinical judgement of whether the treatment effect is clinically relevant is needed.
Results for combined analysis using the subgroup of patients with sentinel pile at baseline are given below.

### Table 2.7.3-7: Change from Baseline in 21- and 56-Day Measurements of 24-Hour Average Pain Intensity (mm) – Combined Analysis of Subgroup with Sentinel Pile at Baseline

<table>
<thead>
<tr>
<th>Time Period</th>
<th>Statistics</th>
<th>Placebo (N=137)</th>
<th>Cellegesic Nitroglycerin Ointment 0.4% (N=117)</th>
<th>P-value&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>N</td>
<td>137</td>
<td>117</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>47.9 (19.86)</td>
<td>50.6 (19.36)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>45.5</td>
<td>49.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Min, Max</td>
<td>0.0, 98.0</td>
<td>7.0, 100.0</td>
<td></td>
</tr>
<tr>
<td>Days 1-21</td>
<td>N</td>
<td>137</td>
<td>116</td>
<td>&lt;0.0007</td>
</tr>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>-20.1 (19.42)</td>
<td>-25.1 (19.23)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>-19.2</td>
<td>-26.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Min, Max</td>
<td>-77.0, 23.7</td>
<td>-76.6, 27.7</td>
<td></td>
</tr>
<tr>
<td>Days 1-56</td>
<td>N</td>
<td>137</td>
<td>116</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>-27.6 (20.39)</td>
<td>-32.4 (19.28)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>-30.5</td>
<td>-34.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Min, Max</td>
<td>-88.2, 18.1</td>
<td>-75.8, 20.1</td>
<td></td>
</tr>
</tbody>
</table>

Combined analysis includes Studies R2 and R3.

<sup>a</sup> Summary statistics displayed at the above intervals are calculated by using the mean of daily change from baseline in 24-hour average pain intensity assessments recorded for each subject during the indicated interval.

<sup>b</sup> Analysis of the raw daily pain intensity assessments from Baseline to Day 21 or 56 used a mixed-effects regression model. The P-values are from the test of the linear component of the treatment-by-day interaction (i.e. the rate of change in pain is different between placebo and Cellegesic-treated subjects).

Note: The N’s in the column headers are the number of subjects in the ITT population. The N’s in the time period rows are the number of ITT subjects having data for the descriptive statistics for that time period.

Statistical assessors comment: This subgroup of patients with sentinel pile at baseline was not pre-specified and therefore there is a concern over multiplicity here. Notwithstanding this concern, the treatment effect seen in this subgroup is slightly larger than for the overall population. It is difficult to assess whether the combined results are a sensible summary of the overall effect without presentation of the treatment effect in this subgroup for each study alone, which should have been included in the submission by the MAH.

As for all other previous analyses, a sensitivity analysis using an approach to missing data which assumes missing data is non-ignorable should have been included the MAH.

**Statistical conclusions**

There were some methodological concerns for the analysis used in the new Study R3. Not imputing data for those patients who dropout of the study for reasons other than headache makes the assumption that their missing data is ignorable. This does not seem appropriate as it is often reasonable to suspect that patients who withdraw from a study systematically differ from those who continue, whether they have dropped out for a headache or for many other reasons. Therefore the MAH should have analysed the primary endpoint and the corresponding day 1-56 endpoint, using an alternative approach which assumed missing data were non-ignorable, regardless of the reason for discontinuation. In addition, the MAH has combined centres randomly with other centres and this is considered inappropriate.
Information on how many centres were pooled, and its effect on the final analyses should have been discussed by the MAH.

It is difficult to interpret the results from the re-analyses and combined analysis of the studies without fully understanding the impact of missing data. Therefore a summary of the patients withdrawal profile, split by treatment group and study should have been included by the MAH together with a re-analyses of the data using an alternative approach, assuming that missing data were non-ignorable.

Notwithstanding these concerns on missing data, there is a large variation in placebo effect across the studies, which the MAH should have discussed further as it is a signal of potential heterogeneity across studies. In addition, the treatment effect seen is largest in Study R1, for which there was a large baseline imbalance. This could account for the larger treatment effect seen in this study compared to the significantly smaller treatment effects seen in the other two studies. However, the results from Study R1 have a relatively small impact on the combined treatment effect seen as it was the smallest study. The treatment effect seen in the new study of 3.2mm for the day 1-21 endpoint and 1.4mm for the day 1-56 endpoint, are smaller than those seen previously.

Although statistical significance has been shown for the re-analysis of the studies alone and the combined analyses, judgement on whether the treatment effect is clinically relevant is needed if it is considered that enough confidence has been established in the estimated effect sizes.

Overall Conclusion

In March 2004 the CSM granted Rectogesic 0.4% ointment a MA for the relief of pain associated with chronic anal fissure in adults over the age of 18 years. The critical question now is whether the results of Study R3, and the associated reanalysis and combined analysis, significantly alter the benefit/risk ratio compared to the position before the CSM in 2004.

Considering:
- Study R3;
- the reanalysis of studies R1 and R2;
- the combined Analysis Report of Studies R1, R2 and R3;

it is concluded that:

a) the demonstrated efficacy of Rectogesic 0.4% ointment applied twice daily in respect of relief of pain associated with chronic anal fissure is essentially the same as that considered by the CSM in 2004 at the time of granting the MA;

b) there are no new safety issues, although the incidence of GTN-related headache remains high;

c) this product has no significant effect on anal fissure healing;

In summary, the benefit/risk ratio for the symptomatic treatment of chronic anal fissure in adults is not significantly different from that in 2004 when the initial MA was granted. On this basis, the variation is approved.

The absence of efficacy in respect of anal fissure healing is in keeping with the latest Cochrane Review of non-surgical therapy for anal fissure. In this review the author

concludes ‘...Medical therapy for chronic anal fissure, acute fissure and fissure in children may be applied with a chance of cure that is only marginally better than placebo, and, for chronic fissure in adults, far less effective than surgery...’

Concerning the incidence of headache, section 4.8 of the current approved SPC for Rectogesic states ‘...In patients treated with Rectogesic® 0.4% Rectal Ointment, the most common adverse event was dose-related headache which occurred with an incidence of 50%...’ based on a combined analysis of studies R1 and R2. When data from study R3 is included, the combined incidence of headache increases to 57.3%. The Applicant suggests that this increase in incidence of headache may have been because patients were specifically prompted for headache in Study R3 using diary cards, but provides no specific evidence to this effect. However, an overall incidence of headache of 57.3%:

- would not affect the CIOMS frequency category, which remains as ‘very common’ i.e. greater than 10%;
- is comparable with the reported incidence with other GTN products.

Decision - Approved

5 December 2005
# Annex I – Study R3: Summary of Patient Demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
<th>Placebo</th>
<th>Rectogesic 0.4% Ointment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>(N=98)</td>
<td>(N=89)</td>
</tr>
<tr>
<td><strong>Sex, n (%)</strong></td>
<td>Male</td>
<td>37 (37.8)</td>
<td>30 (33.7)</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>61 (62.2)</td>
<td>59 (66.3)</td>
</tr>
<tr>
<td><strong>Race, n (%)</strong></td>
<td>Caucasian</td>
<td>94 (95.9)</td>
<td>84 (94.4)</td>
</tr>
<tr>
<td></td>
<td>Black</td>
<td>1 (1.0)</td>
<td>3 (3.4)</td>
</tr>
<tr>
<td></td>
<td>Asian</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td></td>
<td>Hispanic-American or Latino</td>
<td>3 (3.1)</td>
<td>2 (2.2)</td>
</tr>
<tr>
<td></td>
<td>Native American</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td><strong>Age n (%)</strong></td>
<td>≤45 years</td>
<td>34 (34.7)</td>
<td>43 (48.3)</td>
</tr>
<tr>
<td></td>
<td>46-64 years</td>
<td>57 (58.2)</td>
<td>38 (42.7)</td>
</tr>
<tr>
<td></td>
<td>≥65 years</td>
<td>7 (7.1)</td>
<td>8 (9.0)</td>
</tr>
<tr>
<td><strong>Weight (kg)</strong></td>
<td>N</td>
<td>98</td>
<td>89</td>
</tr>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>78.6 (15.49)</td>
<td>77.5 (16.65)</td>
</tr>
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<td></td>
<td>Median</td>
<td>76.5</td>
<td>76.0</td>
</tr>
<tr>
<td></td>
<td>Min – Max</td>
<td>50 – 120</td>
<td>44 – 128</td>
</tr>
<tr>
<td></td>
<td>Missing</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Height (cm)</strong></td>
<td>N</td>
<td>98</td>
<td>89</td>
</tr>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>168.3 (9.18)</td>
<td>169.5 (8.96)</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>166.5</td>
<td>168.0</td>
</tr>
<tr>
<td></td>
<td>Min – Max</td>
<td>150 – 191</td>
<td>154 – 201</td>
</tr>
<tr>
<td></td>
<td>Missing</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Body Mass Index (kg/m²)</strong></td>
<td>N</td>
<td>98</td>
<td>89</td>
</tr>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>27.76 (5.084)</td>
<td>26.90 (5.096)</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>27.36</td>
<td>25.93</td>
</tr>
<tr>
<td></td>
<td>Min – Max</td>
<td>18.9 – 43.0</td>
<td>16.5 – 41.1</td>
</tr>
<tr>
<td></td>
<td>Missing</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Current Alcohol Use</strong></td>
<td>Yes</td>
<td>25 (25.5)</td>
<td>16 (18.0)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>73 (74.5)</td>
<td>73 (82.0)</td>
</tr>
<tr>
<td><strong>Current Tobacco Use</strong></td>
<td>Yes</td>
<td>25 (25.5)</td>
<td>16 (18.0)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>73 (74.5)</td>
<td>73 (82.0)</td>
</tr>
</tbody>
</table>
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT
This is a bibliographic application. During the national assessment, the applicant submitted additional clinical data and analyses in response to concerns raised by the Committee for Safety of Medicines (CSM). These data were considered acceptable.

It is accepted that risk:benefit ratio is favourable.

The product literature has been amended in-line with the current guidelines. The SmPC includes all relevant warnings.

There are no pre-clinical concerns with these applications or with the clinical use of the active ingredient glyceryl trinitrate.