

**glyceryl trinitrate (GTN) 0.4% w/w (4mg/g) rectal ointment  
(Rectogesic<sup>®</sup>)**

**ProStrakan Group plc**

**No. (200/05)**

10 March 2006

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

**ADVICE:** following a resubmission

**Glyceryl trinitrate rectal ointment (Rectogesic<sup>®</sup>)** is not recommended for use within NHS Scotland for the relief of pain associated with chronic anal fissure.

It was associated with very small improvements in pain scores compared with vehicle. The economic case for this product was not demonstrated.

Overleaf is the detailed advice on this product.

**Chairman  
Scottish Medicines Consortium**

**Glyceryl trinitrate (GTN),  
0.4%, rectal ointment  
(Rectogesic ®)**

**Licensed indication under review**

Relief of pain associated with chronic anal fissure.

**Dosing information under review**

A measured dose delivers approximately 375 mg of ointment equivalent to 1.5 mg GTN to be administered anally every 12 hours. Treatment may be continued until the pain abates, up to a maximum of 8 weeks.

**UK launch date**

31st May 2005

**Comparator medications**

Anusol<sup>®</sup>, Anacal<sup>®</sup> and Xyloproct<sup>®</sup> are haemorrhoidal preparations which are licensed for relief of pain associated with anal fissure.

**Cost per treatment period and relevant comparators**

The cost is £32.80 for a 30g tube, which is equivalent to 80 accurately measured doses. A patient using the ointment for the maximum recommended treatment period of eight weeks would require a second tube. The product is not licensed for continuous use.

Estimated cost of a single course up to 8-weeks' duration - £32.80 to £65.60

For comparators, the quantity used per day and the duration of treatment will vary widely, therefore the price per 30g is given below for general comparison only.

| <b>Preparation</b>   | <b>Pack size</b> | <b>Price per 30g</b> |
|--|------------------|----------------------|
| <b>Glyceryl trinitrate 0.4% rectal ointment (Rectogesic<sup>®</sup>)</b> | <b>30g</b>       | <b>£32.80</b>        |
| Anacal ointment <sup>®</sup>   | 30g              | £3.04                |
| Anusol ointment <sup>®</sup>   | 25g              | £2.35                |
| Xyloproct ointment <sup>®</sup>  | 20g              | £3.39                |

## Summary of evidence on comparative efficacy

Hypertonicity of the internal anal sphincter (IAS) predisposes to anal fissures. Glyceryl trinitrate is a donor of nitric oxide, which mediates relaxation of the IAS, thus reducing hypertonicity.

A vehicle-controlled trial was performed to assess the efficacy of twice daily administration of the 0.4% ointment at a daily dose of 1.5 mg GTN twice daily. In all studies, pain scores were determined on a 100 mm visual analogue scale (VAS).

A multicentre, double-blind, placebo-controlled, parallel-group, Phase 3 study recruited adult patients with a single chronic anal fissure and associated symptoms. A total of 187 patients in the 0.4% GTN (n=89) and placebo (n=98) groups were included in the intention-to-treat efficacy population.

The primary analysis was at 21 days, but the full treatment period was 56 days. Patients treated with 0.4% GTN had a statistically greater rate of decrease in average pain intensity over Days 1-21 ( $p<0.031$ ) and Days 1-56 ( $p=0.045$ ) compared with those who received placebo.

**Mean (SD) baseline VAS score for pain intensity (mm) and rate of change in average VAS score over time**

| VAS pain score                    | Placebo<br>(n=98) | 0.4%<br>GTN<br>(n=89) | Treatment effect,<br>GTN vs placebo | p value |
|-----------------------------------|-------------------|-----------------------|-------------------------------------|---------|
| <b>Average daily score<br/>mm</b> |                   |                       |                                     |         |
| Baseline                          | 54.1              | 55.0                  | -                                   | -       |
| Days 1-21                         | -24.9             | -28.1                 | 3.2                                 | 0.031   |
| Days 1-56                         | -33.8             | -35.2                 | 1.4                                 | 0.045   |

In addition, VAS scores for pain on the last defaecation of the day (if any) were significantly reduced at 56 days, though not at 21 days. When reported as percentage change, there was no significant difference between GTN and placebo for either of those measures at either time point. There was no significant difference in the time to 50% improvement of the average pain intensity in the main analysis for this end-point ( $p=0.295$ ).

The company provided details of two unpublished dose-finding trials, the results from which were provided in confidence. The first dose-finding study was principally designed to assess healing rates, which is outside the product licence. In the second dose-finding trial (n=219), investigation of pain relief was the primary objective.

Other data were also assessed but remain commercially confidential.\*

## Summary of evidence on comparative safety

Consistent with other formulations of GTN, the most commonly reported adverse event in clinical trials involving GTN ointment was headache.

Other data were also assessed but remain commercially confidential.\*

## Summary of clinical effectiveness issues

There are no clinical effectiveness issues.

## Summary of comparative health economic evidence

The manufacturer states that “*No pharmaco-economic evaluation has been conducted comparing Rectogesic® with current medical management of the pain associated with chronic anal fissure.*” This is not in line with SMC guidance.

Within the budget impact section an analysis of data from Tayside Pharmaceuticals and data from National Services Scotland is presented to give a range of cost from £29 to £89 for the average prescription of 44g of unlicensed 0.2% GTN. On the basis of a 0.75:1 equivalence ratio, this translated into a requirement of 33g 0.4% GTN rectal ointment (Rectogesic) at a cost of £36. This does not take into account the indivisibilities in terms of tub and tube size. Furthermore, the cost cited for Tayside Pharmaceuticals of £29 includes a handling charge of £12.50. This is a flat fee per order under £50, larger orders consequently significantly reducing the cost per tub. The handling fee is also only applied to non-NHS customers.

This cost comparison, as acknowledged by the manufacturer, does not take into account the current medical management of pain associated with chronic anal fissures and other preparations that may be used and displaced by 0.4% GTN rectal ointment (Rectogesic). A number of these identified by SMC experts are somewhat cheaper than 0.4% GTN rectal ointment (Rectogesic). There is also a considerable placebo effect within the 0.4% GTN rectal ointment (Rectogesic) trials. As a consequence, alternative treatments for the management of pain in chronic anal fissure may be of similar effectiveness to 0.4% GTN rectal ointment (Rectogesic) and somewhat cheaper.

The cost effectiveness of 0.4% GTN rectal ointment (Rectogesic) has not been demonstrated.

## Patient and Public involvement

A Patient Interest Group Submission was not made.

## Budget impact

Patient numbers are difficult to estimate, but the manufacturer presents a case for between 1,800 and 2,500 patients. With an assumption of an average prescription of 33g for Rectogesic this translates into an annual cost of between £65,000 and £90,000.

Unlicensed use of 0.2% GTN will be displaced by this. The cost range for this presented by the manufacturer is between £29 and £89. To the extent that this applies:

- Under the low patient numbers scenario this results in a net cost of between minus £96,000 (saving) to +£12,500 (cost).
- Under the high patient numbers scenario this results in a net cost of between minus £133,300 (saving) to +£17,400 (cost).

Paralleling the absence of an economic evaluation comparing 0.4% GTN rectal ointment (Rectogesic) with current medical management of the pain associated with chronic anal fissure, the budget impact section does not consider the likely net budget impact upon current medical management of the pain associated with chronic anal fissure. Other treatment options other than just the unlicensed use of 0.2% GTN may be displaced. Some of these are likely to be somewhat cheaper than 0.4% GTN rectal ointment (Rectogesic).

## Additional information

In September 2005, the Scottish Medicines Consortium advised that glyceryl trinitrate rectal ointment (Rectogesic®) is not recommended within NHS Scotland for the relief of pain associated with chronic anal fissure. It was associated with improvements in pain scores compared with vehicle but the treatment effect was small. The economic case was not demonstrated.

A review of non-surgical therapy for anal fissure from The Cochrane Collaboration is equivocal about whether various formulations of GTN were significantly better than placebo in healing anal fissures and it presents no data on pain relief. The reviewers found that GTN was significantly less likely than placebo to result in non-healing of anal fissures when the results of several trials were combined. The treatment effect disappeared when two trials were excluded on the grounds of quality and reappeared with the exclusion of another trial that may have included patients with acute rather than chronic anal fissure.

**Advice context:**

*No part of this advice may be used without the whole of the advice being quoted in full.*

*This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.*

*This assessment is based on data submitted by the applicant company up to and including 17 February 2006.*

*Drug prices are those available at the time the papers were issued to SMC for consideration.*

*\* Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: <http://www.scottishmedicines.org.uk/>*

*The undernoted reference was supplied with the submission.*

*Nelson R. Non surgical therapy for anal fissure (Review). The Cochrane Collaboration. 2005.*