

Resubmission

glyceryl trinitrate, 0.4% rectal ointment (Rectogesic®) (No. 200/05)
ProStrakan

11 January 2008

The Scottish Medicines Consortium 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 third resubmission

glyceryl trinitrate 0.4% ointment (Rectogesic®) is not recommended for use within NHS Scotland for relief of pain associated with chronic anal fissure.

It was associated with very small improvements in pain scores compared with vehicle, and therefore little clinically significant effect.

The manufacturer did not present a sufficiently robust economic case to gain acceptance by SMC.

Overleaf is the detailed advice on this product.

**Chairman,
Scottish Medicines Consortium**

Indication

Relief of pain associated with chronic anal fissure.

Dosing information

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

Product availability date

31st May 2005.

Summary of evidence on comparative efficacy

Hypertonicity of the internal anal sphincter (IAS) predisposes to anal fissures. Glyceryl trinitrate (GTN) is a donor of nitric oxide that mediates relaxation of the IAS.

The efficacy of 0.4% GTN ointment (1.5mg twice daily) to relieve the pain of chronic anal fissure (CAF) was investigated in three multicentre, randomised, double-blind, placebo-controlled studies. Patients recorded pain daily on a 100mm visual analogue scale (VAS).

A Phase III study with the primary endpoint of rate of change of 24-hour average pain intensity over 21 days, recruited adult patients with a single CAF and associated symptoms. The full treatment period was 56 days. Eighty-nine and ninety-eight patients in the 0.4% GTN and placebo groups respectively were included in the intention-to-treat (ITT) efficacy population. In the primary analysis using last observation carried forward (LOCF), patients treated with 0.4% GTN had a statistically greater rate of decrease in average pain intensity over days 1 to 21, (corresponding to a treatment difference of 3.2mm on a 100mm VAS), and days 1 to 56, (corresponding to 1.4mm on VAS), compared to placebo. There was no significant difference between 0.4% GTN and placebo on time to 50% improvement in the 3-day average of daily pain intensity measurements. VAS scores for pain during the last bowel movement of the day were significantly reduced with 0.4% GTN ointment compared to placebo, by an average of 3.5mm on VAS, over days 1 to 56, but not over days 1 to 21.

A dose-finding study principally designed to assess healing rates, and for which anal pain was not a requirement for inclusion, randomised 304 patients with CAF to GTN 0.1%, 0.2% and 0.4% or placebo two or three times daily for up to eight weeks. After 56 days, treatment with 0.4% GTN was associated with a significant decrease in the secondary endpoints of average pain intensity, worst pain and pain at defaecation when compared to placebo.

Other data were also assessed but remain commercially confidential.*

Summary of evidence on comparative safety

The only comparative safety data available considers 0.4% GTN relative to 0.1% and 0.2% GTN. Consistent with other formulations of GTN, the most commonly reported adverse event in clinical trials involving 0.4% GTN ointment was headache.

The safety database for 0.4% GTN is small. In clinical studies, 167 patients using 0.4% GTN ointment completed the treatment course, and only 19 were 65 years or over. There were limited data concerning cardiovascular adverse effects, including blood pressure changes and associated adverse effects.

Summary of clinical effectiveness issues

The trial population appears to be representative of the Scottish population although few elderly patients completed treatment. In the clinical studies bulk stool softeners and sitz baths could be used at the patient's discretion but topical preparations for anal fissure and concomitant therapy that might influence response were not allowed.

Limitations of the clinical studies include missing data, high drop out rates, use of endpoints that were not pre-specified and paracetamol use.

The United States Food and Drug Administration commented that all three of the studies (described above) failed to show statistical significance for their primary endpoint analyses. The estimated magnitude of a benefit, if any, of 0.4% GTN in relieving pain of anal fissure was small, e.g., a mean improvement of about 3 mm on a 100 mm visual analogue scale at day 21 even with the sponsor's liberal analysis, and was confounded by many issues regarding analyses not prespecified, data exclusions, excessive dropouts with 0.4% GTN, paracetamol use, and benefit limited to one country. These studies did not provide substantial evidence of efficacy of 0.4% GTN ointment in relief of pain associated with chronic anal fissure.

Summary of comparative health economic evidence

The manufacturer presented a cost-utility analysis comparing 0.4% GTN with 0.2% GTN. This comparator was appropriate, though other comparators could also have been considered. The economic analysis relied upon the change in VAS pain scores reported in the main trial, rather than healing rates. The submission reverted to the 6 week time horizon used in the original submission, despite this being previously criticised by SMC. The reason for choosing this 6-week time horizon was initially unclear as the clinical trial was of 8-weeks duration. The manufacturer subsequently clarified that the 6- week horizon was chosen due to the effect of treatment with 0.4% GTN reaching a plateau after six weeks.

The quality of life increment associated with a change in the VAS pain score was taken from published literature relating to 0.2% GTN ointment. This quality of life increment was assumed to apply to the change in pain score arising from 0.2% GTN ointment within the trial. The quality of life increment for 0.4% GTN ointment was increased proportionately in the light of its slightly greater reduction in the average VAS pain score.

The cost for 0.2% GTN ointment was taken from the NHS PRODIGY website: £25 per 20g tube. This was increased proportionately to £37.50 for 30g, which is in line with a 30g tube of 0.4% GTN ointment which the analysis assumed would last for 6 weeks. Possible indivisibilities in the use of both 0.2% and 0.4% GTN ointment were not explored.

The results of the analysis indicated that 0.4% GTN ointment would yield an additional 0.0004 QALYs whilst also saving £4.70 per patient, and therefore dominated 0.2% GTN ointment.

Weaknesses of the analysis included:

- the reversion to a 6 week time horizon;
- other potentially less costly comparators for the relief of pain were not considered;
- pain being the sole determinant of quality of life with other more general quality of life questionnaire data being ignored;
- non-transparent derivation of quality of life increments;
- no consideration of other cost sources for 0.2% GTN ointment, as presented in previous submissions;
- no consideration of the effects of tub and tube indivisibilities upon the direct drug cost.

As a consequence, the manufacturer did not present a sufficiently robust economic case to gain acceptance by the SMC.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: previous SMC advice

On 9th September 2005, following a full submission, the Scottish Medicines Consortium advised that glyceryl trinitrate rectal ointment (Rectogesic®) was 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.

On 10th March 2006, following a resubmission, the Scottish Medicines Consortium advised that glyceryl trinitrate rectal ointment (Rectogesic®) was 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.

On 9th February 2007, following a second resubmission, the Scottish Medicines Consortium advised that glyceryl trinitrate rectal ointment (Rectogesic®) was 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 was not demonstrated.

Additional information: comparators

Anusol®, Anacal® and Xyloproct® are licensed for relief of symptoms associated with anal fissure.

Cost of 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 is £32.80 to £65.60. For comparators, the quantity used per day and the duration of treatment varies widely, therefore the price per 30g is given below for general comparison only.

Preparation	Pack size	Cost per pack	Cost per 30g (£)
glyceryl trinitrate 0.4% rectal ointment	30g	33	33
Xyloproct® ointment	20g	2.26	3.39
Anacal® ointment	30g	3.13	3.13
Anusol® ointment	25g	1.96	2.35

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 29th October 2007.

Additional information: budget impact

The manufacturer estimated a gross drug cost of £42k in year 1 rising to £63k by year 5. Given the assumed higher cost of the comparator preparation, this resulted in net savings of £6k in year 1 rising to £9k by year 5. These calculations assumed a market share of 40% in year one rising to 60% by year five.

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 12 December 2007.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database.

** 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 references were supplied with the submission. The reference shaded grey is additional to those supplied with the submission.

Nelson R. Non surgical therapy for anal fissure (Review). The Cochrane Collaboration. 2006.

Bailey HR, Beck DE, Billingham RP et al. A study to determine the nitroglycerin dose and dosing interval that best promote the healing of chronic anal fissures. Dis Colon Rectum 2002; 45: 1192-1199

ProStrakan. Study NTG 98-02-01, 2001.

ProStrakan. Study CP125 03-02-01, 2004.

ProStrakan. Study NTG 00-02-01, 2001.

FDA Clinical Review (Cellegesic) www.fda.gov