Scottish Medicines Consortium

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

ProStrakan

9 February 2007

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 second resubmission

glyceryl trinitrate 0.4% ointment (Rectogesic®) 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 was not demonstrated.

Overleaf is the detailed advice on this product.

Vice-Chairman
Scottish Medicines Consortium

Indication

Relief of pain associated with chronic anal fissure.

Dosing information

A measured dose delivers approximately 375 mg of ointment equivalent to 1.5 mg 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

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 which mediates relaxation of the IAS.

The efficacy of 0.4% GTN ointment 1.5 mg twice daily to relieve the pain of chronic anal fissure (CAF) was investigated in three multicentre, randomised, double-blind, placebo-controlled studies. Pain was recorded daily by the patient 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; 89 and 98 patients in the 0.4% GTN and placebo groups respectively were included in the intention-to-treat 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 1-21 ($p<0.05$) (corresponding to a treatment difference of 3.2mm on VAS), and days 1-56 ($p<0.045$) (corresponding to 1.4mm on VAS), compared with placebo.

There was no significant difference between 0.4% GTN vs placebo on time to 50% improvement in the 3-day average of daily pain intensity measurements ($p< 0.295$).

VAS scores for pain during the last bowel movement of the day were significantly reduced by an average of 3.5mm over days 1–56 with 0.4% GTN ointment compared with placebo ($p<0.0306$) but not over days 1-21 ($p<0.072$).

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 twice or three times daily for up to eight weeks. Treatment with 0.4% GTN compared with placebo was associated with a significant decrease in average pain intensity ($p<0.0002$), worst pain ($p<0.0002$) and pain at defaecation ($p<0.003$).

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.

The safety database was small. 167 patients using 04% GTN ointment completed the treatment course, of whom only 19 were = 65 years. There were limited data concerning cardiovascular 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 was not allowed.

Summary of comparative health economic evidence

The manufacturer presented an eight-week cost-utility Markov model with weekly cycles. This modelled 0.4% GTN ointment against 0.2% GTN ointment, and against no treatment. 0.2% GTN ointment was not an appropriate comparator, as it is not licensed.

The model had two health states: healed and not-healed. Healing rates were taken from the literature, with an eight week healing rate for 0.4% GTN ointment of 39% . 'No treatment' was assumed to have the same healing rate as 0.4% GTN ointment (and thus to have a higher healing rate than the active comparator).

Quality of life weights were differentiated by treatment for the not-healed health state. The base values for these were drawn from a published study which involved administering the SF-36 questionnaire to 0.2% GTN ointment treated patients. The quality of life of being treated with 0.2% GTN ointment but not healed was used as the anchor state and the values are included here despite the fact that this dose is not licensed. This resulted in:

- A quality of life of 0.733 for not-healed and no treatment
- A quality of life of 0.756 for not-healed and treated with 0.2% GTN ointment
- A quality of life of 0.759 for not-healed and treated with 0.4% GTN ointment
- A quality of life of 0.852 for healed regardless of treatment

The main results from this were an average additional cost from 0.4% GTN ointment relative to no treatment of £55.44 per patient, but also an additional 0.003 QALYs. This yielded a cost-effectiveness estimate for 0.4% GTN ointment relative to no treatment of £18,489 per QALY.

The quality of life value for 'not-healed when treated with 0.4% GTN ointment' was questionable. This relied upon a second paper within the literature which apparently showed a 7mm (10%) higher value on the VAS pain score for 0.4% GTN ointment compared to 0.2% GTN ointment at eight weeks. This was assumed to imply a 10% greater gain in quality of life from treatment with 0.4% GTN ointment as compared with treatment with 0.2% GTN ointment, this seemingly being applied throughout the eight weeks of treatment.

Combined with general uncertainty about the clinical trial data and the effect size, the cost effectiveness of 0.4% GTN ointment has not been demonstrated.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: previous SMC advice

In September 2005, following a full submission, 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.

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

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.

Additional information: comparators

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

Additional information: costs

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.

Preparation	**Pack size**	**Cost per 30g***
glyceryl trinitrate 0.4% rectal ointment (Rectogesic®)	**30g**	**£32.80**
Xyloproct ointment®	20g	£3.39
Anacal ointment®	30g	£3.13
Anusol ointment®	25g	£2.35

* costs from eVadis accessed on 22nd November 2006

Additional information: budget impact

Based on between 1,786 and 2,500 patients transferring from (unlicensed) GTN 0.2% to 0.4% GTN ointment the gross drug cost was estimated by the manufacturer at between £99k and £138k. The manufacturer estimated the net drug cost at between £63k and £89k. Market share was assumed to be 100%.

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 11 January 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.

The undernoted references were supplied with the submission.

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

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