Scottish Medicines Consortium

Glyceryl trinitrate (GTN), 0.4% w/w (4mg/g), rectal ointment (Rectogesic®) No. (200/05)

ProStrakan Group plc

New formulation and indication in chronic anal fissure

9 September 2005

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 full submission

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.

The licence holder has indicated their decision to resubmit.

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

31 May 2005

Comparator medications

There are no comparator medicines for glyceryl trinitrate 0.4%.

Cost per treatment period and relevant comparators

The company has confirmed a cost of £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.

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. This 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.

Pain scores were determined on a 100 mm visual analogue scale (VAS). 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 (mm) and rate of change in average VAS score for pain intensity over time

VAS score	Placebo (n=98)	0.4% GTN (n=89)	p value
Average daily score			-
Baseline	54.1	55.0	
Days 1-21	-24.9	-28.1	0.031
Days 1-56	-33.8	-35.2	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.

The company provided details of two unpublished dose-finding trials for which results data were provided in confidence which were reviewed.

*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

In one dose-finding trial, compliance as measured by the residual weight of the ointment was outwith the protocol-defined range in more than half of the patients randomised. Compliance rates were much higher in the other two trials considered in this submission.

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

Summary of comparative health economic evidence

The manufacturer submitted an economic evaluation comparing the use of GTN as first choice treatment with surgery (lateral internal sphincterectomy or anal dilatation). Under the assumptions used GTN would be about half the cost of surgery, even when treatment of recurrences was included. Quality Adjusted Life Years (QALY) are also discussed but an incremental analysis estimating the QALY gain from GTN was not presented.

The design of the economic study was flawed as the focus was on healing which is not a licensed indication and led to the choice of surgery as a comparator. Even at best, the economic case for this product would only be proven for people in whom surgery was an

alternative; in 2004 this seems to have only applied to 20% of patients with chronic anal fissure and this percentage is falling.

The handling of health benefits was questionable. It was based on a trial published in 1997 which used an extemporaneous formulation of GTN and recruited surgical out-patients. The company provided confidential pain scale and healing rate data from trials involving their own formulation in a more general population but did not to use these results in their model.

The main problem with the costs presented was the dose and cost of GTN. In the economic study a 6-week course was assumed (requiring one tube of GTN) whereas clinical trial data are based on 8 weeks of treatment (requiring 2 tubes).

The calculation and presentation of QALY gains was unclear. However, as cost savings are the key economic claim this is not necessarily a problem. The sensitivity analysis was limited to changing the cost of surgery so it was not informative.

In summary, the main concern is that the economic case is based on GTN healing rates compared to surgery in a different population and with a different formulation and dose.

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

Budget impact

The manufacturer estimates the net drug budget impact is around £200k per annum in Scotland, based on an 8-week course of treatment requiring a second tube of ointment. Based on a reduced need for surgery, the manufacturer predicts NHS resources will be freed for other uses so in economic terms there should be a saving.

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 16 August 2005.

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/*