NICE advice

Chronic anal fissure: 0.2% topical glyceryl trinitrate ointment

Evidence summary
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www.nice.org.uk/guidance/esuom7

Key points from the evidence

The content of this evidence summary was up-to-date in March 2013. See summaries of product characteristics (SPCs), British national formulary (BNF), BNF for children (BNFc) or the MHRA or NICE websites for up-to-date information.

Currently, 0.4% glyceryl trinitrate rectal ointment (Rectogesic 4 mg/g rectal ointment, ProStrakan) is the only licensed treatment for chronic anal fissure in the UK. It is indicated for the relief of pain associated with chronic anal fissure in adults, but is not licensed for children or young people under 18 years. Topical 0.2% glyceryl trinitrate ointment does not currently have a UK licence for treating chronic anal fissures, or for any other indication. Therefore, its use is unlicensed.

There is some suggestion that the strength of glyceryl trinitrate (0.2% or 0.4%) does not influence the efficacy but increases the incidence of side effects, particularly headache,

hence the requests for use of the 0.2% strength. However, no studies were identified that directly compared 0.2% with 0.4% glyceryl trinitrate ointment for treating chronic anal fissure. Only small placebo controlled trials were available to assess the effect of these different strengths indirectly.

Very limited evidence from indirect comparisons in 2 small randomised controlled trials (RCTs; only 47 and 23 adults were analysed in the 0.2% ointment groups in each trial) suggested that 0.2% glyceryl trinitrate ointment might be as effective as 0.4% glyceryl trinitrate at healing anal fissure after an 8-week treatment period in adults. However, in 1 of these studies, neither glyceryl trinitrate strength showed a statistically significant difference from placebo in healing rate.

Limited evidence from 1 small RCT (181 people analysed) showed that lower glyceryl trinitrate ointment strengths were associated with fewer reported headaches in adults.

No evidence was identified to assess the effectiveness or side effects of 0.2% glyceryl trinitrate ointment to treat chronic anal fissure in children or young people under 18 years.

It is not known whether applying less ointment of the same strength, rather than reducing the strength of ointment applied, might have an effect on the incidence or headache.

The evidence for unlicensed 2% topical diltiazem hydrochloride is discussed in detail in the evidence summary Chronic anal fissure: 2% topical diltiazem hydrochloride.

About this evidence summary

'Evidence summaries: unlicensed or off-label medicines' summarise the published evidence for selected unlicensed or off-label medicines that are considered to be of significance to the NHS, where there are no clinically appropriate licensed alternatives. The summaries provide information for clinicians and patients to inform their decision-making and support the construction and updating of local formularies.

The summaries support decision-making on the use of an unlicensed or off-label medicine for an individual patient, where there are good clinical reasons for its use, usually when there is no licensed medicine for the condition requiring treatment, or the licensed medicine is not appropriate for that individual.

The strengths and weaknesses of the relevant evidence are critically reviewed within this summary, **but this summary is not NICE guidance**.

Overview for healthcare professionals

Regulatory status of 0.2% glyceryl trinitrate

Topical 0.2% glyceryl trinitrate ointment does not currently have a UK licence for treating chronic anal fissures, or for any other indication. Therefore, its use is unlicensed.

In line with the guidance from the General Medical Council (GMC), it is the responsibility of the prescriber to determine the clinical need of the patient and the suitability of using unlicensed 0.2% glyceryl trinitrate ointment.

Topical 0.4% glyceryl trinitrate ointment (Rectogesic 4 mg/g rectal ointment, ProStrakan) is licensed in the UK for the relief of pain associated with chronic anal fissure in adults for a maximum of 8 weeks (see the Rectogesic 4 mg/g rectal ointment summary of product characteristics). It is not indicated for the healing of chronic anal fissure and is not recommended for use in children and young people under 18 years because of a lack of data on safety and efficacy.

The summary of product characteristics states that headache is very commonly reported by people using 0.4% glyceryl trinitrate ointment for chronic anal fissure (frequency greater than 1 in 2). Although this can be treated with analgesics such as paracetamol, headaches may be severe (frequency 1 in 5 people) and cause people to discontinue treatment. Dizziness and nausea are also commonly reported (frequency greater than 1 in 100, but less than 1 in 10).

According to the Scottish Medicines Consortium's assessments (2005 to 2008), 0.4% glyceryl trinitrate ointment was appraised but not recommended for use in NHS Scotland for the relief of pain associated with chronic anal fissure.

The Association of Coloproctology of Great Britain and Ireland has suggested that the strength of glyceryl trinitrate (0.2% or 0.4%) does not influence the efficacy but increases the incidence of side effects, particularly headache (Cross et al. 2008). Additionally, it has suggested that 0.2% glyceryl trinitrate ointment (twice daily) is an option for children with anal fissure. There is currently no licensed medical treatment option for this age group.

Other glyceryl trinitrate formulations (tablets, patches, sprays or intravenous infusions) are licensed for treating and preventing angina and other heart conditions (British national

formulary, January 2013).

Evidence statements

- A Cochrane systematic review (assessed as up-to-date November 2011) found that glyceryl trinitrate (pooled strengths, range unclear) was marginally, but statistically significantly, better than placebo in healing chronic anal fissure (48.9% compared with 35.5%) but late recurrence was common, occurring in about 50% of people whose fissures were initially cured.
- No direct evidence was identified that compared the efficacy of 0.2% with 0.4% glyceryl trinitrate ointment in healing chronic anal fissure or reducing pain symptoms in adults.
- Indirect comparisons from 2 small randomised controlled trials (RCTs; Scholefield et al. 2003 and Carapeti et al. 1999; only 47 and 23 adults respectively were analysed in the 0.2% ointment groups in each trial) provided very limited evidence that 0.2% glyceryl trinitrate ointment might be as effective as 0.4% glyceryl trinitrate ointment at healing anal fissure after an 8-week treatment period in adults. However, in 1 of these (Scholefield et al. 2003), neither strength of glyceryl trinitrate showed a statistically significant difference from placebo in healing rate.
- One small RCT (Scholefield et al. 2003; 181 people analysed) provided limited evidence that lower strengths of glyceryl trinitrate were associated with fewer reported headaches in adults. The study found a statistically significant trend across glyceryl trinitrate ointment strengths of 0.1%, 0.2% and 0.4%.
- It is not known whether applying less ointment of the same strength, rather than reducing the strength of ointment applied, might have an effect on the incidence or headache.
- No evidence was identified that looked at the effect of using 0.2% glyceryl trinitrate ointment in children or young people under 18 years.

Summary of the evidence

This section gives a brief summary of the main evidence. A more thorough analysis is given in the Evidence review section.

This evidence summary is based on published evidence and does not include evidence from unpublished studies submitted for the regulatory approval of 0.4% glyceryl trinitrate ointment.

Both a literature search and a Cochrane systematic review of non-surgical therapy for anal fissure identified 3 small RCTs recruiting adults (n=309 analysed) and 1 pilot RCT recruiting children (n=15 analysed) that included trial arms using different strengths of glyceryl trinitrate ointment to treat chronic anal fissure.

Efficacy

The Cochrane review (75 studies, 5031 patients) of non-surgical therapy for anal fissure included a total of 18 RCTs in 1315 people, mostly adults, involving glyceryl trinitrate. It found that, overall, glyceryl trinitrate (pooled strengths, range unclear) was marginally, but statistically significantly, better than placebo in healing chronic anal fissure (48.9% compared with 35.5%, p<0.0009) but late recurrence was common, occurring in approximately 50% of people whose fissures were initially cured. Of interest for this evidence summary, it pooled results from 4 RCTs to compare 'high' and 'low' strengths of topical glyceryl trinitrate ointment to treat chronic anal fissure in adults and children (n=324 analysed). High and low cut-offs were not defined in the review but glyceryl trinitrate ointment strengths in the individual trials ranged from 0.05% to 0.6%. The meta-analysis found no significant difference in fissure healing between the different strengths of glyceryl trinitrate used (low strength compared with high strength pooled odds ratio [OR] 0.91, 95% confidence interval [CI] 0.57 to 1.45).

This Cochrane review did not report a direct comparison of topical 0.2% with 0.4% glyceryl trinitrate, and no pooled estimate of effect was reported for the outcomes of pain reduction or adverse events due to headaches. The RCTs that were included in the Cochrane review for glyceryl trinitrate strength comparison are discussed below.

Key outcomes for 2 of the RCTs (Scholefield et al. 2003 and Carapeti et al. 1999) are summarised in tables 1 and 2 respectively. The RCT by Bailey et al. (2002) is not included in the tables because it presented most of its key outcomes in a graphical format only, therefore exact figures were not available. The RCT by Simpson et al. (2003) is not included in the tables because it did not use 0.2% or 0.4% glyceryl trinitrate ointment.

Children

No evidence was identified to assess the efficacy or safety of using 0.2% glyceryl trinitrate ointment in children and young people under 18 years. Only 1 pilot RCT (n=15) was identified but this used 0.1% and 0.05% glyceryl trinitrate ointment (Simpson et al. 2003). The authors' rationale for using these lower strength ointments was that the optimum therapeutic strength of glyceryl trinitrate ointment had not been established.

Adults

No studies were identified that were designed specifically to compare the efficacy of 0.2% with 0.4% glyceryl trinitrate ointment for chronic anal fissure, such as an RCT sufficiently powered to detect these differences or a non-inferiority trial.

Three small RCTs (Scholefield et al. 2003, Carapeti et al. 1999 and Bailey et al. 2002) were identified that tested different strengths of glyceryl trinitrate (0.1%, 0.2%, 0.4% and 0.2%–0.6% escalating weekly by 0.1%) against placebo in adults with chronic anal fissure. All included a local twice-daily application of glyceryl trinitrate ointment for 8 weeks and the primary outcome in all studies was fissure healing. This was assessed at 8 weeks in Scholefield et al. (2003) and Bailey et al. (2002) and at 10 weeks (8 weeks treatment, 2 weeks after treatment) in Carapeti et al. (1999). However, no statistical tests were carried out to assess differences between the glyceryl trinitrate strengths for this primary outcome.

One RCT (Carapeti et al. 1999) attempted to assess for statistically significant differences in secondary outcomes between glyceryl trinitrate strengths (table 2). However, it was small (n=70) and was not statistically powered to detect anything but large differences between glyceryl trinitrate strengths.

Indirect comparisons from 2 small RCTs (Scholefield et al. 2003 and Carapeti et al. 1999; tables 1 and 2, only 47 and 23 adults respectively were analysed in the 0.2% ointment groups in each trial) provided very limited evidence that 0.2% glyceryl trinitrate ointment might be as effective as 0.4% glyceryl trinitrate at healing anal fissure after an 8-week treatment period in adults. However, in 1 of these (Scholefield et al. 2003), neither strength showed a statistically significant difference from placebo in healing rate.

The 3 RCTs reported relatively high healing rates in placebo arms after 8 weeks (32% [7/22] in Carapeti et al. 1999, 37.5% [18/48] in Scholefield et al. 2003 and 50% [patient

numbers not reported] in Bailey et al. 2002) suggesting a high spontaneous healing rate. In Scholefield et al. (2003), placebo healing rate reduced from 37.5% (18/48) to 24.3% (9/37) when a stricter definition of chronicity was used. Therefore, heterogeneity in chronic fissure definition may influence reported fissure healing rates.

Using the stricter definition of chronicity, Scholefield et al. (2003) found statistically significantly higher healing rates after 8 weeks in people using 0.1% glyceryl trinitrate ointment (50.0%, 21/42, p=0.05) and 0.4% ointment (56.7%, 17/30, p=0.03) compared with placebo (24.3%, 9/37) and for the trend of all glyceryl trinitrate groups combined compared with placebo (p=0.03). However, the 0.2% glyceryl trinitrate group on its own did not show statistically significant differences from placebo (36.1%, 13/36, p=0.91).

Table 1 Summary of the trial: Scholefield et al. (2003)

	0.2% glyceryl trinitrate ointment	**0.4% glyceryl trinitrate ointment**	**Placebo**	**Analysis**
Randomised	n=51	n=46	n=51	0.2%, 0.4% and placebo arms only
ITT population	n=47	n=37	n=48	Patients who had used some of the study medication and were assessed for healing at the end of the study

Primary outcome: complete healing at 8 weeks[a]	40.4% (19/47) 95% CI 26% to 56%	54.1% (20/37) 95% CI 37% to 71%	37.5% (18/48) 95% CI 24% to 53%	• No statistical comparison between strengths was reported • Healing favoured 0.4% glyceryl trinitrate ointment in percentage terms but 95% CIs overlap suggesting strengths are not significantly different • None of the strengths of glyceryl trinitrate ointment were statistically significantly different from placebo
Sub-analysis:				
Randomised	n=36	n=30	n=37	ITT data restricted to people who had more than 1 of 5 features of chronicity[b]
Complete healing at 8 weeks	36.1% (13/36) 95% CI 21% to 54%	56.7% (17/30) 95% CI 37% to 75%	24.3% (9/37) 95% CI 12% to 41%	• No statistical comparison between strengths was reported • 95% CIs overlap suggesting non-significant difference • A statistically significant higher rate of healing was reported when 0.4% glyceryl trinitrate ointment was compared with placebo (p=0.03) but not when 0.2% ointment was compared with placebo (p=0.91)
Safety:				

Randomised	n=47	n=37	n=48	ITT (0.2% and 0.4% arms only)
Headache	36.1% (17/47)	67.5% (25/37)	12.5% (6/48)	• No statistical comparison between strengths was reported • No CIs reported • A significant increase in the frequency of headaches was reported with increasing glyceryl trinitrate strength (p for trend <0.01, strength range 0.1%, 0.2% and 0.4%). A similar increasing trend was seen for severe headaches by glyceryl trinitrate strength, but no statistical comparison was reported
Severe headache	6.4% (3/47)	24.3% (9/37)	4.2% (2/48)	

Abbreviations: CI, confidence interval; ITT, intention to treat; n, number of patients; SD, standard deviation.

[a] Assessed by visual inspection and measurement of length and width of fissure.

[b] Recognised features of chronicity included sentinel skin tag, hypertrophied anal papillae, exposed internal anal sphincter, fibrotic lateral fissure or fibrotic anal sphincter.

Table 2 Summary of trial: Carapeti et al. (1999)

	0.2% glyceryl trinitrate ointment	**0.2% to 0.6% glyceryl trinitrate ointment weekly 0.1% increments**	**Placebo**	**Analysis**

Randomised	n=24	n=24	n=22	ITT
Analysed	n=23	n=23	n=22	Analysed sample[a]
Primary outcome: fissure healing at 10 weeks (8 weeks treatment, 2 weeks post treatment)[b]	65% (15/23)	70% (16/23)	32% (7/22)	• No statistical comparison between strengths reported • No significant difference between glyceryl trinitrate groups described in text only (no p value) • p=0.008 for placebo versus the glyceryl trinitrate groups combined
Selected secondary outcomes:				
Mean pain score (baseline to 8 weeks)	Not reported, presented graphically	Not reported, presented graphically	Not reported, presented graphically	• No statistically significant difference between glyceryl trinitrate groups (p=0.7) • The average pain score after glyceryl trinitrate (combined) did not differ from placebo (p=0.4)

Symptomatic recurrence of fissure initially healed	33% (5/15)	25% (4/16)	43% (3/7)	• No statistically significant difference between glyceryl trinitrate groups (p=0.7) • Difference from placebo not reported • Median follow-up 9 months, range 6–14 months
Safety:				
Analysed	n=23	n=23	n=22	Analysed sample[a]
Patients reporting headaches	65% (15/23)	78% (18/23)	27% (6/22)	No significant difference between glyceryl trinitrate groups (p=0.5) but statistically significant difference between glyceryl trinitrate and placebo (p<0.001)

Abbreviations: ITT, intention to treat; n, number of patients.

[a] After randomisation: n=1 excluded from 0.2% glyceryl trinitrate group because of lack of fissure on baseline examination, n=1 excluded from 0.2%–0.6% because of failure to attend.

[b] Assessed by clinical examination, anal manometry and laser Doppler flowmetry.

Safety

One small RCT (Scholefield et al. 2003, 181 adults analysed) provided limited evidence that lower glyceryl trinitrate ointment strength was associated with fewer reported headaches over an 8-week treatment period in adults. It showed a statistically significant trend linking increasing glyceryl trinitrate strength (0.1%, 0.2% and 0.4% used) to more frequently reported headache. Frequency of reported headache (baseline to 8 weeks) was 12.5% (6/48) with placebo, 18.3% (9/49) with 0.1% glyceryl trinitrate, 36.1% (17/47) with 0.2% glyceryl trinitrate, and 67.5% (25/37) with 0.4% glyceryl trinitrate (p value for trend less

than 0.01).

No statistical test for trend was reported comparing glyceryl trinitrate strength with the frequency of severe headaches reported in the same trial. The frequency of severe headache was 4.2% (2/48) with placebo, 2.0% (1/49) with 0.1% glyceryl trinitrate, 6.4% (3/47) with 0.2% glyceryl trinitrate, and 24.3% (9/37) with 0.4% glyceryl trinitrate.

It is not known whether applying less ointment of the same strength, rather than reducing the strength of ointment applied, might have an effect on the incidence or headache.

Cost effectiveness and cost

NHS electronic drug tariff (January 2013) data indicate that (unlicensed) 0.2% glyceryl trinitrate rectal ointment costs £57.75 for the minimum 30 g volume and an extra £1.62 for every extra gram above 30 g. The price listed for Rectogesic (0.4% glyceryl trinitrate, 4 mg/g rectal ointment, ProStrakan) is lower at £34.80 for 30 g.

No studies were identified that assessed cost effectiveness of 0.2% glyceryl trinitrate ointment compared with 0.4% glyceryl trinitrate ointment.

Relevance to NICE guidance programmes

The use of 0.2% glyceryl trinitrate for treating chronic anal fissure is not appropriate for referral for a NICE technology appraisal as it is not licensed for this indication. It is not currently planned into any other work programme.

Constipation in children and young people: diagnosis and management of idiopathic childhood constipation in primary and secondary care (NICE clinical guideline 99) identifies anal fissure as a possible finding in children with constipation but does not discuss its treatment specifically.

Intervention and alternatives

Most medical treatments of chronic anal fissure aim to reduce anal sphincter tone (Cross et al. 2008). Glyceryl trinitrate, also known as nitroglycerin, is a vasodilator and muscle relaxant. When applied locally to the anus, it relaxes the anal sphincter.

The evidence for unlicensed 2% topical diltiazem hydrochloride is discussed in detail in the evidence summary Chronic anal fissure: 2% topical diltiazem hydrochloride.

Condition

Adults

Anal fissure is a common and painful problem that involves a tear or ulcer in the squamous epithelium of the anus. It usually occurs between the ages of 20 and 40 with an equal distribution between men and women and a lifetime incidence of 11.1% (Cross et al. 2008). Most of the fissures are in the midline posteriorly, whereas about 8% occur both posteriorly and anteriorly (Cross et al. 2008).

Chronic fissure has both anatomical and temporal definitions that vary. A Cochrane review of non-surgical treatments for chronic anal fissure states that chronicity is defined as a history of pain lasting more than 4 weeks or with pain of less duration but similar episodes in the past. NHS Choices states that chronic anal fissure is where symptoms have lasted for more than 6 weeks. Duration of symptoms was not uniform in the randomised controlled trials (RCTs) considered in this evidence summary. Physical characteristics of chronicity include a sentinel pile at the distal margin of the fissure, heaped up edges of the fissure, visible sphincter fibres at the base of the fissure, or an inflammatory polyp at the inner margin of the fissure (Nelson et al. 2012).

The Association of Coloproctology of Great Britain and Ireland states that symptoms of anal fissure include anal pain during and after defecation that may last several hours. Bleeding is common and the most consistent finding on physical examination is spasm of anal canal because of hypertonia or the internal anal sphincter.

The aetiology of a typical anal fissure is not clear but trauma from passing a large or hard stool is a common cause (Cross et al. 2008). Other less common causes include inflammatory bowel disease, anal cancer, childbirth and sexually transmitted disease (Cross et al. 2008 and Orsay et al. 2004).

Children

It is not certain whether chronic fissure in children is comparable to chronic fissure in adults or has the same aetiology (Nelson et al. 2012).

According to the Association of Coloproctology of Great Britain and Ireland, most fissures occur in children aged between 6 and 24 months, usually as a result of a mechanical tear. If a chronic fissure develops, associated underlying pathologies should be ruled out as in adults. An acute fissure usually heals in 10–14 days with conservative treatment (such as dietary changes). If the fissure persists for 6–8 weeks, medical treatments are usually considered.

Alternative treatment options

Reduction of the increased pressure on the anal sphincter is associated with relief of pain and fissure healing (Samim et al. 2012). Conservative treatments include softening stools through laxatives or a high-fibre diet, as well as using topical anaesthetics or analgesics (Cross et al. 2008). Surgical lateral sphincterotomy is regarded as the current gold standard treatment and is highly effective, resulting in fissure healing in more than 90% of patients (Nelson et al. 2011 and Samim et al. 2012). However, a significant minority of patients who receive surgery experience incontinence, and some reports have suggested that up to 30% of patients have difficulty controlling flatus and 3–10% have episodes of leakage after surgery (Cross et al. 2008; although other reports suggest substantially lower rates). Consequently, non-surgical options have been sought.

In the UK, 0.4% topical glyceryl trinitrate is the only licensed non-surgical treatment for chronic anal fissure. A Cochrane review found that glyceryl trinitrate was marginally, but statistically significantly, better than placebo in healing anal fissure (48.9% compared with 35.5% respectively, $p<0.0009$; most RCTs were in adults), but late recurrence of fissure was common, occurring in about 50% of people whose fissures were initially cured.

The summary of product characteristics for Rectogesic 4 mg/g rectal ointment states headache is very commonly reported by people using 0.4% glyceryl trinitrate. Although this can be treated with analgesics such as paracetamol, headaches may be severe (frequency 1 in 5 people) and cause people to discontinue treatment. Dizziness is also commonly reported (frequency greater than 1 in 100, but less than 1 in 10).

Non-surgical treatments other than topical glyceryl trinitrate include botulinum toxin injection and topical diltiazem (Nelson et al. 2012). The evidence for unlicensed 2% topical diltiazem hydrochloride is discussed in detail in the evidence summary Chronic anal fissure: 2% topical diltiazem hydrochloride.

Children with anal fissure are treated conservatively initially. If this fails, the Association of

Coloproctology of Great Britain and Ireland has suggested trying local glyceryl trinitrate or calcium channel blockers. Surgery is rarely indicated for children, although the surgical technique is the same as for adults.

Evidence review: efficacy

Cochrane systematic review: glyceryl trinitrate compared with placebo

A Cochrane systematic review (assessed as up-to-date September 2011) of non-surgical therapy for anal fissure concluded that glyceryl trinitrate (pooled strengths, range unclear) was found to be marginally, but statistically significantly, better than placebo in healing chronic anal fissure (48.9% compared with 35.5%, $p<0.0009$) but late recurrence was common, occurring in approximately 50% of people whose fissures were initially cured. This was based on the pooled results from 18 randomised controlled trials (RCTs; 1315 patients), of which 4 included only children (165 children); all studies only looked at chronic anal fissure. In children, the statistically significant benefit of glyceryl trinitrate was lost when a study with an abnormally low placebo response was excluded.

Cochrane systematic review: glyceryl trinitrate strength comparisons

The Cochrane review identified 4 RCTs and pooled the results to compare 'high' with 'low' strength topical glyceryl trinitrate ointment to treat chronic anal fissure in adults and children (n=324). High or low cut-offs were not defined in the review but glyceryl trinitrate ointment strength from individual trials included in the meta-analysis ranged from 0.05% to 0.6%. It found no statistically significant difference for fissure healing (pooled odds ratio (OR) favoured low-strength glyceryl trinitrate compared with high strength: OR 0.91, 95% CI 0.57 to 1.45).

Importantly, this finding does not represent a direct 0.2% with 0.4% glyceryl trinitrate comparison. Also, no pooled estimate of effect was reported for pain reduction or adverse events due to headaches. Similarly, the meta-analysis included pooled results from a study in children (which used 0.05% and 0.1% glyceryl trinitrate strengths) and adults (range 0.1% to 0.6% glyceryl trinitrate), which may have confused the individual glyceryl trinitrate

strength response relationships in these distinct groups.

The 4 studies underlying the Cochrane review are summarised below.

Randomised controlled trial by Scholefield et al. (2003)

Scholefield et al. (2003) conducted a parallel group, double-blind, multicentre RCT in 200 adults (mean age 43 years, standard deviation 13 years) with chronic anal fissure (duration of symptoms lasting more than 6 weeks). Participants applied placebo, 0.1%, 0.2% or 0.4% glyceryl trinitrate ointment (1 cm to a site just inside the anus at the junction of the perianal skin and the anal canal) twice daily at approximately 12-hour intervals for 8 weeks. All patients were also instructed to follow a high-fibre diet as well as being given advice on perianal hygiene.

The primary outcome was complete fissure healing at 8 weeks assessed by visual inspection and measurement of the length and width of the fissure. Secondary outcomes included pain intensity on defecation and pain intensity overall, both assessed by a visual analogue score. Maximal anal resting pressure was also recorded in a subset of 38 patients at 1 centre. Patients were withdrawn after 4 weeks if there was a clear lack of efficacy or a complete resolution of symptoms.

The intention-to-treat analysis included 181 patients who had used some of the study medication and were assessed for healing at the end of the study. It did not compare healing outcomes between the different glyceryl trinitrate strengths, only against placebo.

The analysis reported healing rates at 8 weeks of 37.5% (18/48) using placebo, 46.9% (23/49) using 0.1% glyceryl trinitrate ointment, 40.4% (19/47) using 0.2% glyceryl trinitrate ointment, and 54.1% (20/37) using 0.4% glyceryl trinitrate ointment. Each glyceryl trinitrate ointment strength was not statistically significantly different from placebo, which was also the case for all glyceryl trinitrate strengths combined (individual p values for each glyceryl trinitrate strength compared with placebo not given, global test for trend of all glyceryl trinitrate strengths compared with placebo p=0.4).

The differences between pain scores from baseline to 2, 4, 6 and 8 weeks (for pain on defecation and overall pain scores) were not statistically significantly different for each glyceryl trinitrate strength compared with placebo (figures not reported). Reduction in anal

pressure at 8 weeks appeared to increase with increased strength of glyceryl trinitrate. However, this relationship was not statistically significant (pooled glyceryl trinitrate groups compared with placebo p=0.77).

Because of the high healing rates in the placebo arm of the trial (37.5%, 18/48), the authors suspected their study population was a mix of acute (more likely to heal spontaneously) and chronic fissure. A secondary analysis restricted results to patients showing 2 or more recognised features of chronicity (sentinel skin tag, hypertrophied anal papillae, exposed internal anal sphincter, fibrotic lateral fissure or fibrotic anal sphincter). This reduced the intention-to-treat sample from 181 to 145, and found statistically significantly higher healing rates for 0.1% glyceryl trinitrate ointment (50.0%, 21/42 p=0.05) and 0.4% glyceryl trinitrate ointment (56.7%, 17/30 p=0.03) compared with placebo (24.3%, 9/37) and for the effect of the trend of all glyceryl trinitrate groups combined compared with placebo (p=0.03). Interestingly, the 0.2% glyceryl trinitrate group was the only strength in this sub-analysis that did not show a statistically significant difference from placebo (36.1%, 13/36 p=0.91). It is important to note, however, that the numbers of participants in each group were small.

In summary, under restricted criteria for fissure chronicity, albeit only assessed in 145 patients, the combined glyceryl trinitrate groups (0.1%, 0.2% and 0.4%) achieved 47% healing rates at 8 weeks, which was statistically significantly better than placebo (p=0.03). However, on its own, the 0.2% glyceryl trinitrate strength was not found to be statistically significantly better than placebo and noticeably bucked the apparent dose-response trend.

Randomised controlled trial by Bailey et al. (2002)

Bailey et al. (2002) conducted a parallel group, double-blind, multicentre RCT in 304 adults (mean age 42 years, range 19 to 81 years) with chronic anal fissure (fissure symptoms for more than 30 days). Participants were randomised to apply placebo, 0.1%, 0.2% or 0.4% glyceryl trinitrate ointment to the distal anal canal and anus twice daily or 3 times daily for up to 8 weeks using a strength measuring device to standardise the delivery of 374 mg of ointment.

Fissure symptom duration at enrolment ranged from 4 weeks to 2 years but was balanced between groups. Overall, 20.7% (63/304) dropped out of the study before 8 weeks but this did not differ significantly between trial groups (p=0.25).

The statistical analysis did not directly compare the healing outcomes between the glyceryl trinitrate groups, only with placebo. The patient numbers in each trial arm were not reported. The intention-to-treat analysis showed no significant difference in fissure healing at 8 weeks between glyceryl trinitrate groups combined compared with placebo (p value not significant), or when individual glyceryl trinitrate ointment strengths (0.1%, 0.2% or 0.4%) were compared with placebo. Similarly, no significant difference was found between twice-daily and 3-times daily administration of the ointment (p value not significant). For the twice-daily dosage schedule, fissure healing was reported in 50% of people on placebo compared with 31%, 26% and 39% of people using the 0.1%, 0.2% and 0.4% glyceryl trinitrate ointment strengths respectively. The placebo healing rate was markedly high.

Additional outcomes including decrease in pain intensity, worst pain, pain at defecation and frequency of headache were reported for pooled 0.4% glyceryl trinitrate strength only (twice daily and 3 times daily pooled).

Randomised controlled trial by Carapeti et al. (1999)

Carapeti et al. (1999) conducted a small double-blind RCT that included 70 adults (median age 35 to 36 years, range 21 to 81 years across all groups) with chronic anal fissure (3 months or longer with features of chronicity, such as fibrosis of the base of the ulcer or an associated sentinel pile). Participants were randomised to receive 8 weeks of treatment with placebo, 0.2% glyceryl trinitrate ointment 3 times daily, or 0.2% glyceryl trinitrate ointment 3 times daily with weekly 0.1% increments to a maximum 0.6%. This was applied to the skin of the anal verge around the anal opening.

Fissure healing was assessed by clinical examination, anal manometry and laser Doppler flowmetry. If healing occurred in the 8-week treatment period, the patients were followed up at 3, 6 and 12 months, or sooner if recurrent symptoms developed. The study did attempt to statistically compare the 2 glyceryl trinitrate strengths for selected secondary outcomes. However, the study may not have been statistically powered to detect anything but large differences between strengths. Moderate to small differences may have been missed.

After 10 weeks (8 weeks treatment plus 2 weeks after), the primary outcome of healing of the fissure, was reported in 32% (7/22) of patients using placebo; 65% (15/23) using 0.2% glyceryl trinitrate ointment and 70% (16/23) using an escalating strength of glyceryl trinitrate ointment (p=0.008 placebo compared with combined glyceryl trinitrate healing

rate). No statistical test compared 0.2% glyceryl trinitrate with the escalating strength for healing of fissure at 8 weeks (the primary outcome). Median time to healing was 8 weeks (range 4 to 10 weeks). A higher proportion of fissures had healed after 6 weeks treatment in the escalating glyceryl trinitrate group (39%, 9/23) compared with the 0.2% glyceryl trinitrate group (22%, 5/23) but this was not statistically significant (p=0.33). There was no statistically significant difference in mean pain score between the 2 glyceryl trinitrate groups from baseline to 8 weeks (p=0.7). In addition, although statistically significant reductions from the pre-treatment pain score were reported in each glyceryl trinitrate group (both p<0.0001), the average pain score after glyceryl trinitrate (combined) did not differ from placebo (p=0.4). Similarly, no significant difference was found for anodermal blood flow between the 2 glyceryl trinitrate groups (p=0.2), or when the combined average of the 2 glyceryl trinitrate groups was compared with placebo (p=0.5).

There was a reduction in maximal anal sphincter resting pressure from pre-treatment to 8 weeks for all 3 treatment groups (results displayed graphically). However, no significant differences were reported between the 2 glyceryl trinitrate strengths (p=0.7%).

No significant difference was found for recurrence of anal fissure after initial healing during a median follow-up period of 9 months (range 6 to 14 months) for the 2 glyceryl trinitrate groups (p=0.7). A total of 33% (5/15) of fissures recurred in the 0.2% glyceryl trinitrate group compared with 25% (4/16) in the escalating strength group. Recurrence for placebo was 43% (3/7); no p value was reported.

Pilot randomised controlled trial by Simpson et al. (2003)

Simpson et al. (2003) conducted a pilot double-blind RCT in only 15 children (median ages 4.5 and 7 years, range 3 to 13 years for both trial arms) with chronic anal fissure (visible presence of fissure, evidence of fibrosis at the base and persistence of symptoms for more than 3 months). The children were randomised to receive 0.05% (n=7) or 0.1% (n=8) glyceryl trinitrate ointment twice daily, applied to the distal end of the anal canal for 8 weeks. Their parents were shown how to apply the ointment correctly.

The researchers stated they used lower strengths of ointment (0.05% and 0.1%) to minimise the risk of headache in children because a high incidence of headache had been reported in adults using 0.2% glyceryl trinitrate ointment. Most children were taking laxatives at study enrolment (13/15); this medication was not altered.

At 8 weeks, the fissures of all 7 children using 0.05% glyceryl trinitrate ointment, and of 5 out of 8 children using 0.1% glyceryl trinitrate ointment, had healed and 'symptoms had settled' (no significant difference, no p value reported). The fissures in 2 of the 3 children whose fissures had not healed using 0.1% ointment healed after a second 8-week treatment; the fissure in 1 child had not healed at 16 weeks, but became asymptomatic with no evidence of fissure at 1-year follow-up. This child was receiving chemotherapy for leukaemia at enrolment. No fissure recurrence was found in the remaining 14 children followed up for a median 4.5 months (range 2 to 12 months).

Evidence review: safety

The main adverse effect related to glyceryl trinitrate use is headache. Of particular relevance to patient care is where headache is of such severity that it leads to treatment discontinuation (Nelson et al. 2012). The combined risk of headaches using glyceryl trinitrate in the Cochrane review was 30%, which covered all strengths and comparisons with other treatments included in the review. However, the effect of glyceryl trinitrate strength on headache was not assessed in the Cochrane review. See the evidence summary Chronic anal fissure: 2% topical diltiazem hydrochloride for a discussion of randomised controlled trials (RCTs) comparing glyceryl trinitrate with unlicensed 2% topical diltiazem hydrochloride on headache.

It is important to note that, whilst each of the following RCTs attempted to standardise the dose of glyceryl trinitrate (that is, the amount of ointment applied), this was not the same in each RCT. It is not known whether applying less ointment of the same strength, rather than reducing the strength of ointment applied, might have an effect on the incidence or headache.

Randomised controlled trial by Scholefield et al. (2003)

Frequency of headache and frequency of severe headache appeared to be related to glyceryl trinitrate ointment strength in the Scholefield et al. (2003) trial. From the intention-to-treat data, headaches were reported in 12.5% (6/48) of patients using placebo, 18.3% (9/49) using 0.1% glyceryl trinitrate ointment, 36.1% (17/47) using 0.2% glyceryl trinitrate ointment, and 67.5% (25/37) using 0.4% glyceryl trinitrate ointment for 8 weeks. This increase in the frequency of reported headaches with increasing glyceryl trinitrate strength was statistically significant (p value for trend less than 0.01).

The frequency of severe headaches showed a less clear pattern at a rate of 4.2% (2/48) with placebo, 2.0% (1/49) with 0.1% glyceryl trinitrate ointment; 6.4% (3/47) with 0.2% glyceryl trinitrate ointment, and 24.3% (9/37) with 0.4% glyceryl trinitrate ointment (no statistical test for trend reported). Headache was the only adverse event reported in the study; however, the authors commented that no other side effects were correlated with glyceryl trinitrate strength.

Randomised controlled trial by Bailey et al. (2002)

Bailey et al. (2002) pooled the results of twice and 3 times daily use of glyceryl trinitrate ointment and reported only the headache results associated with the 0.4% ointment. This showed that 3.3% of patients discontinued treatment because of headache (no patient numbers reported).

Randomised controlled trial by Carapeti et al. (1999)

In the trial by Carapeti et al. (1999), there was no statistically significant difference (p=0.5) in the number of patients reporting headaches in the 0.2% glyceryl trinitrate ointment group (65%, 15/23) compared with the escalating strength (0.2% up to 0.6% ointment) group (78%, 18/23). None of the patients in the study reported permanent loss of flatus or faecal continence, although 13% (6/46) using glyceryl trinitrate ointment (0.2% and escalating strength group combined) noted some temporary loss of flatus control while using the treatment.

Pilot randomised controlled trial by Simpson et al. (2003)

Out of 15 children, 2 experienced headache in the first few days of the trial by Simpson et al. (2003) (1 in each of the 0.05% and 0.1% glyceryl trinitrate ointment trial arms). These were short-lived (less than 20 minutes), resolved spontaneously and did not affect treatment adherence.

Evidence review: economic issues

Cost effectiveness

No studies were identified that compared the cost effectiveness of 0.2% glyceryl trinitrate ointment with 0.4% glyceryl trinitrate ointment for treating chronic anal fissure in adults or children.

Cost

The NHS electronic drug tariff (March 2013) lists 0.2% glyceryl trinitrate ointment under 'arrangements for payment for specials and imported unlicensed medicines'. The price quoted is £57.75 for the minimum 30 g volume and an extra £1.62 for every extra gram above 30 g. The price listed for Rectogesic (glyceryl trinitrate 0.4%, 4 mg/g rectal ointment, ProStrakan) is 46% lower at £34.80 for 30 g.

Current drug usage

Prescription Cost Analysis in England show that over the last year (December 2011 to November 2012) in general practice, 0.4% glyceryl trinitrate ointment (both Rectogesic and generic prescriptions) accounted for 98% (85,176) of the total prescription items for glyceryl trinitrate ointment dispensed for anal fissures (86,852) and for 96% (approximately £3.1 million) of the total cost (approximately £3.2 million). By contrast, 0.2% glyceryl trinitrate ointment accounted for just 1.8% (1,547) of total glyceryl trinitrate ointment items and 3.4% of the cost (approximately £100,000) in the same period (Personal communication. NHS Business Services Authority February 2013).

The remaining strengths of glyceryl trinitrate ointment that may have been prescribed for managing anal fissure (0.02%, 0.05% and 0.1% glyceryl trinitrate ointments) accounted for only about 0.2% of the total items dispensed and 0.6% of the cost (approximately £20,000).

Among the special order products prescribed in primary care in England in the quarter from July to September 2012, glyceryl trinitrate 0.2% ointment is listed as 95th by number of items (353) and 241st by net ingredient cost (£22,312).

Evidence strengths and limitations

The quality and relevance of the evidence comparing the efficacy and safety of 0.2% glyceryl trinitrate ointment to 0.4% glyceryl trinitrate ointment is very limited for the following reasons:

- No trials were identified that were specifically designed to detect statistical differences between the 0.2% and 0.4% glyceryl trinitrate ointments, such as a randomised controlled trial (RCT) appropriately powered to detect between-group differences or a non-inferiority trial.
- The 3 RCTs that recruited adults, and the 1 pilot RCT that recruited children, were not statistically powered to detect differences in glyceryl trinitrate strength. This means that clinically significant differences in strength-related efficacy and headache side effects may have been missed.
- The 3 RCTs that recruited adults were small. In 2 of the trials, 47 (Scholefield et al. 2003) and 23 patients (Carapeti et al. 1999) were in the 0.2% glyceryl trinitrate arms; however, patient numbers were not reported in the third trial (Bailey et al. 2002). The pilot RCT (Simpson et al. 2003) was even smaller (n=15, all participants).
- The duration of follow-up in the adult studies (8 to 10 weeks) was very short. This is a major limitation as fissures can heal and relapse over various time frames. This is demonstrated in Scholefield et al. (2003), in which the fissures of 37.5% of patients who were given placebo showed healing at 8 weeks. Because of the short-term follow-up, the efficacy estimates do not take into account relapse rates after 8 weeks.
- The only trial (Carapeti et al. 1999) that performed statistical tests comparing glyceryl trinitrate strengths did not compare 0.2% ointment with 0.4% ointment. It compared 0.2% ointment against 0.2% ointment with weekly 0.1% increments to a maximum 0.6%, a non-standard treatment regimen. Non-significant findings between glyceryl trinitrate strengths in this study may be because of a lack of statistical power to detect such differences.
- Assessment of safety and adverse events was generally restricted to the 8-week treatment period.
- The trials used different definitions of chronic anal fissure. Results from Scholefield et al. (2003) indicated that healing rates were influenced by the definition of anal fissure chronicity used.

- Only 1 of the 4 RCTs explicitly described that treatment allocation had been concealed (Carapeti et al. 1999).

A more general limitation to consider is that the method of applying glyceryl trinitrate ointment is imprecise and so, the actual strength of glyceryl trinitrate may vary greatly from patient to patient and application to application, even when using the same strength of ointment. This may confound any association between glyceryl trinitrate strength and fissure healing or between glyceryl trinitrate strength and key side effects such as headache. In addition, it is not known whether applying less ointment of the same strength, rather than reducing the strength of ointment applied, might have an effect on the incidence or headache.

Summary for patients

A summary written for patients is available on the NICE website.

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Development of this evidence summary

This evidence summary was developed for NICE by Bazian Ltd. The interim process statement sets out the process NICE uses to select topics for the evidence summaries for unlicensed/off-label medicines and how the summaries are developed, quality assured and

approved for publication.

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Declarations of interest

No relevant interests declared.

Appendix: Search strategy and evidence selection

Search strategy

General background, guidelines and technology assessments:

- NHS Evidence
- NICE
- Euroscan

- Broad internet search: Google e.g.: allintitle: glyceryl trinitrate anal fissure AND filetype:pdf
- Scirus

MEDLINE (via Ovid)

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>

Search Strategy:

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1. (Rectiv or Rectogesic or Glyceryl trinitrate or glyceryltrinitrate).tw. (2121)
2. (Topical adj3 nitroglycerin).tw. (144)
3. (topical adj3 nitric oxide).tw. (31)
4. Nitroglycerin/ (11424)
5. 1 or 2 or 3 or 4 (12141)
6. Fissure in Ano/ (1839)
7. (anal adj3 fissure?).tw. (1224)
8. (ano adj3 fissure?).tw. (163)
9. 6 or 7 or 8 (2183)
10. 5 and 9 (215)
11. limit 10 to english language (193)
12. exp review/ (1773989)
13. (scisearch or psychinfo or psycinfo or medlars or embase or psychlit or psyclit or cinahl or pubmed or medline).ti,ab,sh. (71599)
14. ((hand adj2 search$) or (manual$ adj2 search$)).ti,ab,sh. (6273)

15. ((electronic or bibliographic or computeri?ed or online) adj4 database$).ti,ab. (14011)
16. (pooling or pooled or mantel haenszel).ti,ab,sh. (46325)
17. (peto or dersimonian or der simonian or fixed effect).ti,ab,sh. (2738)
18. or/13-17 (122776)
19. 12 and 18 (55479)
20. Meta Analysis/ (38678)
21. (meta-analys$ or meta analys$ or metaanalys$).ti,ab,sh. (67568)
22. ((systematic$ or quantitativ$ or methodologic$) adj5 (review$ or overview$ or synthesis$)).ti,ab,sh. (53736)
23. (integrative research review$ or research integration).ti,ab,sh. (83)
24. or/20-23 (104679)
25. 19 or 24 (132915)
26. clinical trials, phase iv/ or clinical trials, phase iii/ or randomized controlled trials/ or multicenter studies/ (242591)
27. (random$ or placebo$ or ((singl$ or double$ or triple$ or treble$) and (blind$ or mask$))).ti,ab,sh. (879710)
28. 26 or 27 (977688)
29. (animal$ not human$).sh. (3735670)
30. 28 not 29 (872591)
31. 25 or 30 (955847)
32. 11 and 31 (90)
33. 11 and (cost$ or economic$).tw.

Embase (via Ovid)

Database: Embase <1988 to 2012 December 14>

Search Strategy:

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1. (Rectiv or Rectogesic or Glyceryl trinitrate or glyceryltrinitrate).tw. (2144)
2. (Topical adj3 nitroglycerin).tw. (144)
3. (topical adj3 nitric oxide).tw. (37)
4. glyceryl trinitrate/ (23129)
5. 1 or 2 or 3 or 4 (23459)
6. Fissure in Ano/ (1971)
7. (anal adj3 fissure?).tw. (1407)
8. (ano adj3 fissure?).tw. (121)
9. 6 or 7 or 8 (2145)
10. 5 and 9 (467)
11. limit 10 to english language (401)
12. exp review/ (1727013)
13. (scisearch or psychinfo or psycinfo or medlars or embase or psychlit or psyclit or cinahl or pubmed or medline).ti,ab,sh. (87309)
14. ((hand adj2 search$) or (manual$ adj2 search$)).ti,ab,sh. (7260)
15. ((electronic or bibliographic or computeri?ed or online) adj4 database$).ti,ab. (17583)
16. (pooling or pooled or mantel haenszel).ti,ab,sh. (51618)
17. (peto or dersimonian or der simonian or fixed effect).ti,ab,sh. (3311)

18. or/13-17 (145092)
19. 12 and 18 (56326)
20. Meta Analysis/ (67804)
21. (meta-analys$ or meta analys$ or metaanalys$).ti,ab,sh. (96320)
22. ((systematic$ or quantitativ$ or methodologic$) adj5 (review$ or overview$ or synthesis$)).ti,ab,sh. (90383)
23. (integrative research review$ or research integration).ti,ab,sh. (88)
24. or/20-23 (159220)
25. 19 or 24 (186718)
26. clinical trials, phase iv/ or clinical trials, phase iii/ or randomized controlled trials/ or multicenter studies/ (27736)
27. (random$ or placebo$ or ((singl$ or double$ or triple$ or treble$) and (blind$ or mask$))).ti,ab,sh. (978983)
28. 26 or 27 (981997)
29. (animal$ not human$).sh. (2454674)
30. 28 not 29 (886030)
31. 25 or 30 (1004543)
32. 11 and 31 (161)
33. limit 32 to exclude medline journals (14)
34. 11 and (cost$ or economic$).tw.

Cochrane Central Register of Controlled Trials (CENTRAL)

glyceryl trinitrate and anal fissure*

CRD HTA, DARE and EED database

(anal fissure) AND (glyceryl trinitrate)

Grey literature and ongoing trials

- FDA
- EMA
- MHRA
- Scottish Medicines Consortium
- All Wales Medicine Strategy Group
- metaRegister of Controlled Trials (mRCT)
- ClinicalTrials.gov

Manufacturer's website

ProStrakan

Evidence selection

The rationale for this evidence summary was that 0.2% glyceryl trinitrate rectal ointment is sometimes prescribed in an effort to reduce the frequency or severity of headaches associated with using the 0.4% glyceryl trinitrate licensed option. Therefore, the evidence selection focused on studies containing a potential comparison of 0.2% and 0.4% glyceryl trinitrate strengths in relation to effectiveness and headache outcomes.

Both the literature search and a 2012 Cochrane systematic review of non-surgical therapy for anal fissure identified 4 RCTs that form the main body of evidence for this review.

Other possible comparators including 0.2% glyceryl trinitrate ointment against placebo, botulinum injection or surgery were not reviewed.

About 'Evidence summaries: unlicensed or off-label medicines'

NICE evidence summaries for off-label or unlicensed medicines summarise the published evidence for selected unlicensed or off-label medicines that are considered to be of significance to the NHS, where there are no clinically appropriate licensed alternatives. They support decision-making on the use of an unlicensed or off-label medicine for an individual patient, where there are good clinical reasons for its use, usually when there is no licensed medicine for the condition requiring treatment, or the licensed medicine is not appropriate for that individual.

This document provides a summary of the published evidence. The strengths and weaknesses of the identified evidence are critically reviewed within this summary, but this summary is not NICE guidance and does not provide formal practice recommendations.

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