

# Chronic anal fissure: 2% topical diltiazem hydrochloride

Evidence summary

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## Key points from the evidence

The content of this evidence summary was up-to-date in January 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.

Diltiazem hydrochloride is a calcium channel blocker and vasodilator. It increases blood flow to smooth muscles and relaxes muscle tone. Oral preparations of diltiazem hydrochloride are licensed in the UK to treat angina and hypertension.

Topical diltiazem hydrochloride is not licensed in the UK for treating chronic anal fissure or any other indication. Therefore, its use for treating chronic anal fissure is unlicensed.

An alternative topical treatment, 0.4% glyceryl trinitrate (Rectogesic 4 mg/g rectal ointment, ProStrakan), is licensed in the UK for the relief of pain associated with chronic anal fissure in adults. However, it is associated with a high frequency of headaches which can be severe and cause people to stop treatment.

One Cochrane systematic review (4 RCTs; assessed as up-to-date November 2011) and 5 additional RCTs (neither considered by nor excluded from the Cochrane review) provide the evidence for this summary. The Cochrane review and 2 additional RCTs found that the efficacy of 2% topical diltiazem hydrochloride was not statistically significantly different from topical glyceryl trinitrate in adults, but limited evidence indicates a reduced frequency of headaches. An additional RCT found that the efficacy of 2% topical diltiazem hydrochloride was not statistically significantly different from botulinum toxin injection. Two additional RCTs suggest that topical diltiazem was less effective than surgical sphincterotomy, but statistical analysis was not performed. An additional small RCT in children aged 0–12 years found that 2% topical diltiazem hydrochloride was more effective than 0.2% topical glyceryl trinitrate. Fissure healing and recurrence rate estimates from the studies varied widely because of variation in the study methodologies, populations, and follow-up.

Mild headache, perianal itching and perianal dermatitis have been reported with the use of 2% topical diltiazem hydrochloride.

The NHS price for 2% diltiazem cream is £73.83 per 30 g tube and the NHS price for 2% diltiazem ointment is £163.07 per 30 g tube. The licensed topical glyceryl trinitrate product, Rectogesic 4 mg/g rectal ointment, costs £34.80 per 30 g tube (costs exclude VAT and are taken from the [Drug Tariff](#), February 2013).

An application for a marketing authorisation (product licence) for 4% diltiazem hydrochloride cream for use in chronic anal fissure is in the process of submission by S.L.A. Pharma (UK) Ltd but this product is not expected to come to market until the last quarter of 2013/14 at the earliest.

### 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

Diltiazem hydrochloride is a calcium channel blocker and vasodilator. It is licensed in the UK for oral use to treat angina and hypertension.

## Regulatory status of topical diltiazem hydrochloride

Topical diltiazem hydrochloride is not currently licensed in the UK for treating chronic anal fissure (or for treating any other condition or patient group), 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 diltiazem outside its authorised indications.

An alternative topical treatment, 0.4% glyceryl trinitrate, is licensed in the UK for the relief of pain associated with chronic anal fissure in adults (Rectogesic 4 mg/g rectal ointment, ProStrakan). It is not recommended for use in children and young people under 18 years because of a lack of data on safety and efficacy<sup>[1]</sup>. Headache is very commonly reported by people using 0.4% topical 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)<sup>[1]</sup>.

An application for a marketing authorisation (product licence) for 4% diltiazem cream for use in chronic anal fissure is in the process of submission by S.L.A. Pharma (UK) Ltd but this product is not expected to come to market until quarter 4 of 2013/14 at the earliest<sup>[2]</sup>.

## Evidence statements

One Cochrane systematic review (4 RCTs; assessed as up-to-date November 2011) and 5 additional RCTs (neither considered by nor excluded from the Cochrane review) provided the evidence for this summary. The studies reviewed described using either 2% topical diltiazem hydrochloride cream or ointment. For summary purposes below, both formulations are referred to as 2% topical diltiazem. They are described separately in the [Evidence review: efficacy](#) section.

- Evidence from a Cochrane review of 4 RCTs and 2 additional RCTs found that 2% topical diltiazem had similar efficacy to topical glyceryl trinitrate in adults. One additional small RCT in children aged 0–12 years found that 2% topical diltiazem hydrochloride was more effective than 0.2% topical glyceryl trinitrate.
- Only 1 small study included in the Cochrane review compared topical diltiazem with no treatment (in which diltiazem was superior).
- 2% topical diltiazem has also been compared with injection of botulinum toxin (1 study: no significant difference in healing rates) and surgery (2 studies: numerically inferior healing rates with 2% topical diltiazem but statistical analysis not performed).
- Rates of complete fissure healing associated with 2% topical diltiazem from the 5 RCTs additional to the Cochrane review varied from 43.0% to 92.9%. These studies varied in their methodologies, populations, and follow-up.
- Limited evidence suggests that use of 2% topical diltiazem is associated with a lower risk headache than topical glyceryl trinitrate. Mild headache, perianal itching and perianal dermatitis have been reported with the use of 2% topical diltiazem.
- No other significant short term safety issues or side effects were reported as being associated with 2% topical diltiazem (use for 3 months or less), including in the single trial conducted in children. Longer term use was not assessed.

## 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.

One Cochrane systematic review (4 RCTs; assessed as up-to-date November 2011) and 5 additional RCTs (neither considered by nor excluded from the Cochrane review) provided the evidence for this summary. The key outcomes of complete fissure healing and headache from the 5 RCTs not included in the Cochrane systematic review are summarised in table 1.

### Efficacy

The Cochrane review ([Nelson et al. 2012](#); assessed as up-to-date November 2011) included 4 RCTs that compared 2% topical diltiazem with topical glyceryl trinitrate. Studies lasted 6–8 weeks and used 0.2% glyceryl trinitrate (3 studies, n=200 participants receiving active treatment) or 0.5% glyceryl trinitrate (1 study, n=43). All 4 studies found no statistically significant difference in healing rates between the 2 treatments<sup>[3]</sup>. One of the 4 RCTs included in the Cochrane review ([Shrivastava et al. 2007](#)) also included a no-treatment group (n=30). The healing rate in the diltiazem group was statistically significantly superior to that in the no-treatment group (80% compared with 33% respectively,  $p=0.014$ )<sup>[4]</sup>.

None of the 5 RCTs additional to the Cochrane review compared 2% topical diltiazem with no treatment or placebo; comparisons were made with topical glyceryl trinitrate, topical lidocaine, botulinum toxin or surgical sphincterotomy. Of these 5 trials, 1 recruited children (mean age 32 months, range 2–144 months).

Rates of complete fissure healing associated with 2% topical diltiazem from the 5 RCTs additional to the Cochrane review varied from 43.0% to 92.9%. Recurrence rates ranged from 10.4% to 65.0%. Such widespread variation may be due in part to the differences in study methods, including length of treatment, concurrent treatments (such as a high-fibre diet), time period to assess healing, healing criteria, and follow-up time to assess recurrence.

The Cochrane review found that glyceryl trinitrate was statistically significantly better than placebo in healing anal fissure (48.9% compared with 35.5% respectively,  $p<0.0009$ ). It reported that late recurrence of fissure was common, in the range of 50% of those initially

cured<sup>[3]</sup>.**Table 1 Summary of the 5 RCTs additional to the Cochrane review**

Study	Fissure healing rate		Analysis	Rate of headache		Analysis
	Diltiazem	Comparator		Diltiazem	Comparator	
<u>Sanei et al. 2009<sup>a</sup></u> (n=102)	66.7% (after 12 weeks treatment)	GTN: 54.9%	p=0.2	0	GTN: 58.8%	p=0.001
<u>Abd Elhady et al. 2009<sup>b</sup></u> (n=160)	80.0% (at 8 weeks, after 4–6 weeks treatment)	GTN: 90% Surg: 95% Bot: not reported	Not reported	5%	GTN: 15%	Not reported
<u>Samim et al. 2012<sup>c</sup></u> (n=134)	43.0% (after 12 weeks treatment)	Bot: 43%	p=0.992	0	0	—
<u>Suvarna et al. 2012<sup>d</sup></u> (n=200)	69.2% (after 6 weeks treatment)	Surg: 95.9%	Not reported	5.5%	0	p<0.0001
<u>Cevik et al. 2012<sup>e</sup></u> (n=93, children aged 0–12 years)	82.1% (8 weeks treatment)	GTN: 39.3%	p<0.001	Not assessed	Not assessed	—
	92.9% (16 weeks treatment)	GTN: 82.1%	p<0.05	Not assessed	Not assessed	—

All studies were in adults unless otherwise indicated.

Abbreviations: Bot, botulinum toxin; GTN, 0.2% topical glyceryl nitrate; n, number of study participants; Surg, surgical sphincterotomy.

<sup>a</sup> Sanei B, Mahmoodieh M, Masoudpour H (2009) Comparison of topical glyceryl trinitrate with diltiazem ointment for the treatment of chronic anal fissure: a randomized clinical trial. Acta Chirurgica Belgica 109: 727–30

<sup>b</sup> Abd Elhady HM, Othman IH, Hablus MA et al. (2009) Long-term prospective randomised clinical and manometric comparison between surgical and chemical sphincterotomy for treatment of chronic anal fissure. South African Journal of Surgery 47: 112–4

<sup>c</sup> Samim M, Twigt B, Stoker L et al. (2012) Topical diltiazem cream versus botulinum toxin a for the treatment of chronic anal fissure: a double-blind randomized clinical trial. Annals of Surgery 255: 18–22

<sup>d</sup> Suvarna R, Panchami, Guruprasad RD (2012) Chemical sphincterotomy versus surgical sphincterotomy in the management of chronic fissure in ANO: A prospective, randomized trial. Journal of Clinical and Diagnostic Research 6: 1018–21

<sup>e</sup> Cevik M, Boleken ME, Koruk I et al. (2012) A prospective, randomized, double-blind study comparing the efficacy of diltiazem, glyceryl trinitrate, and lidocaine for the treatment of anal fissure in children. Pediatric Surgery International 28: 411–6

## Safety

Limited evidence suggests that 2% topical diltiazem is associated with a much lower risk of severe headache than topical glyceryl trinitrate. Mild headache, perianal itching and perianal dermatitis have been reported with the use of 2% topical diltiazem.

## Cost effectiveness and cost

No studies on cost effectiveness were identified. The NHS price for 2% diltiazem cream is £73.83 per 30 g tube and the NHS price for 2% diltiazem ointment is £163.07 per 30 g tube. The licensed topical glyceryl trinitrate product, Rectogesic 4 mg/g rectal ointment, costs £34.80 per 30 g tube (costs exclude VAT and are taken from the [Drug Tariff](#), February 2013).

In the most recent quarter for which data are available (July to September 2012), there were 5076 prescriptions for 2% diltiazem hydrochloride cream in primary care in England at

a net ingredient cost of £592,505 (a mean of £116.73 per prescription). Among all the special order products prescribed in primary care in England that quarter, 2% diltiazem hydrochloride cream ranked 6<sup>th</sup> by number of prescription items and 8<sup>th</sup> by net ingredient cost<sup>[5]</sup>.

<sup>[1]</sup> ProStrakan (2012) [Rectogesic 4 mg/g rectal ointment summary of product characteristics](#)

<sup>[2]</sup> SLA Pharma (UK) Ltd: personal communication November 2012

<sup>[3]</sup> Nelson RL, Thomas K, Morgan J et al. (2012) [Non surgical therapy for anal fissure](#). Cochrane Database of Systematic Reviews issue 2: CD003431

<sup>[4]</sup> Shrivastava UK, Jain BK, Kumar P et al. (2007) [A comparison of the effects of diltiazem and glyceryl trinitrate ointment in the treatment of chronic anal fissure: a randomized clinical trial](#). Surgery Today 37:482–5

<sup>[5]</sup> NHS Business Services Authority. (2012) [Volume and cost of special order products](#)

## Relevance to NICE guidance programmes

Topical diltiazem hydrochloride has not been assessed as part of a NICE technology appraisal work programme and is not currently listed as a proposed technology appraisal or an appraisal in development.

[Constipation in children and young people](#) (NICE clinical guideline 99) identifies anal fissure as a possible finding in children with constipation but does not discuss its treatment specifically.

## Interventions and alternatives

Diltiazem hydrochloride is a calcium channel blocker and potent vasodilator. It increases blood flow to smooth muscles and relaxes muscle tone.



## Condition

Anal fissure is a common and painful problem that involves a tear or ulcer in the squamous epithelium of the anus, usually located in the posterior midline. Anal fissure typically causes perianal itching and bleeding, and pain during defecation and for 1–2 hours afterwards<sup>[6],[7]</sup>. The most common cause of anal fissure is passing particularly hard stools, leading to trauma. Other causes include inflammatory bowel disease, childbirth and sexually transmitted infection<sup>[8]</sup>. Although the aetiology of chronic anal fissure is uncertain, it is assumed that pain causes an increased sphincter pressure leading to ischaemia of the anal sphincter. This inhibits fissure healing, generating a vicious circle of pain, constipation and prolonging of the healing process<sup>[7]</sup>.

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<sup>[6]</sup>. Duration of symptoms was not uniform in the RCTs in adults considered in this evidence summary. In the study of 2% topical diltiazem in children considered in this evidence summary, an inclusion criterion was a history of anal fissure lasting more than 15 days<sup>[9]</sup>.

## Alternative treatment options

Reduction of the increased pressure on the anal sphincter is associated with relief of pain and fissure healing<sup>[7]</sup>. Conservative treatments include softening stools through laxatives or a high-fibre diet, as well as using topical anaesthetics or analgesics<sup>[8]</sup>. 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<sup>[10],[7]</sup>. 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<sup>[8]</sup> (although other reports suggest substantially lower rates<sup>[10]</sup>). 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 statistically significantly, better than placebo in healing anal fissure (48.9% compared with 35.5% respectively,  $p < 0.0009$ ), but late recurrence of fissure was common, in the range of 50% of those initially cured<sup>[6]</sup>. Headache is very commonly reported by people using topical glyceryl trinitrate 0.4%. 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)<sup>[11]</sup>.

Non-surgical treatments other than topical diltiazem include botulinum toxin injection. However, a Cochrane review found that healing of anal fissure was more likely with sphincterotomy than with botulinum toxin (89.3% compared with 59.0% respectively)<sup>[6]</sup>.

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<sup>[6]</sup> Nelson RL, Thomas K, Morgan J et al. (2012) Non surgical therapy for anal fissure. Cochrane Database of Systematic Reviews issue 2: CD003431

<sup>[7]</sup> Samim M, Twigt B, Stoker L et al. (2012) Topical diltiazem cream versus botulinum toxin a for the treatment of chronic anal fissure: a double-blind randomized clinical trial. Annals of Surgery 255: 18–22

<sup>[8]</sup> Cross KLR, Massey EJD, Fowler AL et al. (2008) The Management of Anal Fissure: ACPGBI Position Statement. Colorectal Disease 10 (Suppl. 3): 1–7

<sup>[9]</sup> Cevik M, Boleken ME, Koruk I et al. (2012) A prospective, randomized, double-blind study comparing the efficacy of diltiazem, glyceryl trinitrate, and lidocaine for the treatment of anal fissure in children. Pediatric Surgery International 28: 411–6

<sup>[10]</sup> Nelson RL, Chattopadhyay A, Brooks W et al. (2011) Operative procedures for fissure in ano. Cochrane Database of Systematic Reviews issue 11: CD002199

<sup>[11]</sup> ProStrakan (2012) Rectogesic 4 mg/g rectal ointment summary of product characteristics

## Evidence review: efficacy

One Cochrane systematic review (4 RCTs; assessed as up-to-date November 2011) and 5 additional RCTs (neither considered by nor excluded from the Cochrane review) provided the evidence for this summary.

## Cochrane review

The Cochrane review (Nelson et al. 2012, assessed as up-to-date November 2011)

identified 4 RCTs that compared 2% topical diltiazem with glyceryl trinitrate for anal fissure. Studies lasted 6–8 weeks and used 0.2% glyceryl trinitrate (3 studies, n=200 participants receiving active treatment) or 0.5% glyceryl trinitrate (1 study, n=43)<sup>[12]</sup>.

In 1 of the RCTs included in the Cochrane review ([Shrivastava et al. 2007](#)), participants (n=90, mean age 36 years, range 18–58 years) were randomised in equal numbers to 2% diltiazem ointment, 0.2% glyceryl trinitrate ointment or no treatment. Participants also received a high-fibre diet. The time point at which healing was assessed is not clear from the published study, but patients in whom there was no improvement after 6 weeks were offered surgery. Allocation methods and blinding were not discussed<sup>[13]</sup>.

The rate of complete healing in the topical diltiazem group (80%) was statistically significantly higher than in the no-treatment group (33%,  $p=0.014$ ), but not statistically significantly different from the glyceryl trinitrate group (73%,  $p=0.303$ ). Recurrence of fissure was statistically significantly lower in the diltiazem group (12.5%) compared with the no-treatment group (50%,  $p=0.012$ ), but not statistically significantly different from the glyceryl trinitrate group (32%,  $p=0.303$ )<sup>[13]</sup>. The 3 other RCTs in the Cochrane review also found no statistically significant difference in healing rates between diltiazem and glyceryl trinitrate<sup>[12]</sup>.

For the purposes of comparison, the Cochrane review found that glyceryl trinitrate was statistically significantly better than placebo in healing anal fissure (48.9% compared with 35.5% respectively,  $p<0.0009$ ), but late recurrence of fissure was common, in the range of 50% of those initially cured<sup>[12]</sup>.

## Randomised controlled trials additional to the Cochrane review

### Sanei et al. 2009

In this RCT, 102 adults (mean age 30 years, range 17–61 years) with symptoms of anal fissure for more than 6 weeks or presence of a sentinel anal tag were randomised in equal numbers to receive 2% topical diltiazem ointment or 0.2% glyceryl trinitrate ointment, both applied twice daily for 12 weeks<sup>[14]</sup>. Participants were not prescribed stool softeners or bulk laxatives. Allocation concealment was not discussed but the study was double blind.

Fissure healing (defined as complete skin closure over the fissure, confirmed by anoscopy)

at 12 weeks occurred in 66.7% of participants in the diltiazem group and in 54.9% of participants in the glyceryl trinitrate group ( $p=0.2$ ). Mean time to complete healing was  $7.58\pm 2.01$  weeks in the diltiazem group and  $4.85\pm 1.84$  weeks in the glyceryl trinitrate group ( $p=0.001$ ). Recurrence rates were not reported.

### **Abd Elhady et al. 2009**

In this RCT 160 adults (mean age 34 years, range 17–70 years) with anal fissure (duration of symptoms not stated) were randomised in equal numbers to 4 treatment groups: internal lateral sphincterotomy, 2% topical diltiazem ointment twice daily for 4–6 weeks, 0.2% glyceryl trinitrate ointment twice daily for 4–6 weeks, or botulinum toxin injection<sup>[15]</sup>. Allocation concealment was not discussed. Participants who were lost to follow-up were excluded and replaced by new participants receiving the same treatment.

Fissure healing was defined as complete re-epithelialisation of the fissure and absence of symptoms. At 8 weeks, 80% of participants receiving diltiazem ointment showed complete healing, compared with 95% who had sphincterotomy surgery and 90% of those receiving glyceryl trinitrate (data for participants receiving botulinum toxin were not reported, statistical significance not reported).

The average time to fissure healing was  $5.1\pm 1.13$  weeks in the diltiazem group and  $5.0\pm 1.1$  weeks in the glyceryl trinitrate group. The time to healing in all groups was similar and not statistically significant ( $p=0.067$ ). Of the 40 participants in each treatment group, recurrence occurred in 26 participants (65%) in the diltiazem group compared with 4 (10%) in the sphincterotomy surgery group, 23 (57.5%) in the glyceryl trinitrate group and 21 (52.5%) in the botulinum toxin group (statistical significance not reported). The average time to recurrence was not reported.

### **Samim et al. 2012**

In this RCT, 134 adults (mean age  $46\pm 16$  years) with anal fissure for more than 4 weeks were randomised to receive either 2% topical diltiazem cream applied twice daily for 3 months combined with placebo injection ( $n=74$ ), or botulinum toxin injection with placebo cream for 3 months ( $n=60$ )<sup>[16]</sup>. Allocation concealment was not discussed. The study was stated to be double blind but although participants were randomised, treatment days were also randomised to botulinum toxin or placebo so that the same vial of botulinum toxin was used for treating 4 people. Analysis was by intention to treat.

Fissure healing was defined as epithelialisation or macroscopic healing after 3 months. Healing rates were the same in both groups (43% in each,  $p=0.992$ ). During a median follow-up time of 39 months, 17.6% of participants randomised to diltiazem cream experienced recurrence of fissure compared with 11.7% of participants randomised to botulinum toxin ( $p=0.469$ ).

### Suvarna et al. 2012

In this RCT, 200 adults (mean age 40 years, range 18–65 years) with anal fissure for more than 8 weeks were randomised in equal numbers to receive 2% topical diltiazem ointment twice daily for 6 weeks or surgical sphincterotomy<sup>[17]</sup>. Allocation concealment was not discussed. Twelve participants dropped out of the study (9 from the diltiazem group and 3 from surgical group) and were not included in the analysis.

Fissure healing (complete disappearance of fissure on examination) was observed by 6 weeks in 69.23% of the diltiazem group compared with 95.87% in the surgery group (statistical significance not reported). Recurrence 2 months after treatment was reported in 6 out of 58 (10.43%) participants in the diltiazem group compared with none of the 89 participants in the surgery group.

### Cevik et al. 2011

In this RCT, 93 children (mean age 32 months, range 2–144 months) with anal fissure for more than 15 days were randomised to receive topical treatment with 2% diltiazem ointment, 0.2% glyceryl trinitrate ointment or 10% lidocaine ointment, applied twice daily for 8 weeks<sup>[18]</sup>. Children with constipation also received lactulose, a sitz bath twice a day, toilet training and dietary regulation. Allocation concealment was not discussed but the study was double blind. If healing had not occurred by 8 weeks, the same 8-week treatment was offered again.

Nine children were lost to follow-up and 2 experienced dermatitis and withdrew from the study (1 in the diltiazem group and 1 in the glyceryl trinitrate group); these 11 children were excluded from the analysis. After the first 8-week treatment course, the healing rate in the diltiazem group was 82.1% (23 out of 28), which was statistically significantly higher than that in the other treatment groups: 39.3% (11 out of 28) in the glyceryl trinitrate group and 25.0% (7 out of 28) in the lidocaine group ( $p<0.0001$ ).

After a repeated 8-week course, the healing rate in the diltiazem group was 92.9%

compared with 82.1% in the glyceryl trinitrate group and 64.3% in the lidocaine group ( $p < 0.05$ ). If the anal fissures had not healed after 2 courses, treatment was switched to topical diltiazem for an additional 8 weeks; all children were symptom-free after this third treatment course. The recurrence rate during 1-year follow-up was 11.1% in the diltiazem group compared with 37.0% in the glyceryl trinitrate group and 57.1% in the lidocaine group (statistical significance not reported).

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<sup>[12]</sup> Nelson RL, Thomas K, Morgan J et al. (2012) Non surgical therapy for anal fissure. Cochrane Database of Systematic Reviews issue 2: CD003431

<sup>[13]</sup> Shrivastava UK, Jain BK, Kumar P et al. (2007) A comparison of the effects of diltiazem and glyceryl trinitrate ointment in the treatment of chronic anal fissure: a randomized clinical trial. Surgery Today 37: 482–5

<sup>[14]</sup> Sanei B, Mahmoodieh M, Masoudpour H (2009) Comparison of topical glyceryl trinitrate with diltiazem ointment for the treatment of chronic anal fissure: a randomized clinical trial. Acta Chirurgica Belgica 109: 727–30

<sup>[15]</sup> Abd Elhady HM, Othman IH, Hablus MA et al. (2009) Long-term prospective randomised clinical and manometric comparison between surgical and chemical sphincterotomy for treatment of chronic anal fissure. South African Journal of Surgery 47: 112–4

<sup>[16]</sup> Samim M, Twigt B, Stoker L et al. (2012) Topical diltiazem cream versus botulinum toxin A for the treatment of chronic anal fissure: a double-blind randomized clinical trial. Annals of Surgery 255: 18–22

<sup>[17]</sup> Suvarna R, Panchami, Guruprasad RD (2012) Chemical sphincterotomy versus surgical sphincterotomy in the management of chronic fissure in ANO: A prospective, randomized trial. Journal of Clinical and Diagnostic Research 6: 1018–21

<sup>[18]</sup> Cevik M, Boleken ME, Koruk I et al. (2012) A prospective, randomized, double-blind study comparing the efficacy of diltiazem, glyceryl trinitrate, and lidocaine for the treatment of anal fissure in children. Pediatric Surgery International 28: 411–6

## Evidence review: safety

Two of the RCTs (n=140) included in the Cochrane review found that glyceryl trinitrate had

significantly more adverse effects than topical diltiazem (details not given, pooled odds ratio [OR] 3.57, 95% confidence interval [CI] 1.28 to 9.97)<sup>[19]</sup>. In a third study (Shrivastava et al. 2007), none of the 30 participants randomised to topical diltiazem ointment reported side effects, whereas 20 (67%) participants randomised to the glyceryl trinitrate reported headache<sup>[20]</sup>.

In 1 of the additional RCTs (Sanei et al. 2009), headache occurred in 58.8% of participants randomised to glyceryl trinitrate and none in those randomised to diltiazem ( $p=0.001$ )<sup>[21]</sup>. Of the 51 participants randomised to glyceryl trinitrate, 14 (27.5%) discontinued treatment because of headache and elected to receive surgery. Two participants (3.9%) randomised to diltiazem reported pruritus but none of those randomised to glyceryl trinitrate reported this.

In 1 RCT (Abd Elhady et al. 2009), headache was reported by 2 (5%) participants randomised to diltiazem and 6 (15%) participants randomised to glyceryl trinitrate ( $p$  value not stated)<sup>[22]</sup>.

In 1 RCT (Samim et al. 2012), perianal itching after application of the cream was reported in 1 (1.7%) participant randomised to botulinum toxin and 11 (14.9%) participants randomised to diltiazem ( $p=0.012$ ). No other adverse effects were reported<sup>[23]</sup>.

In 1 RCT (Suvarna et al. 2012), mild headache was reported in 5 (5.5%) participants randomised to diltiazem and none of those randomised to surgery ( $p<0.0001$ )<sup>[24]</sup>.

In the single RCT in children (Cevik et al. 2009), 1 participant randomised to glyceryl trinitrate ointment and 1 randomised to topical diltiazem ointment experienced perianal dermatitis<sup>[25]</sup>. The authors stated that no other children experienced significant side effects, but that headache could not be assessed because of the age of the children.

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<sup>[19]</sup> Nelson RL, Thomas K, Morgan J et al. (2012) Non surgical therapy for anal fissure. Cochrane Database of Systematic Reviews issue 2: CD003431

<sup>[20]</sup> Shrivastava UK, Jain BK, Kumar P et al. (2007) A comparison of the effects of diltiazem and glyceryl trinitrate ointment in the treatment of chronic anal fissure: a randomized clinical trial. *Surgery Today* 37: 482–5

<sup>[21]</sup> Sanei B, Mahmoodieh M, Masoudpour H (2009) Comparison of topical glyceryl trinitrate with diltiazem ointment for the treatment of chronic anal fissure: a randomized clinical trial.

Acta Chirurgica Belgica 109: 727–30

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[25] Cevik M, Boleken ME, Koruk I et al. (2012) A prospective, randomized, double-blind study comparing the efficacy of diltiazem, glyceryl trinitrate, and lidocaine for the treatment of anal fissure in children. Pediatric Surgery International 28: 411–6

## Evidence review: economic issues

### Cost

No studies on cost effectiveness were identified. The NHS price for 2% diltiazem cream is £73.83 per 30 g tube and the NHS price for 2% diltiazem ointment is £163.07 per 30 g tube (costs exclude VAT and are taken from the [Drug Tariff](#), February 2013).

### Current drug usage

In the most recent quarter for which data are available (July to September 2012), there were 5076 prescriptions for 2% diltiazem hydrochloride cream in primary care in England at a net ingredient cost of £592,505 (a mean of £116.73 per prescription). Among all the special order products prescribed in primary care in England that quarter, 2% diltiazem hydrochloride cream ranked 6<sup>th</sup> by number of prescription items and 8<sup>th</sup> by net ingredient cost<sup>[26]</sup>.

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[26] NHS Business Services Authority. (2012) Volume and cost of special order products



## Evidence strengths and limitations

This summary is based on evidence from a Cochrane review of 4 RCTs<sup>[27]</sup> and 5 additional RCTs<sup>[28],[29],[30],[31],[32]</sup>. These sources presented similar conclusions although their precise estimates of effect varied.

None of the studies compared 2% topical diltiazem with 0.4% topical glyceryl trinitrate (the licensed strength), which limits the conclusions which can be drawn regarding comparative efficacy and risk of adverse effects, especially headache. Although several of the 5 additional RCTs included a power calculation, they were relatively small. Most were conducted in countries outside northern Europe (for example, Egypt<sup>[29]</sup>, India<sup>[31]</sup>, Iran<sup>[28]</sup>, and Turkey<sup>[32]</sup>), as well as the Netherlands<sup>[30]</sup>, but the findings are still likely to be applicable to the UK population because of the simple nature of the treatment.

The studies showed some degree of heterogeneity in terms of their definition of chronic fissure: treatment duration; concurrent treatments (such as a high-fibre diet or use of laxatives), child or adult populations, methods and time points for assessing fissure healing, and length of follow-up to assess recurrence. This may partly explain the large variation in the estimates of healing and recurrence observed in the RCTs, in addition to random sampling error.

The long-term efficacy, safety and fissure recurrence while using topical diltiazem was not assessed in the RCTs because most patients underwent surgery after first recurrence or healed completely and left the studies. The authors of the Cochrane review note the relapsing-remitting nature of chronic anal fissure and suggest that short follow-up periods may give rise to misleading results<sup>[27]</sup>.

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<sup>[27]</sup> Nelson RL, Thomas K, Morgan J et al. (2012) Non surgical therapy for anal fissure. Cochrane Database of Systematic Reviews issue 2: CD003431

<sup>[28]</sup> Sanei B, Mahmoodieh M, Masoudpour H (2009) Comparison of topical glyceryl trinitrate with diltiazem ointment for the treatment of chronic anal fissure: a randomized clinical trial. Acta Chirurgica Belgica 109: 727–30

<sup>[29]</sup> Abd Elhady HM, Othman IH, Hablus MA et al. (2009) Long-term prospective randomised clinical and manometric comparison between surgical and chemical sphincterotomy for treatment of chronic anal fissure. South African Journal of Surgery 47: 112–4

<sup>[30]</sup> Samim M, Twigt B, Stoker L et al. (2012) [Topical diltiazem cream versus botulinum toxin a for the treatment of chronic anal fissure: a double-blind randomized clinical trial](#). *Annals of Surgery* 255: 18–22

<sup>[31]</sup> Suvarna R, Panchami, Guruprasad RD (2012) [Chemical sphincterotomy versus surgical sphincterotomy in the management of chronic fissure in ANO: A prospective, randomized trial](#). *Journal of Clinical and Diagnostic Research* 6: 1018–21

<sup>[32]</sup> Cevik M, Boleken ME, Koruk I et al. (2012) [A prospective, randomized, double-blind study comparing the efficacy of diltiazem, glyceryl trinitrate, and lidocaine for the treatment of anal fissure in children](#). *Pediatric Surgery International* 28: 411–6

## Summary for patients

A [summary written for patients](#) is available on the NICE website.

## References

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## Development of this evidence summary

This evidence summary has been developed 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

The sources are:

1. NHS Evidence (including guidelines)
2. NICE
3. Broad internet search: Google, for example: anoheal OR diltiazem "anal fissures" filetype:pdf

## Medline & Embase (via Ovid)

1. Fissure in Ano/ (1837)
2. ((anal or ano) adj3 (fissure? or ulcer\$)).tw. (1645)
3. or/1-2 (2463)
4. Diltiazem/ (5857)
5. (Acalix or Adizem or Altiazem or Anginyl or Angizem or Anoheal or Apo-Diltiaz or Britiazim or Bruzem or Calcicard or Cardil or Cardizem or Cardizen LA or Cartia XT or Citizem or Cormax or Corzem or CRD-401 or Deltazen or Dilacor or Diladel or Dilatam or Dilcontin or Dilpral or Dilren? or Dilt-cd or Dilt-xr or Dilta-Hexal or Diltia or Diltiazem or Diltiact or Dilticard or Diltelan or Diltime or Dilzem or Dilzen or Dyalec or Endrydil or Filazem or Herben or Herbesser or Incoril AP or Masdil or Novo-Diltazem or Nu-Diltiaz or Progor or Syn-Diltiazem or Tiamate or Tiazac or Tildiem or Tiazac or Taztia or Vasmulax or Vasocardol or Viazem or Zandil or Zemtrial).tw. (7904)

6. (42399-41-7 or 144604-00-2 or 33286-22-5).rn. (5857)
7. or/4-6 (8781)
8. and/3,7 (57)
9. exp review/ (1748413)
10. (scisearch or psychinfo or psycinfo or medlars or embase or psychlit or psyclit or cinahl or pubmed or medline).ti,ab,sh. (68813)
11. ((hand adj2 search\$) or (manual\$ adj2 search\$)).ti,ab,sh. (6089)
12. ((electronic or bibliographic or computeri?ed or online) adj4 database\$).ti,ab. (13361)
13. (pooling or pooled or mantel haenszel).ti,ab,sh. (45041)
14. (peto or dersimonian or der simonian or fixed effect).ti,ab,sh. (2605)
15. or/10-14 (118668)
16. 9 and 15 (53361)
17. Meta Analysis/ (36967)
18. (meta-analys\$ or meta analys\$ or metaanalys\$).ti,ab,sh. (64961)
19. ((systematic\$ or quantitativ\$ or methodologic\$) adj5 (review\$ or overview\$ or synthesis\$)).ti,ab,sh. (51347)
20. (integrative research review\$ or research integration).ti,ab,sh. (83)
21. or/17-20 (100591)
22. 16 or 21 (128067)
23. clinical trials, phase iv/ or clinical trials, phase iii/ or randomized controlled trials/ or multicenter studies/ (237120)
24. (random\$ or placebo\$ or ((singl\$ or double\$ or triple\$ or treble\$) and (blind\$ or mask\$))).ti,ab,sh. (863488)
25. 23 or 24 (958923)

26. (animal\$ not human\$).sh. (3705442)
27. 25 not 26 (855414)
28. 27 and 22 (47787)
29. 8 and 22 (12)
30. 8 and 27 (22)
31. (cost? or economic\$).tw. (384144)
32. 8 and 31 (2)

## **CRD HTA, DARE and EED database**

1. (diltiazem) OR (anoheal) 52
2. (anal fissure\*) 20
3. MeSH DESCRIPTOR Fissure in Ano EXPLODE ALL TREES 13
4. #2 OR #3 21
5. #1 AND #4 1

## **Cochrane CENTRAL**

#1 anal fissure\*:ti,ab,kw

#2 MeSH descriptor: [Fissure in Ano] explode all trees

#3 #1 or #2

#4 anoheal or diltiazem:ti,ab,kw

#5 #3 and #4

## **Euroscan**

Diltiazem

## Grey literature and ongoing trials search

1. [FDA](#)
2. [EMA](#)
3. [MHRA](#)
4. [Scottish Medicines Consortium](#)
5. [All Wales Medicine Strategy Group](#)
6. Manufacturers' websites as applicable
7. [metaRegister of Controlled Trials \(mRCT\)](#)
8. [ClinicalTrials.gov](#)

## Manufacturer's websites

[S.L.A. Pharma](#)

## Evidence selection

Studies were included based on predetermined criteria for relevance to the question set at scoping. Systematic review level evidence and RCTs were prioritised over other types of evidence for this review.

## Changes since publication

February 2013: updated with costs from the February 2013 [drug tariff](#).

## 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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