

## Topical diltiazem (SPOT-List)

Topical diltiazem appears in the top ten Specials Prescribing Optimisation Tool list (SPOT-List). In England and Wales, there is a total annual spend of £1.4 million on topical diltiazem products (ePACT Sep to Nov 2015). Unlicensed topical diltiazem preparations are often used for treatment of anal fissures. This bulletin discusses the evidence available and alternative treatments.

### Recommendations

- Ensure a high fibre diet and bulk forming laxatives to improve stool softening have been tried before considering any drug treatment. Refer for specialist management if laxative treatment is unsuccessful.<sup>1,2</sup>
- Topical treatments for anal fissure are for short term use only and therefore should not be added to repeat prescribing systems.
- Licensed glyceryl trinitrate 0.4% ointment (Rectogesic ®) should be considered prior to diltiazem. Its licensed use is for a maximum of eight weeks. If side effects such as headaches are experienced with its use, consider managing with analgesics.
- If a specialist advises diltiazem, consider whether prescribing should remain in secondary care, or the full short course (usually a maximum of eight weeks) should be prescribed and dispensed from the hospital.
- If prescribed in primary care, the prescriber must determine the clinical need of the patient and the suitability of using diltiazem, taking full responsibility for its use, as it is unlicensed. See GMC guidelines on prescribing unlicensed medicines for further advice on prescribing unlicensed medicines.<sup>3</sup> [http://www.gmc-uk.org/guidance/ethical\\_guidance/14327.asp](http://www.gmc-uk.org/guidance/ethical_guidance/14327.asp)
- Consider evidence before prescribing:
  - » Evidence suggests the difference in efficacy of 2% topical diltiazem hydrochloride vs. topical glyceryl trinitrate in adults is not statistically significant, but limited evidence indicates a reduced frequency of headaches.<sup>4</sup>

### Background

An anal fissure is a tear or ulcer in the lining of the anal canal, immediately within the anal margin.<sup>1</sup> Anal fissures are termed 'acute' when present for fewer than six weeks and as 'chronic' when present for six weeks or longer.<sup>1</sup> The management of anal fissures requires stool softening by increasing dietary fibre in the form of bran or by using a bulk-forming laxative. Short term use of local anaesthetic preparations may help.<sup>2</sup> If these measures are inadequate, referral for specialist treatment in hospital is advised.<sup>2</sup> The use of a topical nitrate (e.g. glyceryl trinitrate 0.4% ointment) may be a treatment option before considering surgery.<sup>2</sup> Topical diltiazem 2% (unlicensed preparation) may be used twice daily if chronic anal fissures are unresponsive to topical nitrates.<sup>2</sup>

## Evidence

Evidence is summarised in the NICE Advice [ESUOM3]: Chronic anal fissure: 2% topical diltiazem hydrochloride.<sup>4</sup>

One Cochrane systematic review (four RCTs; assessed as up-to-date November 2011) and five additional RCTs (neither considered by nor excluded from the Cochrane review) provide the evidence for this summary. The Cochrane review and two 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 also 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.<sup>4</sup>

In one of the RCTs included in the Cochrane review participants 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 six weeks were offered surgery. Allocation methods and blinding were not discussed. The rate of complete healing in the topical diltiazem group was statistically significantly higher than in the no-treatment group, but not statistically significantly different from the glyceryl trinitrate group. Recurrence of fissure was statistically significantly lower in the diltiazem group, compared with the no-treatment group, but not statistically significantly different from the glyceryl trinitrate group. The three other RCTs in the Cochrane review also found no statistically significant difference in healing rates between diltiazem and glyceryl trinitrate. For the purposes of comparison, the Cochrane review found that glyceryl trinitrate was statistically significantly better than placebo in healing anal fissure, but late recurrence of fissure was common, in the range of 50% of those initially cured.<sup>4</sup>

An application for a marketing authorisation (product licence) for 4% diltiazem cream for use in chronic anal fissure was in the process of submission by S.L.A. Pharma (UK) Ltd, however following a company merger this product is no longer in development.<sup>5</sup>

## Safety

Limited evidence suggests that 2% topical diltiazem is associated with a 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.<sup>4</sup>

## Alternative treatments

Glyceryl trinitrate 0.4% is licensed in the UK for the relief of pain associated with chronic anal fissure in adults (Rectogesic 4mg/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>4</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 one in five people) and cause people to discontinue treatment. Dizziness is also commonly reported (frequency greater than one in ten, but less than one in 100).<sup>4</sup> In some instances glyceryl trinitrate is made up at lower weight per volume ratio, to reduce adverse effects to the patient however at this strength it is an unlicensed preparation.<sup>4</sup>

The SMC have reviewed glyceryl trinitrate 0.4% ointment (Rectogesic®) and have stated is not recommended for use within NHS Scotland for relief of pain associated with chronic anal fissure. It was associated with very small improvements in pain scores compared with vehicle, and therefore little

clinically significant effect. The manufacturer did not present a sufficiently robust economic case to gain acceptance by SMC.<sup>6</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>4</sup>

The Association of Coloproctology of Great Britain and Ireland (ACPGBI) prefers topical diltiazem as it has similar efficacy to glyceryl trinitrate (GTN) but with fewer side effects.<sup>7</sup> The American Society of Colon and Rectal Surgeons (ASCRS) suggests conservative nonoperative treatment as first line; topical treatment is included as an acceptable option, using either a nitrate or calcium-channel blocker.<sup>8</sup>

## Cost<sup>2,9</sup>

Product name	Pack size (minimum volume on prescription)	Price for minimum volume	Price for each additional gram
Diltiazem 2% cream (unlicensed)	30g	£68.93	8p
Diltiazem 2% ointment (unlicensed)	30g	£55.41	1p
Glyceryl trinitrate 0.2% ointment (unlicensed)	30g	£24.44	19p
Rectogesic (glyceryl trinitrate 0.4%) ointment (licenced)	30g	£39.30	N/A

SLA Pharma Ltd (UK) makes the unlicensed special diltiazem 2% cream (Anoheal), and it can be ordered directly from the manufacturer at a cost of £42 per 30g tube with £5 delivery cost.<sup>10</sup> However, even if prescribed as Anoheal and endorsed as Anoheal the prescription will still be reimbursed at the price in the Drug Tariff part VIII B, i.e. £68.93 for 30g. Anoheal is in the DM+D (dictionary of medicines and devices) as an invalid listing.<sup>11</sup>

## Savings available

There is a spend of £1.4 million annually for topical diltiazem products in England and Wales (ePACT September to November 2015). Prescribing the licenced product Rectogesic® for anal fissure instead of the unlicensed topical diltiazem products could save over £500,000 in England (switch data not available for Wales). This equates to £881 per 100,000 patients.

## References

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## Additional PrescQIPP resources



Briefing



Data pack



Implementation resources

Available here: <https://www.prescqipp.info/resources/viewcategory/460-topical-diltiazem-spot-list>

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