

Health Technology Briefing

August 2024

Diltiazem hydrochloride cream for treating anal fissures

Company/Developer

Leith Healthcare / SLA Pharma

New Active Substance

Significant Licence Extension (SLE)

NIHRIO ID: 8306

NICE ID: Not available

UKPS ID: 674923

Licensing and Market Availability Plans

Currently in phase III clinical trial

Summary

Diltiazem hydrochloride cream is in clinical development for the treatment of chronic anal fissure. An anal fissure is a small tear or cut in the lining of the skin around the back passage (anus). The most common symptoms of anal fissures include pain around the anus and bleeding when passing stools. Anal fissures often arise from constipation, persistent diarrhoea, inflammatory bowel disease, pregnancy, and childbirth. The treatment options for anal fissures are generally based on reducing the anal pressures and include non-surgical and surgical modalities. Lateral internal sphincterotomy (surgical incision into one of the anal sphincter muscles) is used for definitive management of anal fissure though anal incontinence is a serious complication of the procedure. The only pharmacological treatment licensed in UK for treatment of chronic anal fissure is glyceryl trinitrate rectal ointment, however this is also associated with side effects.

Diltiazem hydrochloride cream is used to promote the healing of the tear that has occurred in the skin of the anus and reduce the symptoms of pain caused by the tear. Diltiazem hydrochloride cream is a calcium channel blocker and vasodilator that is topically applied on the skin around the tear. It works by relaxing the muscle around the anus which reduces the anal pressure and increases the blood flow to the area to allow healing to occur and subsequently ease pain. It also has a low side effect profile. If given a licence extension, diltiazem hydrochloride cream will offer an additional treatment option for adult patients with anal fissures.

Proposed Indication

This briefing reflects the evidence available at the time of writing and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information. A version of the briefing was sent to the company for a factual accuracy check. The company was available to comment.

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Treatment of adults having anal fissure (AF) with AF-related pain.¹

Technology

Description

Diltiazem hydrochloride (Anotop) is an antianginal agent and calcium antagonist. Diltiazem hydrochloride inhibits transmembrane calcium entry in myocardial muscle fibres and in vascular smooth muscle fibres, thereby decreasing the quantity of intracellular calcium available to the contractile proteins.² It works by blocking slow L-type calcium channels, thus preventing the influx of calcium into the smooth-muscle cell, and decreasing intracellular calcium concentration. This reduces the amount of calcium available to combine with calmodulin and subsequently prevents activation of the myosin light-chain kinase required for smooth muscle cell contraction.³ Diltiazem hydrochloride is thought to work by helping the ring muscle (sphincter) that goes around the anus to relax and allow blood to flow to the lining of the anus. This aids the healing process and relieves the pain associated with anal fissures.⁴

Diltiazem hydrochloride was in a phase III clinical trial (NCT01217515) where 2.5cm 2% or 4% diltiazem hydrochloride cream was applied peri-anally three times daily for eight weeks.¹

Key Innovation

Chronic anal fissures have traditionally been treated surgically. Initial enthusiasm for chemical sphincterotomy has waned because of poor outcomes with glyceryl trinitrate ointment.⁵ Glyceryl trinitrate is also associated with side effects such as headaches, dizziness, nausea and flushing.⁶ The main complication after sphincterotomy surgery is incontinence. Up to 3 in 10 people may have some problems controlling their bowels at first, including when they defecate or pass wind.⁷ Chemical sphincterotomy has proven effective in treating chronic anal fissure, however, many patients experience headaches as a side effect of this treatment.⁸

The aim of pharmacological manipulation in the treatment of anal fissures is to reduce the resting anal pressure, improve anal mucosal blood flow and promote healing of the fissure without causing any sphincter damage.⁹ The internal anal sphincter has a calcium dependent mechanism to maintain tone. It may therefore be possible to lower anal sphincter pressure using calcium channel blockers.¹⁰ Diltiazem hydrochloride is a calcium channel blocker and vasodilator. It increases blood flow to smooth muscles and relaxes muscle tone.⁴ Topical calcium channel blockers are an acceptable choice for medical management of chronic anal fissures with reasonable healing potential and low side-effect profile.¹¹

If given a significant licence extension, diltiazem hydrochloride cream will offer a novel treatment approach for adult patients with anal fissure.

Regulatory & Development Status

Diltiazem hydrochloride as a capsule or tablet has marketing authorisation in the UK for the following indications:¹²

- prophylaxis and treatment of angina in adults and elderly adults
- mild to moderate hypertension in adults and elderly adults

Diltiazem is used for the treatment of chronic anal fissures, but it is not licensed for this indication.¹²

Patient Group

Disease Area and Clinical Need

Anal fissure is a linear or oval shaped tear in the anal canal starting just below the dentate line extending to the anal verge. Chronic fissures are present for more than 6 to 8 weeks. Features of a chronic fissure are exposed fibres of internal anal sphincters at the base, hypertrophied anal papilla proximally, and a skin tag or sentinel pile distally. The exact cause of an anal fissure is not entirely clear, but it is thought to result from trauma to the anal canal. This includes trauma to the anoderm during the passage of hard or large bowel movements (constipation), local irritation from diarrhoea, anorectal surgery, and anoreceptive intercourse. As a response to the fissure, patients typically experience increased pressure within the anal canal.¹¹ Anal fissures often arise from constipation, persistent diarrhoea, inflammatory bowel disease, pregnancy, and childbirth.¹³ Despite their small size, these fissures can significantly impact patients' quality of life, leading to chronic pain, bleeding, and, in some cases, fear of defecation due to anticipated pain.¹⁴ Symptoms associated with acute fissures include anal pain, spasm, and/or bleeding with defecation.¹¹

Annual incidence is thought to be around 1.1 per 1000 person-years. Peak incidence occurs in people aged 15–40 years but anal fissures can occur at any age¹⁵ In England, (2022-23), there were 6,394 finished consultant episodes (FCE) and 6,203 admissions for anal fissure, unspecified (ICD-10 code K60.2) which resulted in 4,432-day cases and 1,501 FCE bed days.¹⁶

Recommended Treatment Options

There are currently no National Institute for Health and Care Excellence (NICE) recommended treatment options for the treatment of anal fissures.

Currently, 0.4% glyceryl trinitrate rectal ointment is the only licensed pharmacological treatment for chronic anal fissures in the UK. It is indicated for the relief of pain associated with chronic anal fissure in adults.⁴

Clinical Trial Information

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| Trial | <p>NCT01217515 : A Randomised, Double-Blind, Placebo-Controlled Trial of the Safety and Efficacy of Diltiazem Hydrochloride Cream in Subjects with Anal Fissure</p> <p>Phase: III – Completed</p> <p>Location(s): 5 EU countries, and the UK</p> <p>Study completion date: May 2012</p> |
| Trial Design | Randomised, parallel assignment, quadruple masked |
| Population | N=465 (actual) adult participants with anal fissure aged 18 years and older |
| Intervention(s) | Diltiazem hydrochloride 4% cream Diltiazem hydrochloride 2% cream |
| Comparator(s) | Placebo |
| Outcome(s) | <p>Primary outcome measure:</p> <ul style="list-style-type: none"> Change From Baseline in Average of Worst Anal Pain Associated with or Following Defaecation for Week 4 (for the 7 Treatment Days Immediately Preceding the Week 4 Visit). |

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| | See trial record for full list of other outcomes. |
| Results (efficacy) | See trial record |
| Results (safety) | See trial record |

| Estimated Cost | |
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| Diltiazem cream and ointment are included in the NHS Drug Tariff Part VIII B. The August 2024 price for Diltiazem 2% cream 30g is £12.48, and Diltiazem 2% ointment 30g is £13.74. ¹⁷ | |

| Relevant Guidance | |
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| NICE Guidance | |
| No relevant NICE guidance identified. | |
| NHS England (Policy/Commissioning) Guidance | |
| Other Guidance | |
| <ul style="list-style-type: none"> • The Association of Coloproctology of Great Britain and Ireland . The Association of Coloproctology of Great Britain and Ireland guideline on the management of anal fissure. November 2023.¹⁸ • The American Society of Colon and Rectal Surgeons (ASCRS). The American Society of Colon and Rectal Surgeons Clinical Practice Guidelines for the Management of Anal Fissures. February 2023.¹⁹ • Gilani A, Tierney G. Chronic anal fissure in adults. 2021.²⁰ • Stewart, David B. Sr M.D.; Gaertner, Wolfgang M.D.; Glasgow, Sean M.D.; Migaly, John M.D.; Feingold, Daniel M.D.; Steele, Scott R. M.D. Clinical Practice Guideline for the Management of Anal Fissures. January 2017.²¹ • National Institute for Health and Care Excellence. Chronic anal fissure: 0.2% topical glyceryl trinitrate ointment: Evidence summary [ESUOM7]. March 2013.²² • National Institute for Health and Care Excellence. Chronic anal fissure: 2% topical diltiazem hydrochloride: Evidence summary [ESUOM3]. January 2013.⁴ • National Institute for Health and Care Excellence. Chronic anal fissure: botulinum toxin type A injection: Evidence summary [ESUOM14]. June 2013.²³ | |

| Additional Information | |
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NB: This briefing presents independent research funded by the National Institute for Health and Care Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.