

Health Technology Briefing

July 2024

Nifedipine–lidocaine for treating chronic anal fissure

Company/Developer

Flynn Pharma

New Active Substance

Significant Licence Extension (SLE)

NIHRIO ID: 38746

NICE ID: Not Available

UKPS ID: 674889

Licensing and Market Availability Plans

Has been clinically developed.

Summary

Nifedipine-lidocaine has been clinically developed for the treatment of chronic anal fissure. An anal fissure is a tear or open sore (ulcer) that develops in the lining of the large intestine, near the anus. Many fissures heal by themselves, or certain medicines can be prescribed to treat them. However, sometimes a fissure does not heal and becomes a long-term (chronic) problem. In these cases, an injection or surgery may be prescribed. These treatments may lead to complications such as weakening of the anal sphincter muscles and bowel incontinence (difficulty controlling the bowel). There is a need for effective treatments with limited side effects for chronic anal fissure.

Nifedipine–lidocaine is a fixed-dose combination of nifedipine and lidocaine, administered as an ointment. Lidocaine is a local anaesthetic while nifedipine is a calcium-channel blocker that reduces the influx of calcium ions into the cell, causing blood vessels to relax and receive more blood, thus favoring healing. If licensed, nifedipine-lidocaine could offer an additional treatment option for patients with chronic anal fissure.

Proposed Indication

Patients with chronic anal fissure.

Technology

Description

Nifedipine-lidocaine is a fixed-dose topical ointment.¹ Nifedipine is a specific and potent calcium antagonist of the 1, 4-dihydropyridine type. Calcium antagonists reduce the transmembranal influx of calcium ions through the slow calcium channel into the cell, causing blood vessels to relax and receive more blood.^{2,3} Nifedipine acts particularly on the cells of the myocardium and the smooth muscle cells of the coronary arteries and the peripheral resistance vessels.³ It blocks the opening of the voltage-dependent calcium channels resulting in the relaxation of the internal anal sphincter and re-establishment of the blood flow to the area, thus favouring healing.^{4,5} Lidocaine is a local anaesthetic of the amide type. Lidocaine reversibly stabilises neuronal membranes and prevents initiation and conduction of nerve impulses, thus providing local anaesthesia. At high plasma concentrations, lidocaine may also decrease conduction of excitatory neural membranes in the brain and in heart muscle.⁶

Nifedipine-lidocaine has been clinically developed for the treatment of chronic anal fissure. In a pivotal study, patients treated with nifedipine (n=55) used topical 0.3% nifedipine and 1.5% lidocaine ointment every 12 hours.¹

Key Innovation

Existing treatment options for chronic anal fissures, such as surgery, can come with some risk of complications, for example, weakening of the anal sphincter muscles and bowel incontinence.⁷ A clinical trial that investigated nifedipine-lidocaine in patients with chronic anal fissure, demonstrated promising results with a favourable adverse event profile. Healing of chronic anal fissure was achieved after 6 weeks of therapy in 94.5 percent of the nifedipine-lidocaine treated patients (P< 0.001) as opposed to 16.4 percent of the controls.¹

Nifedipine-lidocaine is a fixed-dose combination treatment for patients with chronic anal fissure. licensed, nifedipine-lidocaine could offer an additional treatment option for patients with chronic anal fissure.

Regulatory & Development Status

Nifedipine-Lidocaine currently has Marketing Authorisation in various EU countries for the treatment of chronic anal fissure, anal fissure, proctalgia generally associated with anal sphincter hypertonia^{8,9}

Nifedipine is currently marketed in the UK as a monotherapy for the following indications:¹⁰

- all grades of hypertension
- Prophylaxis of chronic stable angina pectoris
- Prinzmetal (variant) angina when diagnosed by a cardiologist

Lidocaine is currently marketed in the UK in combination with other technologies for the following indications:¹¹

- pain caused by recurrent mouth ulcers, denture irritation
- pain and irritation associated with external haemorrhoids
- severe sore throats

- pain and discomfort associated with teething in children from 5 months of age, where non-pharmacological treatments have failed to provide sufficient relief.

Lidocaine is currently marketed in the UK as a monotherapy for the following indications:¹¹

- moderate acute pain during cervical and intrauterine procedures, in adults and adolescents from 15 years of age
- anaesthetic, pain control and nerve blockade (various applications)
- neuropathic pain associated with previous herpes zoster infection.
- Suppression of ventricular extrasystoles and ventricular tachycardia, especially after an acute myocardial infarction.

Nifedipine-lidocaine is not in phase II/III clinical development for the treatment of any other indications.

Patient Group

Disease Area and Clinical Need

An anal fissure is a tear or open sore (ulcer) that develops in the lining of the large intestine, near the anus.¹² Many fissures heal by themselves, or certain medicines can be prescribed to treat them. However, sometimes a fissure does not heal and becomes a long-term (chronic) problem.⁷ There is no consensus on the timeframe that makes a fissure chronic, but most sources consider the cut-off to range from four to 12 weeks.^{13,14} If someone has a chronic fissure, it is thought that the reason it has not healed is that the ring muscle (sphincter) that goes around the anus (back passage) has become so tense that the flow of blood to the lining of the anus is reduced.¹⁵ The most common symptoms of anal fissures are a sharp pain often followed by a deep burning pain that lasts several hours and/or bleeding when defecating.¹² Anal fissures are quite common, with around 1 in every 10 people affected at some point in their life. They affect both sexes equally and people of all ages can get them. But children and young adults between 15 and 40 years of age are more likely to get anal fissures.¹² Anal fissures are caused by damage to the lining of the anus or anal canal, the last part of the large intestine due to things like constipation, persistent diarrhoea, inflammatory bowel disease, pregnancy and childbirth, and occasionally a sexually transmitted disease.¹²

There is no publicly available data on incidence and prevalence of anal fissure in the United Kingdom. However, a retrospective analysis of all persons who were enrolled in one large regional managed care system and treated for anal fissure during calendar years 2005–2011 in the United States found an annual incidence of 0.11% (1.1 cases per 1,000 person-years), which ranged widely by age.¹⁶ In England (2022 – 23), there were 2,213 finished consultant episodes (FCEs) and 2,157 admissions for a primary diagnosis of chronic anal fissure (ICD 10 code K60.1), resulting in 367 FCE bed days and 1,904 day cases.¹⁷

Recommended Treatment Options

There is no treatment option recommended by NICE for chronic anal fissure.

Unlicensed treatment options that may be used off-label include:

- 2% topical diltiazem hydrochloride¹⁵
- 0.2% topical glyceryl trinitrate ointment¹⁸
- botulinum toxin type A injection¹⁹

Clinical Trial Information

Trial	<p>No clinical trial ID available; Topical Nifedipine With Lidocaine Ointment vs. Active Control for Treatment of Chronic Anal Fissure.¹</p> <p>Phase III- Completed</p> <p>Location - Italy</p> <p>Study completion date - Unknown</p>
Trial Design	Randomised, prospective, double-blind, active treatment control
Population	N=110 (actual); adult subjects with chronic anal fissure
Intervention(s)	Nifedipine-lidocaine (topical 0.3% nifedipine and 1.5% lidocaine ointment) every 12 hours for 6 weeks.
Comparator(s)	Topical 1.5% lidocaine and 1% hydrocortisone acetate ointment
Outcome(s)	<p>Primary outcome: healing of the fissure with epithelialization or formation of a scar on examination at day 42 from baseline.</p> <p>See published article for other outcomes.¹</p>
Results (efficacy)	<p>Healing of chronic anal fissure was achieved after 6 weeks of therapy in 94.5% of the nifedipine-lidocaine treated patients as opposed to 16.4% of the controls ($P < 0.001$).</p> <p>Mean anal resting pressure decreased from a mean value +/- standard deviation of 47.2 +/- 14.6 to 42 +/- 12.4 mmHg in the nifedipine-lidocaine group. This represents a mean reduction of 11% ($P < 0.002$).</p> <p>Changes of maximal voluntary contraction in nifedipine-lidocaine treated patients were not significant.</p> <p>No changes in mean anal resting pressure and maximal voluntary contraction were observed in the control group. After the blinding was removed, recurrence of the fissure was observed in three of 52 patients in the nifedipine-lidocaine group within one year of treatment, and two of these patients healed with an additional course of topical nifedipine and lidocaine ointment.¹</p>
Results (safety)	No patient treated with the nifedipine-lidocaine ointment developed postural hypotension or showed any systemic side effect (e.g., headache, flushing, or ankle edema). Only one patient (1.8%) in the nifedipine-lidocaine treated group and three patients (5.4%) in the control group showed slight local hyperemia, which disappeared when therapy was discontinued. ¹

Estimated Cost

The cost of nifedipine-lidocaine is not yet known. However, the NHS indicative price of a pack of 28 nifedipine 60mg modified-release capsules is £7.34.²⁰ A lidocaine 5% (50mg per gram) ointment has an NHS indicative price of £15.²¹

Relevant Guidance

NICE Guidance

- NICE Evidence Summary. Chronic anal fissure: botulinum toxin type A injection (ESUOM14). June 2013
- NICE Evidence Summary. Chronic anal fissure: 0.2% topical glyceryl trinitrate ointment (ESUOM7). March 2013
- NICE Evidence Summary. Chronic anal fissure: 2% topical diltiazem hydrochloride (ESUOM3). January 2013.

NHS England (Policy/Commissioning) Guidance

- NHS City and Hackney Clinical Commissioning Group. Anal Fissure-Management guidance in adults. 2013.²²

Other Guidance

- Davids JS, Hawkins AT, Bhama AR, Feinberg AE, Grieco MJ, Lightner AL, et al. The American Society of Colon and Rectal Surgeons Clinical Practice Guidelines for the Management of Anal Fissures. 2022²³

Additional Information

This technology briefing is based on results from a pivotal study in the literature shared by Flynn Pharma. Flynn Pharma did not conduct this study nor any other study to assess nifedipine-lidocaine in the patients with the proposed indication. Therefore, there are no clinical trial IDs associated with this technology briefing submission. The pivotal study on the treatment of chronic anal fissure used in this technology briefing is referenced below.

- Perrotti P et al. Topical nifedipine with lidocaine ointment vs. active control for treatment of chronic anal fissure: results of a prospective, randomized, double-blind study. *Dis Colon Rectum*. 2002 Nov; 45(11): 1468-75. doi: 10.1007/s10350-004-6452-1

References

- 1 Perrotti P, Bove A, Antropoli C, Molino D, Antropoli M, Balzano A, et al. Topical Nifedipine With Lidocaine Ointment vs. Active Control for Treatment of Chronic Anal Fissure. *Diseases of the Colon & Rectum*. 2002;45(11):1468-75. Available from: <https://doi.org/10.1007/s10350-004-6452-1>.
- 2 British Heart Foundation. *Drug cabinet: Calcium channel blockers*. Available from: <https://www.bhf.org.uk/informationsupport/heart-matters-magazine/medical/drug-cabinet/calcium-channel-blockers> [Accessed 29 May 2024].
- 3 electronic Medicines Compendium (eMC). *Coracten SR 20 mg Capsules*. 1991. Available from: <https://www.medicines.org.uk/emc/product/2143/smpc> [Accessed 29 May 2024].
- 4 Khan KM, Patel JB, Schaefer TJ. Nifedipine. StatPearls [Internet]: Treasure Island (FL): StatPearls Publishing; 2023.
- 5 Michigan Medicine. *Nifedepine Ointment*. 2017. Available from: <https://www.med.umich.edu/1libr/MBCP/NifedipineOintment.pdf> [Accessed 18 July 2024].
- 6 electronic Medicines Compendium (eMC). *Lidbree 42 mg/mL intrauterine gel*. 2020. Available from: <https://www.medicines.org.uk/emc/product/14171/smpc> [Accessed 29 May 2024].
- 7 NHS UK. *Anal fissure treatment - Overview*. Available from: <https://www.guysandstthomas.nhs.uk/health-information/anal-fissure-treatment> [Accessed 30 May 2024].
- 8 Agence nationale de securite du medicament et des produits de sante. *Directory of Proprietary Medicinal Products*. 2020. Available from: <http://agence-prd.ansm.sante.fr/php/ecodex/extrait.php?specid=63967022> [Accessed 03 July 2024].
- 9 Italian Medicines Agency. *ANTROLIN 0.3 % ,1.5 % CREMA RETTALE*. 2004. Available from: <https://medicinali.aifa.gov.it/en/#/en/dettaglio/0000035133> [Accessed 03 July 2024].
- 10 electronic Medicines Compendium (eMC). *Search results for nifedipine*. Available from: <https://www.medicines.org.uk/emc/search?q=nifedipine> [Accessed 13 June 2024].
- 11 electronic Medicines Compendium (eMC). *Search results for lidocaine*. Available from: <https://www.medicines.org.uk/emc/search?q=lidocaine> [Accessed 13 June 2024].
- 12 NHS UK. *Anal fissure - overview*. Available from: <https://www.nhs.uk/conditions/anal-fissure/> [Accessed 29 May 2024].
- 13 Gilani A, Tierney G. Chronic anal fissure in adults. *British Medical Journal*. 2022;376:e066834. Available from: <https://doi.org/10.1136/bmj-2021-066834>.
- 14 Mathur N, Qureshi W. Anal fissure management by the gastroenterologist. *Current Opinion in Gastroenterology*. 2020;36(1):19-24. Available from: <https://doi.org/10.1097/mog.0000000000000599>.
- 15 National Institute for Health and Care Excellence (NICE). *Chronic anal fissure: 2% topical diltiazem hydrochloride*. 2013. Available from: <https://www.nice.org.uk/advice/esuom3/ifp/chapter/what-is-a-chronic-anal-fissure> [Accessed 29 May 2024].
- 16 Mapel DW, Schum M, Von Worley A. The epidemiology and treatment of anal fissures in a population-based cohort. *BioMed Central Gastroenterology*. 2014;14(1):129. Available from: <https://doi.org/10.1186/1471-230X-14-129>.
- 17 NHS Digital. *Hospital Admitted Patient Care Activity, 2022-23*. 2023. Available from: <https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2022-23> [Accessed 29 May 2024].

- 18 National Institute for Health and Care Excellence (NICE). *Chronic anal fissure: 0.2% topical glyceryl trinitrate ointment*. 2013. Available from: <https://www.nice.org.uk/advice/esuom7/chapter/Key-points-from-the-evidence> [Accessed 13 June 2024].
- 19 National Institute for Health and Care Excellence (NICE). *Chronic anal fissure: botulinum toxin type A injection*. 2013. Available from: <https://www.nice.org.uk/advice/esuom14/chapter/Key-points-from-the-evidence> [Accessed 13 June 2024].
- 20 National Institute for Health and Care Excellence (NICE). *Nifedipine Medicinal forms*. Available from: <https://bnf.nice.org.uk/drugs/nifedipine/medicinal-forms/> [Accessed 19 July 2024].
- 21 National Institute for Health and Care Excellence (NICE). *Lidocaine hydrochloride Medicinal forms*. Available from: <https://bnf.nice.org.uk/drugs/lidocaine-hydrochloride/medicinal-forms/> [Accessed 19 July 2024].
- 22 NHS City and Hackney Clinical Commissioning Group. *ANAL FISSURE-Management guidance in adults*. Available from: <https://gps.cityandhackneyccg.nhs.uk/cdn/serve/prescribing-guideline-downloads/1533291489-eecc402f93206d3ed870df8c40d859ab.pdf> [Accessed 30 May 2024].
- 23 Davids JS, Hawkins AT, Bhamra AR, Feinberg AE, Grieco MJ, Lightner AL, et al. The American Society of Colon and Rectal Surgeons Clinical Practice Guidelines for the Management of Anal Fissures. *Disease of the Colon and Rectum*. 2023;66(2):190-9. Available from: <https://doi.org/10.1097/dcr.0000000000002664>.

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