Health Technology Briefing
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Sumatriptan-Naproxen for the treatment of acute migraine

Company/Developer	Orion Pharma (UK) Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 38486	NICE ID: Not Available	UKPS ID: 674402

Licensing and Market Availability Plans

Sumatriptan-naproxen has completed phase III clinical development.

Summary

Sumatriptan-naproxen is for the acute treatment of migraine. Migraine is a headache that is usually characterised by throbbing in one side of the head and other symptoms including sensitivity to light and sound, nausea and vomiting. The cause of migraines is not known but triggers include tiredness, anxiety and caffeine. Migraines are also thought to be genetic. The two major types are migraine with aura and migraine without aura. Patients experiencing aura can experience numbness, dizziness, and problems with sight. Migraines without aura are the most common and usually last 4-72 hours. Current treatment recommends the combination of triptans (a type of drug which works by narrowing blood vessels around the brain) and nonsteroidal anti-inflammatory drugs (NSAIDs), but there is no single fixed-dose combination therapy currently recommended, leaving an unmet need in the acute treatment of migraine.

Sumatriptan-naproxen is an orally administered combination therapy of a triptan (sumatriptan) and an NSAID (naproxen). Sumatriptan is a selective 5-hydroxytryptamine-1d receptor agonist. Stimulation of this receptor results in cranial vessel constriction and reduces the release of neuropeptides (signalling molecules found in the brain). Naproxen inhibits the enzyme prostaglandin synthetase which reduces inflammation. In combination, these medications treat migraines and have the potential to prolong therapeutic response. Therefore, if licensed sumatriptan-naproxen could offer a novel, fixed dose combination therapy for patients with migraine.

Proposed Indication

The acute treatment of migraine attacks in adult patients aged 18 to 65 years.[1]

Technology

Description

Sumatriptan-naproxen (Suvexx, sumatriptan 85mg/naproxen sodium 500mg) is a combination therapy of a triptan and a nonsteroidal anti-inflammatory drug (NSAID).[2] Triptans reduce calcitonin gene-related peptide–mediated vasodilation, inhibit release of inflammatory mediators from trigeminal nerves and decrease transmission of pain impulses to the trigeminal nucleus caudalis.[2] Specifically, sumatriptan is a selective 5-hydroxytryptamine-1d receptor agonist. This receptor is found predominantly in the cranial blood vessels and has a vasoconstrictor effect.[3] In experimental animals, it has been shown that sumatriptan causes vasoconstriction of the arterioles and the arteriovenous anastomata of the carotid vascular bed.[3] This vascular bed provides the blood supply to the extracranial and intracranial tissues, such as the meninges.[3] It has been proposed that dilatation of these arterial vessels, and the formation of oedema here, is the underlying cause of a migraine attack in humans.[3] There is also evidence from animal experiments to suggest that sumatriptan inhibits the activity of the trigeminal nerve.[3] Both effects (cranial vasoconstriction and inhibition of the activity of the trigeminal nerve) might contribute to the anti-migraine effect of sumatriptan in humans.[3] NSAIDs inhibit the synthesis of prostaglandins and may mitigate meningeal inflammation while preventing or reversing central sensitisation arising from activation of glial cells in the brain stem.[2] In particular, naproxen inhibits prostaglandin synthetase which is responsible for the synthesis of prostaglandins which ultimately potentiate pain; however, the exact mechanism of its anti-inflammatory action is not known.[4,5] Together, a triptan and an NSAID could alter both peripheral activation of central pathways during the early stages of a migraine attack, and the later-developing central sensitisation that is independent of peripheral input.[2]

Sumatriptan-naproxen is currently in phase III clinical development for the acute treatment of multiple migraine attacks during the mild pain phase.[1] In this trial, sumatriptan-naproxen was orally administered during the mild pain phase and within one hour of onset of head pain at the following dose: sumatriptan 85mg/naproxen sodium 500mg.[1]

Key Innovation

There are no licensed combination treatments in a single formulation for moderate to severe migraine. Clinically, the lack of a single fixed-dose tablet may lead to variability in dosing and potentially higher levels of sumatriptan; sumatriptan tablets and naproxen sodium tablets are each available in three doses, potentially resulting in numerous combinations, and if not administered concurrently may lead to the suboptimal “step care approach” to treatment.[2] Therefore, there is an unmet need for specific combination therapies for patients suffering with acute migraine pain.

Sumatriptan–naproxen sodium has been shown to be more effective than placebo for headache relief at 2 hours after dosing as well as absence of photophobia and phonophobia at 2 hours.[2] Similarly, for 2-24 hours sustained pain-free response, sumatriptan–naproxen sodium has been shown to be superior to sumatriptan monotherapy, naproxen sodium monotherapy and placebo.[2] Similarly, Sumatriptan-naproxen as early-intervention treatment was more effective than placebo in treating single[6-8] or multiple migraine[9] episodes, as assessed by pain-free responses at 2 hours, 2-24 hours, or both endpoints. Sumatriptan-naproxen was effective in women with menstrual migraine and dysmenorrhoea[6] and in patients with poor

response or intolerance to short-acting triptan therapy.[7] In a multiple-episode study, pain-free responses were consistent within individual patients.[9] Sumatriptan-naproxen also improved various migraine-related symptoms and reduced the use of rescue medication within 24 h post-dose.[6-9] Therefore, if licensed sumatriptan-naproxen could offer an additional, fixed dose combination therapy for patients with migraine.[2]

Regulatory & Development Status

Sumatriptan-naproxen does not currently have marketing authorisation in the UK for any indication. Sumatriptan-naproxen does have marketing authorisations for acute migraine in Finland, Sweden, Denmark, Norway, Poland, Hungary, Latvia, Lithuania and Estonia.[10] Sumatriptan is currently marketed in the EU/UK as a monotherapy for the acute treatment of migraine attacks with or without aura.[3]

Naproxen is also currently marketed in the EU/UK as a monotherapy for the treatment of:[4,11]

- rheumatoid arthritis and juvenile rheumatoid arthritis
- osteoarthrosis (degenerative arthritis)
- ankylosing spondylitis
- acute gout
- acute musculoskeletal disorders
- acute migraine
- dysmenorrhea

Patient Group

Disease Area and Clinical Need

Migraine is a moderate to severe headache characterised by throbbing pain on one side of the head.[12] Other common symptoms include an increased sensitivity to light, sound and odour, and nausea and vomiting.[13] Some symptoms develop before the migraine starts including tiredness, changes in mood, a stiff neck, urinating more frequently, craving certain foods and feeling thirsty. The two major types are migraine with aura and migraine without aura. Aura can include numbness, dizziness, a tingling feeling, and difficulties with sight and speaking.[12] Migraines without aura are the most common type of migraine and usually last between 4 and 72 hours.[14] The cause of migraine is not known, but the pain is caused by the activation of nerve fibres within the wall of brain blood vessels travelling inside the meninges (three layers of membranes protecting the brain and spinal cord).[13] However, there are multiple migraine triggers including anxiety and depression, stress and tiredness, not eating regularly, too much caffeine, a lack of exercise and the start of a period.[12] Migraines are also genetic and most migraine sufferers have a family history of the disorder. In addition, migraines frequently occur in people who have other medical conditions. Depression, anxiety, bipolar disorder, sleep disorders, and epilepsy are more common in individuals with migraine than in the general population.[13]

An estimated 190,000 migraine attacks are experienced every day in England with an overall prevalence of 15% (males 7.6%, females 19.1%, weighted according to UK population demographic characteristics).[15] In England, 2022-23, there were 1,539 finished consultant episodes (FCEs) and 1,458 admissions for migraine without aura [common migraine] (ICD-10 code G43.0) which resulted in 402 FCE bed days and 1,152 day cases.[16]

Recommended Treatment Options

The National Institute for Health and Care Excellence (NICE) recommended treatments for adults with acute migraine include:

- Rimegepant for the acute treatment of migraine with or without aura in adults, with restrictions.[17]
- Combination therapy of oral triptan with an NSAID or paracetamol.[18]
- Monotherapy with an oral triptan, NSAID, aspirin, or paracetamol.[18]

Clinical Trial Information

Trial	NCT00240617; A Randomized, Double-blind, Multi-center, Placebo-controlled, Cross-over Study to Determine the Consistency of Response for Trexima* (Sumatriptan 85mg/Naproxen Sodium 500mg) Administered During the Mild Pain Phase for the Acute Treatment of Multiple Migraine Attacks (*Treximet) **Phase III** – Completed **Location:** USA **Actual study completion date:** June 2006
Trial Design	Randomised, double-blind, placebo-controlled
Population	N = 623 (actual); subjects with physician-diagnosed migraine attacks with moderate to severe pain preceded by a mild pain phase; aged 18 to 65 years
Intervention(s)	Sumatriptan succinate/naproxen sodium (treximet, previously known as trexima)
Comparator(s)	Matched placebo
Outcome(s)	Primary outcome: score on a 4-point migraine pain scale for multiple migraine attacks within a 2-to-24-hour time period See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The cost of sumatriptan-naproxen was confidential at the time of producing this briefing.

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. STS101 for treating acute migraine (GID-TA11147). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Galcanezumab for migraine (GID-TA11311). Expected date of issue to be confirmed.
- NICE technology appraisal. Rimegepant for treating migraine (TA919). October 2023.
- NICE clinical guideline. Headaches in over 12s: diagnosis and management (CG150). December 2021.
- NICE quality standard. Headaches in over 12s (QS42). August 2013.

- NICE interventional procedure guidance. Transcutaneous electrical stimulation of the supraorbital nerve for treating and preventing migraine (IPG740). October 2022.
- NICE interventional procedure guidance. Transcutaneous stimulation of the cervical branch of the vagus nerve for cluster headache and migraine (IPG552). March 2016.
- NICE interventional procedure guidance. Transcranial magnetic stimulation for treating and preventing migraine (IPG477). January 2014.
- NICE interventional procedure guidance. Percutaneous closure of patent foramen ovale for recurrent migraine (IPG370). December 2010.

NHS England (Policy/Commissioning) Guidance

- NHS England. NHS Standard Contract for Specialised Pain. D08/S/a.
- NHS England. NHS Standard Contract for Neurosurgery. D03/S/a.
- NHS England. Clinical Commissioning Policy: Occipital Nerve Stimulation for Adults with Intractable Chronic Migraine and Medically Refractory Chronic Cluster Headaches. D08/P/c. July 2015.

Other Guidance

- Scottish Intercollegiate Guidelines Network. Pharmacological management of migraine. 2023.[19]
- British Association for the Study of Headache. National Headache Management System for Adults. 2019.[20]

Additional Information

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