

**EVIDENCE BRIEFING
October 2018**

**Apremilast for oral ulcers in active Behçet's
disease**

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| NIHRI ID | 6000 | NICE ID | 9544 |
| Developer/Company | Celgene Ltd | UKPS ID | 383972 |

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| Licencing and market availability plans | Currently in phase III clinical trials. |
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SUMMARY

Apremilast is in development as an oral treatment for oral ulcers in people with active Behçet's disease. Behçet's disease (or Behçet's syndrome) is a rare and poorly understood condition that results in inflammation of the blood vessels and tissues. The condition is characterised by flare-ups (relapses) followed by periods where the symptoms disappear (remission). The cause of Behçet's disease is thought to be an interaction between genetics and environmental factors. As Behçet's disease affects multiple systems it has various symptoms such as mouth or genital ulcers, painful eyes and blurred vision, acne-like spots and painful joints. The most commonly reported symptoms are oral and genital ulcers.

Apremilast works by suppressing the activity of inflammatory pathway caused by molecules such as interleukins and tumour necrosis factors. In turn this reduces inflammation. Currently, specific curative treatment options for Behçet's disease are very limited and treatment relies on controlling symptoms and relieving pain. Apremilast has shown promise in targeting oral ulcers in patients with Behçet's disease, and if licensed it could be an effective treatment option for this patient group.

PROPOSED INDICATION

Oral ulcers in active Behçet's disease in adults.^a

TECHNOLOGY

DESCRIPTION

Apremilast (Otezla; CC-10004) is in clinical development for the treatment of oral ulcers in active Behçet's disease in adults.^a Apremilast is an oral small-molecule inhibitor of phosphodiesterase 4 (PDE4) that works intracellularly to modulate a network of pro-inflammatory and anti-inflammatory mediators. PDE4 is a cyclic adenosine monophosphate (cAMP)-specific PDE and the dominant PDE in inflammatory cells. PDE4 inhibition elevates intracellular cAMP levels, which in turn down-regulates the inflammatory response by modulating the expression of tumour necrosis factor alpha (TNF- α), interleukin 23 (IL-23), interleukin 17 (IL-17) and other inflammatory cytokines. Cyclic AMP also modulates levels of anti-inflammatory cytokines such as IL-10. These pro- and anti-inflammatory mediators have previously been implicated in psoriatic arthritis and psoriasis.¹

Apremilast is in development for the treatment of oral ulcers in active Behçet's disease in adults.^a In the phase III clinical trial (NCT02307513), patients receive apremilast orally, at a dose of 30mg twice daily for 64 weeks.²

INNOVATION AND/OR ADVANTAGES

Apremilast and its ability to inhibit PDE4 and modulate the activity of inflammatory cytokines make it a promising treatment for chronic inflammatory conditions.³

Currently there is no cure for Behçet's disease, however, symptom control is a possibility.⁴ Oral ulcers are frequently observed in patients with active Behçet's disease,⁵ and are commonly recognised as the primary manifestation of the condition.⁶ The use of apremilast in active Behçet's disease demonstrated a reduction in the amount of oral ulcers and oral ulcer pain,⁶ therefore indicating its potential to treat this painful and persistent symptom of the condition. Furthermore, apremilast has shown to maintain rapid improvements in patients with refractory mucocutaneous ulcers in Behçet's disease.⁷

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Apremilast (Otezla) is currently licensed for the following indications in the EU:¹

- Active psoriatic arthritis; as a monotherapy or combination with disease modifying antirheumatic drug (DMARD), in adult patients who have had an inadequate response or who have been intolerant to a prior DMARD therapy.
- Moderate to severe chronic plaque psoriasis in adult patients who failed to respond to or who have a contraindication to, or are intolerant to other systemic therapy including cyclosporine, methotrexate or psoralen and ultraviolet-A light.

^a Company information

The very common ($\geq 1/10$) adverse events (AEs) observed in patients using apremilast are diarrhoea and nausea, whilst common ($\geq 1/100$ to $< 1/10$) AEs reported were fatigue, back pain, vomiting, dyspepsia, cough, migraine, insomnia, decreased appetite, bronchitis etc.¹

Apremilast is in phase II development for the treatment of ulcerative colitis.⁸

PATIENT GROUP

DISEASE BACKGROUND

Behçet's disease (also known as Behçet's syndrome) is a rare, chronic, multisystem inflammatory condition.⁹ The natural history of Behçet's disease is relapsing and remitting, and it can affect different organs and systems from patient to patient. The disease course further varies between men and women.²¹ Behçet's disease is often characterised by recurrent oral aphthous ulcers, genital ulcers, uveitis and skin lesions,¹⁰ and its aetiology is thought to involve a genetic predisposition interacting with environmental risk factors such as an oral infection.^{5,11}

The most common symptom associated with Behçet's syndrome is mouth ulcers, or aphthous ulcers. These ulcers occur on the soft mucous membrane located in the mouth, and are defined as painful round or oval sores, usually with a surrounding red ring of inflammation. They can have the same appearance as mouth ulcers experienced in the general population.¹² Recurrent ulcers on the genitals, are also commonly seen in Behçet's disease. These are often painful, non-contagious and leave scarring in half of all cases.¹³

According to the International Criteria for Behçet's Disease, oral aphthosis are one of three defining symptoms used to obtain a diagnosis of Behçet's disease. Oral aphthosis, genital aphthosis and ocular lesions are each scored 2 points, whereas 1 point is assigned to each of skin lesions, vascular manifestations and neurological manifestations. A patient scoring 4 points or above is classified as having Behçet's disease.¹⁴

Whilst almost all patients with Behçet's disease have recurrent oral ulceration, many patients also experience genital ulcers, with fewer experiencing comparable skin lesions, arthritis, uveitis, thrombophlebitis, and gastrointestinal and central nervous system involvement.¹⁵ This is further evidenced by International Team for the Revision of the International Criteria for Behçet's disorder (from 27 countries) from 2,556 clinically diagnosed Behçet's disease patients.¹⁴

CLINICAL NEED AND BURDEN OF DISEASE

Behçet's disease and its corresponding symptoms can present themselves at any age, although they more frequently begin in a person's twenties or thirties.¹⁶ Median diagnosis can take as long as 12 years which leaves a considerable amount of time for patient morbidity to increase. As a result of this, approximately 66% of adults diagnosed with Behçet's disease receive some form of illness benefit.¹⁰

The human leukocyte antigen (HLA)-B51 allele is most strongly associated with Behçet's disease patients compared to unaffected subjects and is most prevalent in countries along the ancient trading route known as the "Silk Road," stretching from Turkey and Iran to Korea and Japan.¹⁷

In the UK, the prevalence of Behçet's disease is unknown but estimates suggest that the prevalence is 0.64 per 100,000 of the population.¹⁰ Using the latest mid-year population estimates (2016) for the UK this equates to approximately 420 patients who have Behçet's disease.¹⁸

Following a prospective, international, multicentre, diagnostic accuracy study, data from over 2,556 Behçet's patients from 27 different countries were reviewed. It was reported that 98% of Behçet's patients had oral aphthous ulceration as a feature.¹⁴ Therefore the prevalence of these symptoms in the UK population who have Behçet's disease would be similar to the overall population of patients with Behçet's disease irrespective of symptomology.

PATIENT TREATMENT PATHWAY

PATIENT PATHWAY

There is currently no cure for Behçet's disease, and symptomatic treatment is currently the only method of treatment.⁴ Due to the relapsed and remitting nature of the condition and the variable extent to which systems are affected, individualised treatment is recommended.²¹ Early diagnosis and treatment are crucial to prevent irreparable damage and diminished quality of life.¹⁰

Treatment is aimed at reducing inflammation through the use of corticosteroids, immunosuppressants and biological therapies.⁴

CURRENT TREATMENT OPTIONS

Topical corticosteroids reduce inflammation and are the mainstay of topical treatment. All topical corticosteroid therapies are best applied as soon as the ulcer starts to develop and should be continued until the ulcer has completely disappeared.¹² Current treatment options are:

- Oral corticosteroids can be used to reduce inflammation as a tablet or capsule.⁴
- Corticosteroid mouthwashes can be used where there is widespread development of crops of ulcers. Betamethasone soluble 500 microgram tablets are licensed for the management of oral ulcers, alternatively, soluble prednisolone 5 mg tablets can be used. These should be dissolved in water and used as a mouth wash.¹²
- Mucoadhesive buccal tablets can be placed on the ulcers and allowed to dissolve. Alternatively, an aerosol preparation such as a steroid inhaler used in the management of asthma or allergic rhinitis (e.g. hay fever) may be considered. The aerosol can be sprayed directly onto ulcers. Suitable inhalers are beclometasone metered-dose inhaler 50–100 micrograms sprayed twice daily onto the affected area or fluticasone propionate aqueous spray 50 micrograms, 2 puffs sprayed on to the ulcers three times daily.¹²
- Immunosuppressants such as azathioprine, ciclosporine, colchicine, methotrexate, mycophenolate mofetil and thalidomide can be used to reduce the activity of the immune system. These are available as tablets, capsules and injections.⁴ Recurrent oral ulceration that has failed to previous topical treatments alone, may be treated by oral colchicine. This requires close monitoring by a doctor.^{12,19}
- Mucosal coating agents such as carmellose sodium and polyvinylpyrrolidone/hyaluronic acid can be used to physically cover severely ulcerated areas to reduce unpleasant symptoms associated with activities such as speaking, smiling, swallowing or yawning.¹²
- Biological therapies can be used more selectively in severe and refractory cases of Behçet's disease, in particular the use infliximab and interferon alpha. These are delivered via intravenous and subcutaneous injection but require hospital funding for their use.⁴

PLACE OF TECHNOLOGY

There are currently no treatment options recommended by NICE for Behçet’s disease, or for oral ulcers in Behçet’s disease. If licensed, apremilast could be an effective treatment option for patients with oral ulcers who have Behçet’s disease.

CLINICAL TRIAL INFORMATION

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| Trial | NCT02307513 , CC-10004-BCT-002; placebo + apremilast vs apremilast; phase III |
| Sponsor | Celgene |
| Status | Ongoing |
| Source of Information | Trial registry, ² press release ⁶ |
| Location | EU (not incl UK), USA and other countries |
| Design | Randomised, placebo-controlled, parallel group study |
| Participants | n=208; aged ≥18 years; active Behçet’s disease meeting the ISG criteria; have received prior treatment with at least one non-biologic Behçet’s disease therapy such as, but not limited to, topical corticosteroids or systemic treatment |
| Schedule | Randomised to either receive placebo tablets by mouth twice daily for the first 12 wks followed by 52 wks of 30mg apremilast tablets, orally, twice daily, or pts receive 30 mg apremilast tablets, orally, twice daily for 64 wks. |
| Follow-up | 12 wk placebo-controlled period, 52 wk active treatment, 4 wk follow-up |
| Primary Outcomes | <ul style="list-style-type: none"> • Number of oral ulcers from baseline to Wk 12 |
| Secondary Outcomes | <p>Change from baseline to 12 wks unless otherwise stated</p> <ul style="list-style-type: none"> • Complete response rate for oral ulcers • Pain of oral ulcers • Complete response rate for genital ulcers • Pain of genital ulcers • Disease activity • Behçet’s Disease Quality of Life score • Behçet’s Syndrome Activity Score • Time to complete response of oral ulcers • Proportion of subjects with no oral ulcers following complete response • Number of oral ulcers following loss of complete response • Time to recurrence of oral ulcers following loss of complete response • Static Physician’s Global Assessment • Complete response rate for oral ulcers at wk 6 <p>Time frame 64 wks:</p> <ul style="list-style-type: none"> • Adverse events • Number of subjects discontinue • Clinically significant changes |
| Key Results | In the study, a total of 207 patients were randomized to apremilast 30 mg twice daily or placebo. At week 12, the area under the curve (AUC) for the number of oral ulcers was statistically significantly reduced with apremilast 30 mg BID versus placebo (129.5 vs. 222.1; P<0.0001), the trial’s primary endpoint. The AUC assesses the change in the number of oral ulcers over time, accounting for the clinical characteristic that oral ulcers repeatedly remit and recur. Statistically significant improvements were also seen with apremilast in multiple secondary endpoints, including oral ulcer pain (P<0.0001), overall disease activity (Behçet’s Syndrome |

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| | Activity Score: P<0.0001; Behçet's Disease Current Activity Index: P=0.0335) and quality of life (P=0.0003). |
| Adverse effects (AEs) | The most common adverse events (AEs) observed in the trial were diarrhoea (41.3 percent with apremilast, 19.4 percent for placebo), nausea (19.2 percent with apremilast, 10.7 percent for placebo), headache (14.4 percent for apremilast, 9.7 percent for placebo) and upper respiratory tract infection (11.5 percent for apremilast, 4.9 percent for placebo). The safety profile was consistent with the known safety profile of apremilast. |
| Expected reporting date | Study completion date reported as Aug 2021 |

ESTIMATED COST

The NHS indicative price for apremilast (Otezla) 30mg tablets x 56 is listed as £550.00.²⁰

ADDITIONAL INFORMATION

RELEVANT GUIDANCE

NICE GUIDANCE

- No guidance available

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract For Behçet's Syndrome Service (Adults and Adolescents). A13/S(HSS)a

OTHER GUIDANCE

- European League Against Rheumatism (EULAR) Standing Committee for Clinical Affairs. Update of the EULAR recommendations for the management of Behçet's syndrome. 2018²¹

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