

apremilast 10mg, 20mg, 30mg tablets (Otezla®) SMC No. (1053/15)

Celgene Ltd.

08 May 2015

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

apremilast (Otezla®) is accepted for restricted use within NHS Scotland.

Indication under review: alone or in combination with disease modifying anti-rheumatic drugs (DMARDs), for the treatment of active psoriatic arthritis (PsA) in adult patients who have had an inadequate response or who have been intolerant to a prior DMARD therapy.

SMC restriction: for use in adult patients with active PsA who have had an inadequate response with at least two prior DMARD therapies or who are intolerant to such therapies.

In three phase III, randomised, placebo-controlled studies in patients with active psoriatic arthritis, a significantly greater proportion of patients who received apremilast achieved at least 20% improvement in the American College of Rheumatology response criteria (ACR 20) at 16 weeks compared with those who received placebo.

Overleaf is the detailed advice on this product.

**Chairman,
Scottish Medicines Consortium**

Indication

Alone or in combination with disease modifying anti-rheumatic drugs (DMARDs), for the treatment of active psoriatic arthritis (PsA) in adult patients who have had an inadequate response or who have been intolerant to a prior DMARD therapy.

Dosing Information

30mg twice daily taken orally, morning and evening, approximately 12 hours apart, swallowed whole, with no food restrictions.

An initial titration schedule over 5 days from 10mg daily on day 1 to 30mg twice daily on day 6 is recommended. See the summary of product characteristics (SPC) for details.

If the patient shows no evidence of therapeutic benefit after 24 weeks, treatment should be reconsidered. The patient's response to treatment should be evaluated on a regular basis. Clinical experience beyond 52 weeks is not available.

Treatment should be initiated by specialists experienced in the diagnosis and treatment of (psoriasis or) psoriatic arthritis.

Product availability date

16 February 2015

Summary of evidence on comparative efficacy

Psoriasis is a chronic, inflammatory, immune-mediated condition mainly affecting the skin and joints. Psoriatic arthritis (PsA), an inflammatory arthritis, is present in approximately 20% of patients with psoriasis and is characterised by several clinical patterns of joint involvement including distal arthritis, asymmetric oligoarthritis, symmetric polyarthritis, arthritis mutilans and spondyloarthritis. The disease can have a significant impact on health-related quality of life and is linked with an increase in the standardised mortality ratio. The aim of treatment is to control joint pain, stiffness and damage, thereby preventing long-term disability and improving the patient's quality of life.¹ Apremilast is the first of a new class of treatment for psoriatic arthritis, inhibiting phosphodiesterase-4 (PDE4) which leads to increased intracellular cyclic adenosine monophosphate (cAMP) levels. This down-regulates the inflammatory response by modulating the expression of tumour necrosis factor-alpha (TNF- α), interleukin-23, interleukin-17 and other inflammatory cytokines which have been implicated in psoriatic arthritis. Apremilast has also been accepted by SMC for restricted use in adult patients with moderate to severe plaque psoriasis who failed to respond to or who have a contraindication to, or are intolerant to other systemic therapy including ciclosporin, methotrexate or psoralen and ultraviolet-A light (PUVA). Apremilast is restricted for use in patients with severe psoriasis before the use of biologic therapies and for use in patients with moderate psoriasis who are ineligible for biologic therapy and would otherwise receive best supportive care.²

The submitting company has requested that SMC considers this product when positioned for use in adult patients with active PsA who have had an inadequate response with at least two prior DMARD therapies or who are intolerant to such therapies.

Clinical evidence derives from three phase III, randomised, multicentre, double-blind, placebo-controlled studies, all of similar design, to establish the efficacy, tolerability and safety of apremilast in patients with active PsA (PALACE 1, PALACE 2, PALACE 3).³⁻⁷

The studies recruited patients aged ≥ 18 years with an active PsA diagnosis. The PALACE 3 study also specified the need for active skin involvement, with patients required to have at least one psoriasis lesion ≥ 2 cm.⁶ Pre-existing (for at least 16 weeks) DMARD treatment could be continued if the dose was stable for 4 weeks before screening. Each of the studies had a 24-week placebo-controlled phase where patients were randomly allocated to oral treatment with placebo, apremilast 20mg twice daily, or apremilast 30mg twice daily, stratified by their baseline DMARD use. At week 16, those patients receiving placebo who did not have $\geq 20\%$ improvement in swollen and tender joint counts according to the modified American College of Rheumatology response criteria (ACR20) were re-randomised to treatment with apremilast at a dose of either 20mg or 30mg twice daily (defined as 'early escape'). By week 24, those patients still receiving placebo were re-randomised to apremilast 20mg or 30mg twice daily, with all patients subsequently entering a 28-week active-treatment phase.

The primary outcome was the ACR20 response at week 16. A significantly higher proportion of patients in the apremilast treatment groups, compared with the placebo groups, achieved the primary outcome in the PALACE 1, 2 and 3 studies.³⁻⁷ The results of the primary outcome for the licensed 30mg dose for each of the studies are shown in the table below:

Proportion of patients achieving ACR20 response at week 16 in the PALACE studies⁷

	Placebo % (n)	Apremilast 30mg twice daily % (n)	p-value versus placebo
PALACE 1	19 (32/168)	38 (64/168)	0.0001
PALACE 2	19 (30/159)	32 (51/162)	0.006
PALACE 3	18 (31/169)	41 (68/167)	<0.0001

The pooled ACR20 response for all three PALACE studies were reported in the European Public Assessment Report (EPAR).⁷ Overall, 37% (184/497) of patients in the apremilast 30mg group and 19% (93/496) of patients in the placebo group achieved an ACR20 response at 16 weeks ($p \leq 0.0001$). In the apremilast 30mg and placebo groups, respectively, 77% (382/497) and 76% (376/496) of patients had prior use of DMARDs; within these respective groups, 39% (150/382) and 22% (81/376) had an ACR20 response at week 16.⁷

The key secondary outcome was a change from baseline in the Health Assessment Questionnaire–Disability Index (HAQ-DI) score at week 16. Statistically significantly greater improvements were achieved in the HAQ-DI score in the apremilast 30mg groups compared with placebo at week 16 in all three studies. In the pooled analysis, least squares mean (standard error) changes from baseline were -0.07 (0.02) for the placebo group and -0.21 (0.02) for the apremilast 30mg group ($p=0.0003$).⁷

Other secondary outcomes included ACR20 response at weeks 24 and 52, ACR50 and ACR70 responses at weeks 16, 24 and 52, Psoriatic Arthritis Response Criteria (PsARC) response and Short Form Health Survey (SF-36v2) score. In the pooled analysis of all three PALACE studies, a significantly greater proportion of patients in the apremilast 30mg group achieved ACR20 at 24 weeks compared with placebo. The pooled analysis also showed a significantly greater proportion of patients achieving an ACR50 response and an ACR70 response at 16 weeks for apremilast 30mg twice daily versus placebo. The ACR20, ACR50 and ACR70 responses were

maintained at weeks 24 and 52. There was a significantly greater proportion of patients who achieved a PsARC response for apremilast 30mg twice daily versus placebo. In all three PALACE studies there was a significant improvement in the SF-36v2 physical functioning score.⁷

Other data were also assessed but remain commercially confidential.*

Summary of evidence on comparative safety

In the pooled PALACE studies, the occurrence of any adverse event was reported in 43% (288/671) of patients in the placebo group and in 53% (516/973) of patients in the apremilast 30mg group. Serious adverse events were reported in 3.3% (22/671) and 2.2% (21/973) of patients respectively. Adverse events occurring more commonly in the apremilast 30mg group compared with placebo (data up to week 16) included diarrhoea (13% versus 2.5%), nausea (12% versus 3.9%), headache (7.9% versus 3.6%) and upper respiratory tract infection (3.8% versus 2.4%).⁷

No comparative safety data are available. Refer to the apremilast summary of product characteristics for details of adverse effects.

Summary of clinical effectiveness issues

Apremilast is the first of a new class of treatment for PsA. The current treatment pathway for PsA involves the use of a DMARD (leflunomide, sulfasalazine, or methotrexate) with or without the addition of intra-articular steroids. Patients may be considered for treatment with an anti-tumour necrosis factor alpha (TNF α) biologic therapy if they have failed to respond to, are intolerant of, or have had contraindications to, treatment with at least two DMARDs (despite at least 12 weeks treatment at therapeutic dose).^{1,10}

The submitting company has requested that SMC considers apremilast for use in adult patients with active PsA who have had an inadequate response to at least two prior DMARD therapies or who are intolerant to such therapies, prior to an anti-TNF α therapy.

Clinical experts consulted by SMC considered that there is unmet need in this therapeutic area with regards to the limited treatment options available to patients with PsA who don't respond to traditional DMARDs.

In the PALACE studies, the primary outcome (proportion of patients meeting ACR20 at week 16) was achieved in a significantly higher proportion of patients in the apremilast 30mg treatment group, compared with placebo. The ACR joint count is a commonly used tool to assess peripheral joint disease, and the ACR20 criterion is a consistent measurement of response used in arthritis clinical trials.⁸

The PALACE studies were placebo-controlled and therefore no data are available for apremilast versus an active comparator. There are also no comparative data for apremilast versus placebo beyond 24 weeks as all patients were re-randomised to an apremilast treatment group at this stage. The PALACE 1 study provided two-year follow-up data and data from PALACE 2 and 3 are available for up to 52 weeks.

A Bayesian network meta-analysis (NMA) was presented in the submission, ranking treatment outcomes for apremilast and the anti-TNF α therapies (adalimumab, etanercept, golimumab and infliximab) in adult patients with PsA. The NMA included 12 studies of placebo versus adalimumab, etanercept, infliximab, golimumab and apremilast. Outcomes included ACR20/50/70 response, PsARC response, Psoriasis Area Severity Index (PASI) 50/75/90 score, HAQ-DI, and HAQ conditional on PsARC response. The results cannot be shared as they remain commercially confidential.

The submitting company noted that heterogeneity was observed in the apremilast HAQ estimates; however, no further discussion of this was made in the submission and no steps were taken to investigate the cause or effects of these differences. Heterogeneity was also observed in the NMA with regards to mean disease duration, study durations, primary outcomes, and relevance of inclusion of the PALACE 4 study (which was conducted in DMARD-naïve patients).

No indirect comparison was presented against the DMARDs and there are therefore no data to suggest apremilast is as/more effective than the DMARDs.

Clinical experts consulted by SMC considered that apremilast is a therapeutic advancement as it has a unique mode of action and is administered orally. The place in therapy for apremilast is likely to be following the failure of DMARD therapy.

Apremilast would provide an additional step in the current treatment pathway for PsA which could potentially replace or delay the use of biologic therapy in some patients.

*Other data were also assessed but remain commercially confidential.**

Summary of comparative health economic evidence

The company presented a cost-utility analysis comparing a sequence including apremilast and a comparator sequence. The apremilast sequence modelled apremilast then subsequent anti-TNF therapy; adalimumab, etanercept then best supportive care (BSC). The comparator sequence comprised of the same sequence without the inclusion of apremilast. The company has positioned the submission for use in adults who have had an inadequate response to at least two prior DMARD therapies or who are intolerant to such therapies.

A lifetime Markov model was used which followed patients as they moved through the health states based upon PsARC. The model had a short-term phase where the initial response to treatment was evaluated after 16 weeks for apremilast and 12 weeks for the anti-TNFs. Patients who responded at the end of the trial period were assumed to continue treatment until they dropped out due to a lack of efficacy or withdrawal due to other reasons. Patients who did not respond to a treatment in the treatment phase of the model transitioned to the next treatment option in the pathway. Patients who did not respond to any of the anti-TNF therapies were assumed to receive BSC as a last line of therapy and were assumed to stay in that state for the remainder of the model. The source of the clinical data in the model was the NMA described above.

The utility values in the model were derived by mapping HAQ-DI and PASI scores to EQ-5D data collected in the pivotal studies using a regression analysis. A utility mapping algorithm was estimated which resulted in different utilities associated with each response according to patients' HAQ-DI and PASI scores. No adverse events disutilities were included in the model.

Drug acquisition costs were included for apremilast and the anti-TNFs. In addition, administration costs were included for the anti-TNFs and BSC. Monitoring costs were included in the model, which included a range of procedures such as laboratory tests and monitoring appointments with a rheumatologist. Disease management costs associated with psoriasis were also included and other healthcare such as hospitalisations, these healthcare costs were estimated as a function of the HAQ-DI score.

The cost-utility analysis estimates an incremental cost effectiveness ratio (ICER) of £14,691 per quality adjusted life year (QALY) for the apremilast sequence versus the comparator sequence. This is based upon an incremental cost of £10,879 and an incremental QALY gain of 0.74. The company also provided a sub-group analysis of patients who were biologic therapy naive. The analysis was performed by applying response rates estimated based on the sub-population in the NMA described above. This resulted in an estimated ICER of £14,697 per QALY, with an incremental cost of £10,680 and an incremental QALY gain of 0.73. There is no notable difference in the results between both groups. The main driver of the difference in cost is associated with the inclusion of another medicine in the apremilast sequence. The additional QALY gain is based on patients being on an active treatment for a longer period of time and thus less time in BSC in the apremilast sequence (due to the inclusion of apremilast) than the comparator sequence.

The company presented a variety of sensitivity analyses, which showed the results to be most sensitive to assuming a lower HAQ-DI progression while on BSC, reducing the time until patients receive anti-TNFs and BSC, changes in the time horizon and varying the utility estimation regression equation.

All the above analyses are based on non-significant differences from in the NMA.

The following issues were noted:

- There was no analysis which includes certolizumab and ustekinumab in the apremilast and comparator sequences. Both these treatments are accepted by SMC for use in PsA. SMC clinical experts highlighted these as potential comparators, and the company therefore provided some additional analysis against these therapies. In alternative sequences of therapy including these medicines, the ICERs ranged between £13k and £14k.
- The base case analysis includes non-significant differences. When these differences were removed the ICER decreased to £11k per QALY.
- As noted above, the additional QALY gain was based on patients being on an active treatment for a longer period of time and thus less time in BSC in the apremilast sequence (due to the inclusion of apremilast) than the comparator sequence. The ICER was sensitive to this assumption, specifically assuming a lower HAQ-DI progression while on BSC, reducing the time until patients receive anti-TNFs and BSC. Assuming a low HAQ-DI progression increased the ICER to £38k per QALY or £35k when non-significant differences were removed.
- When an alternative utility estimation regression equation was used, the base case

ICER increased to £17k per QALY. However, the utility estimation regression equation used in the base case was consistent with the method used in the NICE technology appraisal.

- The results were sensitive to reducing the time horizon. When the time horizon was reduced to 10 years the ICER increased to £33k per QALY, based on an incremental cost of £5.5k and an incremental QALY gain of 0.16 (£28k when non-significant differences were removed). However, the lifetime horizon adopted in the base case was appropriate as it has been used in previous psoriatic arthritis models.

Despite these issues, the economic case was considered to have been demonstrated.

Other data were also assessed but remain commercially confidential.*

Summary of patient and public involvement

The following information reflects the views of the specified Patient Groups.

- Submissions were received from The Psoriasis and Psoriatic Arthritis Alliance (PAPAA), Psoriasis Association and Psoriasis Scotland Arthritis Link Volunteers (PSALV). All three are registered charities.
- The Psoriasis Association and PSALV have received pharmaceutical company funding in the past two years, including from the submitting company. PAPAA has not received any pharmaceutical company funding.
- Psoriatic arthritis (PsA) is an inflammatory arthritis associated with the skin condition psoriasis. For most people affected, their joints become inflamed, causing pain, swelling and stiffness. Joints affected are often fingers and toes through to larger joints. The impact on work, social life, ability to self-care and relationships can be marked. Enthesitis is a feature of PsA that can be difficult to treat.
- Current therapies have limitations. DMARDs and biologic agents require monitoring and are not always effective. As an oral tablet, apremilast is convenient, allowing patients to self-manage. It does not require repeated monitoring at clinics. It is a new treatment option, targeting a chemical pathway not covered by other agents. It may help treat enthesitis.
- Apremilast is a convenient, effective treatment for PsA that gives patients who cannot use other currently available therapies, or who find them no longer effective, a further option.

Additional information: guidelines and protocols

The Scottish Intercollegiate Guidelines Network (SIGN) guideline 121 on the diagnosis and management of psoriasis and psoriatic arthritis in adults¹ (October 2010) advises that treatment of psoriatic arthritis, depending on the type and severity of the condition, may include the use of non-steroidal anti-inflammatory drugs (NSAIDs), disease-modifying anti-rheumatic drugs (DMARDs) and intra-articular steroid injections. Recommendations in the guideline include:

- NSAIDs for short-term symptom relief in patients with psoriatic arthritis

- Leflunomide for the treatment of active peripheral psoriatic arthritis (or sulfasalazine as an alternative)
- Methotrexate in the treatment of psoriatic arthritis
- Adalimumab, etanercept or infliximab for the treatment of active psoriatic arthritis in patients who have failed to respond to, are intolerant of, or have had contraindications to, at least two DMARDs.

The National Institute for Health and Care Excellence (NICE) technology appraisal guidance 199 on etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis⁹ (August 2010) advises that etanercept, infliximab and adalimumab are recommended for the treatment of adults with active and progressive psoriatic arthritis when:

- The person has peripheral arthritis with three or more tender joints and three or more swollen joints, and
- The psoriatic arthritis has not responded to adequate trials of at least two standard DMARDs, administered either individually or in combination.

Treatment should be discontinued in those patients whose psoriatic arthritis has not shown an adequate response in the Psoriatic Arthritis Response Criteria (PsARC) at 12 weeks.

The British Society for Rheumatology and The British Health Professionals in Rheumatology guideline for the treatment of psoriatic arthritis with biologics¹⁰ (2012) provides a treatment algorithm for the management of the condition. If there is an inadequate response to the use of NSAIDs and/or local intra-articular steroids, use of up to two DMARDs (alone or in combination) should be trialled before the use of biologic therapies. In the absence of a response to the DMARDs (i.e. intolerance or active disease despite at least 12 weeks treatment at a therapeutic dose), a trial of up to two anti-TNF α therapies is indicated in those patients with more than three tender or swollen joints or in those with persistent severe oligoarthritis. In those patients with active disease, the presence of five or more swollen joints and a raised c-reactive protein for at least 3 months, or structural joint damage, use of a biologic can be considered after inadequate response to just one DMARD. Choice of anti-TNF α therapy is at the discretion of the physician, taking into account patient co-morbidities, preference and cost. Treatment with an anti-TNF α therapy should continue if there is an adequate response within three months of treatment. In those patients with only a partial response to treatment (i.e. some improvement in the swollen/tender joint score and no decline in the Psoriatic Arthritis Response Criteria global scores), a further 12 weeks of treatment can be considered, continuing if a full response is achieved.

Additional information: comparators

Adalimumab, etanercept, golimumab, infliximab, certolizumab pegol, ustekinumab.

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
Apremilast	30mg orally twice daily	7,150
Infliximab [‡]	Initially 5mg/kg by intravenous infusion followed by 5mg/kg two and six weeks after the first infusion, then every eight weeks.	First year: 12,088 - 13,424 Subsequent years: 9,066 to 11,749
Ustekinumab	45mg administered subcutaneously, followed by 45mg four weeks later, and then every 12 weeks. Alternatively, 90mg may be used in patients with a body weight >100kg.	First year: 12,882 Subsequent years: 8,588 to 10,735
Certolizumab pegol	Loading dose of 400mg subcutaneously on weeks zero, two, and four, followed by maintenance dose of 200mg subcutaneously every two weeks	First year: 10,725 Subsequent years: 9,295
Etanercept	25mg subcutaneously twice weekly or 50mg once weekly	9,295
Adalimumab	40mg subcutaneously every second week	9,156
Golimumab	50mg subcutaneously once per month	9,156

Doses are for general comparison and do not imply therapeutic equivalence. Costs for apremilast, ustekinumab and certolizumab pegol from eVadis on 04 February 2015; costs for all other drugs from MIMS online 04 February 2015. Cost for apremilast does not include initial titration schedule. Cost for infliximab assumes a bodyweight of 70kg. [‡]Costs for infliximab reflect the range of list prices for the reference product and biosimilar products. Cost for ustekinumab based on 45mg dose regimen.

Additional information: budget impact

The submitting company estimated there to be 26,540 patients eligible for treatment with apremilast in years 1 to 5, with an estimated uptake rate of 0.04% in year 1 and 0.6% in year 5. From SMC expert responses this estimate may be overestimated.

The gross medicines budget impact was estimated to be £63k in year 1 and £951k in year 5. As other medicines were assumed to be displaced, the net medicines budget impact was estimated to be a saving of £1k in year 1 and savings of £161k in year 5. This was estimated on the basis that there would be initial displacement of biologic therapies in the treatment pathway as a result of the use of apremilast as a treatment prior to commencing biologic therapy.

References

The undernoted references were supplied with the submission. Those shaded in grey are additional to those supplied with the submission.

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3. Kavanaugh A, Mease PJ, Gomez-Reino JJ *et al*. Treatment of psoriatic arthritis in a phase 3 randomised, placebo-controlled trial with apremilast, an oral phosphodiesterase 4 inhibitor. *Ann Rheum Dis* 2014;73 1020–26.
4. NCT01172938. A phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group, efficacy and safety study of two doses of apremilast (CC-10004) in subjects with active psoriatic arthritis. www.clinicaltrials.gov (accessed 13/02/15).
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7. European Medicines Agency. European Public Assessment Report for Otezla® EMEA/H/C/003746. 20 November 2014. www.ema.europa.eu
8. American College of Rheumatology Committee to re-evaluate improvement criteria. A proposed revision to the ACR20: The hybrid measure of American College of Rheumatology response. *Arthritis Rheum* 2007;57(2):193–202.
9. National Institute for Health and Care Excellence (NICE). Technology Appraisal 199. Etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis. August 2010. <http://www.nice.org.uk/guidance/TA220>.
10. Coates L, Tillett W, Chandler D *et al*. The 2012 British Society for Rheumatology and The British Health Professionals in Rheumatology guideline for the treatment of psoriatic arthritis with biologics. *Rheumatology (Oxford)* 2013 Oct;52(10):1754-7.

This assessment is based on data submitted by the applicant company up to and including 17 April 2015.

*Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:

http://www.scottishmedicines.org.uk/About_SMC/Policy_Statements/Policy_Statements

Drug prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.