Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2132

certolizumab pegol 200mg solution for injection in pre-filled syringe and pen (Cimzia®)

UCB Pharma Ltd

8 March 2019

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 NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission

certolizumab pegol (Cimzia®) is accepted for restricted use within NHSScotland.

Indication under review: the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy

SMC restriction: patients who have failed to respond to standard systemic therapies (including ciclosporin, methotrexate and phototherapy), are intolerant to, or have a contra-indication to these treatments.

Certolizumab pegol has shown a similar reduction in the signs and symptoms of psoriasis in adults with moderate to severe plaque psoriasis compared with another tumour necrosis factor (TNF) antagonist.

This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of certolizumab pegol. This advice is contingent upon the continuing availability of the PAS in NHSScotland or a list price that is equivalent or lower.

Chairman
Scottish Medicines Consortium

Indication

Treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy.[1]

Dosing Information

Certolizumab pegol 400mg subcutaneously (SC) at weeks 0, 2, and 4. Then a maintenance dose of certolizumab pegol 200mg SC every two weeks. A dose of certolizumab pegol 400mg SC every two weeks can be considered in patients with insufficient response.

A clinical response is usually achieved within 16 weeks of treatment. Continued therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit within the first 16 weeks of treatment. Some patients with an initial partial response may subsequently improve with continued treatment beyond 16 weeks.

Treatment with certolizumab pegol should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of conditions for which it is indicated. Patients should be given a special alert card.[1]

Product availability date

7 June 2018

Summary of evidence on comparative efficacy

Certolizumab pegol is an antagonist of tumour necrosis factor (TNF), which is a pro-inflammatory cytokine with a central role in inflammatory processes in psoriasis. This submission relates to the use of certolizumab pegol for the treatment of adults with moderate to severe plaque psoriasis.[1] The submitting company initially requested that SMC considers certolizumab pegol in two separate subgroups: (1) patients who are inadequate responders to standard non-biologic systemic therapy; and (2) patients who are candidates for non-biologic systemic therapy.

Three phase III studies (CIMPASI-1, CIMPASI-2 and CIMPACT) recruited adults who had at least a six month history of plaque psoriasis, which was moderate-to-severe, defined by a psoriasis area and severity index (PASI) score at least 12, body surface area (BSA) involvement at least 10% and physician global assessment (PGA) score at least 3 (on 5-point scale). They had not received more than two previous biologic therapies, with secondary failure on no more than one and primary failure on none. Patients were randomised, with stratification for study site, to 16 weeks' double-blind treatment with placebo or certolizumab pegol 400mg SC at weeks 0, 2 and 4, then a maintenance dose of 400mg or 200mg SC every two weeks. The CIMPACT study randomisation also included a single-blind active-control comparison with etanercept 50mg SC twice weekly for 12 weeks. The primary outcome, proportion of patients achieving at least a 75% improvement from baseline in PASI (PASI75), was assessed at week 12 in the CIMPACT study and at week 16 in

the CIMPASI-1 and -2 studies. The latter studies included a co-primary outcome of physician global assessment (PGA) response, defined by a score of one or less with at least a two category improvement, at week 16. Outcomes were assessed in all randomised patients.[2-4]

In CIMPACT and CIMPASI studies, the primary outcomes and key secondary outcomes as detailed in table 1, were achieved by significantly more patients in the certolizumab pegol 400mg and 200mg groups compared with placebo. In CIMPACT study, certolizumab pegol 400mg but not certolizumab pegol 200mg, was associated with significantly greater PASI75 response rate at week 12 compared with etanercept. For this outcome certolizumab pegol 200mg was non-inferior to etanercept at a pre-specified 10% non-inferiority margin. [1-4]

Table 1: Primary and Secondary Outcomes in CIMPACT, CIMPASI-1 and CIMPASI-2.[1-4]

	Placebo	**Certolizumab 200mg**	**Certolizumab 400mg**	**Etanercept**
CIMPACT	**N=57**	**N=165**	**N=167**	**N=170**
PASI75 week 12*	5.0%	61%	67%	53%
PGA 0/1 week 12	1.9%	40%	50%	39%
PASI90 week 12	0.2%	31%	34%	27%
PASI75 week 16	3.8%	68%	75%	-
PGA 0/1 week 16	3.4%	48%	58%	-
PASI90 week 16	0.3%	40%	49%	-
Mean change DLQI week 16	-1.1	-8.1	-11	
CIMPASI-1	**N=51**	**N=95**	**N=88**	
PASI75 week 16*	6.5%	66%	76%	-
PGA 0/1 week 16*	4.2%	47%	58%	-
PASI90 week 16	0.4%	36%	44%	-
Mean change DLQI week 16	-3.3	-8.9	-9.6	
CIMPASI-2	**N=49**	**N=91**	**N=87**	
PASI75 week 16*	12%	81%	83%	-
PGA 0/1 week 16*	2.0%	67%	72%	-
PASI90 week 16	4.5%	53%	55%	-
Mean change DLQI week 16	-2.9	-11.1	-10	

PASI75 and PASI90 improvement of 75% and 90%, respectively, in psoriasis area and severity index (PASI). PGA = physician global assessment of psoriasis (assessed on 5-point scale, where 0 = clear and 1 = almost clear). PASI and PGA response rates from regression models using Markov Chain Monte Carlo imputation of missing data. DLQI = dermatology life quality index. * (co)-primary outcome.

In all studies there were improvements in quality-of-life with both doses of certolizumab pegol compared with placebo, as indicated by significantly greater mean change from baseline to week 16 on the dermatology life quality index (DLQI), as detailed in table 1.[2]

In the CIMPASI studies at week 16 patients in the certolizumab groups who had a PASI50 response and those in the placebo group who had a PASI75 response continued to receive their assigned treatment in a double-blind maintenance phase up to week 48. Those in the placebo group with a

PASI50 response (but not PASI75) received blinded certolizumab pegol 200mg SC every two weeks and all other patients without PASI50 were rescued with open-label certolizumab pegol 400mg SC every two weeks during the maintenance phase. Any patient that did not have a PASI50 at week 32 and 40 were withdrawn from the study at these points. At week 48 regression models, with Markov Chain Monte Carlo (MCMC) imputation of missing data and non-responder imputation for patients with week-16 rescue criteria, estimated PASI75 response rates in the certolizumab pegol 200mg and 400mg groups of 67% and 87% in CIMPASI-1 and 79% and 81% in CIMPASI-2, and PGA 0/1 response rates of 53% and 70% in CIMPASI-1 and 73% and 67% in CIMPASI-2. This suggests that treatment effect is generally maintained or increased at week 48.[2]

At week 16 in the CIMPACT study PASI75 responders in the placebo group continued assigned treatment in the double-blind maintenance phase up to week 48, while those in the etanercept group were re-randomised in a 2:1 ratio to receive certolizumab pegol 200mg SC every two weeks or placebo and those in the certolizumab pegol groups were re-randomised in a 1:2:2 ratio to receive placebo, certolizumab pegol 200mg SC every two weeks or certolizumab pegol 400mg SC every two weeks (in the initial 400mg dose group) or every four weeks (in the initial 200mg dose group). Patients who did not achieve a week 16 PASI75 response were rescued with open-label certolizumab pegol 400mg SC every two weeks during the maintenance phase. Any patients who did not have a PASI50 at assessments after week 32 were withdrawn. As all patients were PASI75 responders at the start of the maintenance phase, PASI75 response at week 48 could only be maintained or decreased. At week 48 analyses were performed in patients re-randomised at week 16, with non-responder imputation for missing data and those withdrawn due to relapse (loss of PASI50). These indicated that PASI75 response at week 48 was generally maintained in patients who continued on their initial assigned dose of certolizumab pegol 200mg and 400mg, 80% (35/44) and 98% (48/49) and in those initially assigned to these respective doses who switched to certolizumab pegol 400mg and 200mg, 89% (39/44) and 80% (40/50), respectively. PASI75 response rates at week 48 were decreased over the maintenance period in those who were switched from certolizumab pegol 200mg and 400mg to placebo, 45% (10/22) and 36% (9/25), respectively.[2]

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

Summary of evidence on comparative safety

The European Medicines Agency (EMA) concluded that the safety profile for certolizumab pegol in plaque psoriasis was consistent with its safety profile in other licensed indications (rheumatoid arthritis, psoriatic arthritis and axial spondyloarthritis) and was in line with other TNF antagonists.[2]

Direct comparative data with etanercept were available from the initial 12-week period of the CIMPACT study. Across the placebo, etanercept and certolizumab pegol 200mg and 400mg groups the rates of treatment-emergent adverse events were 56% (32/57), 46% (78/168), 47% (78/165)

and 49% (82/167), which were treatment-related for 12%, 12%, 9.7% and 13% and were serious in 5 (8.8%), 1 (0.6%), 1 (0.6%) and 4 (2.4%) patients, respectively.[2,3]

In pooled analyses of the three pivotal studies (CIMPACT, CIMPASI-1 and -2) within certolizumab pegol 400mg, certolizumab pegol 200mg and placebo groups at the end of the 16-week induction period treatment-emergent adverse events were reported in 64% (217/342), 56% (197/350) and 62%, (97/157), which were treatment-related in 16%, 13% and 13% and were serious in 4.7%, 1.4% and 4.5% of patients respectively. Discontinuation due to treatment-emergent adverse events was reported for 4 (1.2%), 4 (1.1%) and 0 patients. Over the maintenance phase pooled safety analyses focussed on the certolizumab pegol groups as some patients in the placebo group were re-randomised from certolizumab pegol to placebo during the maintenance period they had a shorter duration of exposure to placebo. At 48 weeks (end of maintenance period) within the certolizumab pegol 200mg and 400mg groups treatment-emergent adverse events were reported by 66% (230/348) and 65% (352/540), respectively, and were drug-related in 14% in both groups. In the respective dose groups serious adverse events were reported by 5.2% and 4.6%, and discontinuation due to adverse events was reported for 2.6% and 3.7% of patients.[2]

Pooled data from the three pivotal studies indicate that the commonly reported adverse events in the certolizumab pegol 200mg, certolizumab pegol 400mg and placebo groups during the 16-week induction period were in the group infections and infestations (31%, 36% and 34%), with the most frequent being nasopharyngitis (12%, 13% and 12%) and upper respiratory tract infection (4.9%, 6.7% and 7.0%). Rates in other system organ classes were: skin and subcutaneous tissue disorders (9.7%, 13% and 14%), musculoskeletal and connective tissue disorders (6.9%, 7.9% and 11%) and nervous system disorders (5.1%, 9.4% and 8.3%). The EMA noted a possible small trend towards dose response in general disorders and administration site conditions (5.7%, 6.0% and 8.8%), which was driven by injection site reactions. At 48 weeks, exposure-adjusted incidence rates in both of the certolizumab pegol dose groups were generally comparable, suggesting that the risks after long-term exposure under both dose regimens are similar, though injection site reactions remained slightly higher in the 400mg group.[2]

Summary of clinical effectiveness issues

Certolizumab pegol is the fourth TNF antagonist (after adalimumab, etanercept and infliximab) licensed for treatment of adults with moderate to severe plaque psoriasis. Several other biologic medicines are also licensed for this indication, including an interleukin (IL)-12 and IL-23 inhibitor (ustekinumab), IL-23 inhibitors (guselkumab and tildrakizumab), IL-17 inhibitors (secukinumab and ixekizumab) and an IL-17A receptor antagonist (brodalumab). With the exception of the recently licensed tildrakizumab, these have all been accepted by SMC for restricted use within NHSScotland, with restrictions to use in patients who have failed to respond to standard systemic therapies (including ciclosporin, methotrexate and phototherapy), are intolerant to, or have a contra-indication to these treatments.

In the pivotal phase III studies certolizumab pegol 200mg and 400mg regimens were superior to placebo for the primary outcomes of PASI75 and PGA 0/1 response at week 16 in the CIMPASI studies and PASI75 response at week 12 in the CIMPACT study. Benefits with certolizumab pegol were seen in secondary outcomes that also assessed symptoms of psoriasis and in quality of life, assessed on DLQI. Efficacy, assessed by PASI75 and PGA 0/1 response, was maintained up to week 48 in those who continued certolizumab pegol. In the CIMPACT study certolizumab pegol 400mg was superior to etanercept 50mg twice weekly for PASI75 response at week 12, while certolizumab pegol 200mg was non-inferior to etanercept at a pre-specified non-inferiority margin of 10%.[2-4]

Subgroup analyses of week-16 PASI75 and PGA 0/1 response using pooled data from the pivotal three studies were performed for baseline demographics (age, gender, race, region, weight, body mass index) and disease characteristics (duration of psoriasis, concomitant psoriatic arthritis, prior therapies, baseline PASI and BSA). These were generally consistent with analyses in the total study population and suggest that certolizumab pegol has similar efficacy regardless of prior exposure to biologic therapies.[2] The submitting company has requested that SMC considers certolizumab pegol in two separate subgroups: (1) patients who are inadequate responders to standard non-biologic systemic therapy; and (2) patients who are candidates for non-biologic systemic therapy. Treatment of patients in population 2 would represent a significant change in the current treatment pathway for plaque psoriasis in NHSScotland.

The CIMPACT and CIMPASI studies excluded patients with a history of primary failure to biologic therapy or secondary failure (relapse after an initial response) to more than one biologic medicine. This may limit the application of results to disease that is difficult to control. The populations recruited to the CIMPACT and CIMPASI-1 and -2 studies were mainly naïve to biologic therapies, 72%, 68% and 66%, respectively. Across all three studies only 34 patients (4%) had primary failure on a previous biologic therapy. In this very small subgroup PASI and PGA response rates were lower than in the total study population. However, a definitive conclusion on efficacy in patients who have failed on one biologic cannot be made from such a small sample. The company suggested that evidence of efficacy in patients who have failed on a biologic could be provided by patients in the CIMPACT study within the etanercept group who switched to certolizumab pegol 400mg at week 16. Failure to achieve a week-16 PASI75 response following 12 weeks of etanercept and a 4-week washout may not be an appropriate definition of failure on a biologic medicine. The EMA also noted that etanercept is one of several available biologic medicines and has efficacy towards the lower end of the range of those medicines, which further limits the relevance of this with respect to providing evidence in biologic treatment failure across the range of available medicines.[2]

Evidence in patients who were naïve to systemic non-biologic and biologic medicines is limited to about 30% of the pooled population of the three phase III studies.[2]

The only direct comparative data are with etanercept, which had has been noted by the EMA to have efficacy in the lower range when compared with other biologics in this indication.[2]

In relation to subgroup (1), Bayesian network meta-analyses (NMA) were performed to compare certolizumab pegol 200mg and 400mg with other biologic medicines in adults with moderate to severe psoriasis who were biologic-naïve and -experienced, with a sensitivity analysis performed in biologic-naïve patients. Data were included from 65 studies and presentation of results for PASI response rates (PASI50, PASI75 and PASI90) focused on adalimumab, secukinumab, ixekizumab and ustekinumab (with comparisons to etanercept, infliximab, guselkumab and brodalumab also available). These suggest that both doses of certolizumab pegol had comparable efficacy to the other biologic medicines. The NMA was limited by heterogeneity in definition of moderate-to-severe psoriasis, baseline disease severity, prior biologic and non-biologic treatment, time-points for response assessment, placebo response rates and statistical analyses. There were also limitations with the multinomial modelling approach used and the NMA did not assess long-term outcomes, quality-of-life or safety. Despite these limitations, it is reasonable to suggest comparable efficacy with certolizumab pegol and other biologic medicines.

In relation to subgroup (2), the Bayesian NMA also compared certolizumab pegol with the non-biologic systemic therapies: methotrexate, acitretin, apremilast, dimethyl fumarate and ciclosporin. The results suggested that certolizumab pegol was superior to these. However, in addition to limitations already noted these comparisons were weakened by further issues. The methotrexate studies had heterogeneity in dose. Some studies had small sample sizes and some may have included patients with less than moderate to severe disease, as they had atypical definitions of moderate to severe disease and mean PASI scores lower than the majority of the studies. This was the case for the studies that provided the single sources of data in the NMA for ciclosporin (population, n=80) and acitretin (population, n=42), respectively. The limitations of the NMA are such that it cannot support any conclusion on the relative efficacy of certolizumab pegol compared with systemic non-biologic medicines.

The EMA noted that differences in response rates between certolizumab pegol 200mg and 400mg were not large (approximately 5% to 10%). It was also noted that, although there is a possibility of increased risk of adverse events with a higher (400mg) certolizumab pegol maintenance dose, the updated safety data and the fact that some of the events are too sparse to evaluate lead to a conclusion that there is currently no firm evidence that the safety profile of long-term dosing with certolizumab pegol 400mg significantly differs from 200mg. These points were taken into account in determining certolizumab pegol 200mg as the recommended initial maintenance dose.[2]

Clinical experts consulted by SMC noted that certolizumab pegol is another medicine within the class of TNF antagonists, currently used to treat moderate to severe plaque psoriasis. They stated that available data suggest it may be a potential treatment option in women of childbearing potential.

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

Summary of comparative health economic evidence

The company submitted a cost utility analysis comparing certolizumab pegol to comparators within the following subgroups;

(1) patients who are inadequate responders to standard non-biologic systemic therapy; and
(2) patients who are candidates for non-biologic systemic therapy.

For patients who are candidates for systemic non biologic therapy, certolizumab pegol was compared to standard of care (SoC), which was assumed to consist of a mixture of methotrexate, ciclosporin and acitretin. For patients who are inadequate responders to standard non-biologic systemic therapy, the company compared certolizumab pegol to adalimumab, ustekinumab, secukinumab and ixekizumab.

A lifetime Markov model was used which modelled each treatment as part of a sequence. Patients entered the model on active treatment (in the induction phase), and continued into the maintenance phase depending on their PASI response. Patients were considered responders if they achieved a PASI75-89 and PASI90+ response. Patients who do not respond to treatment (have a PASI score <75) are assumed to discontinue and move on to the next treatment within the sequence. The model allows for up to three lines of treatment before patients receive Best Supportive Care (BSC), which was assumed to consist of the same treatments as SoC.

The clinical data used within the economics came from two sources. For the candidates for systemic non biologic therapy subgroup, PASI response rates for both certolizumab pegol and SoC were based on a non-biologic and biologic naïve subpopulation analysis of the pooled certolizumab pegol studies. Standard of care was represented by the pooled placebo arms within these studies. Based on this analysis, certolizumab pegol was associated with a higher PASI75-<90 response rate compared to standard of care. For the patients with inadequate response to standard non-biologic systemic therapy, direct head to head data versus all relevant comparators were not available, although some direct data were available versus etanercept. A NMA was therefore used, however results of this analysis contained non-significant differences in terms of PASI response rates. The company provided an additional cost- minimisation analysis (CMA) for this subgroup. This was considered as the most appropriate set of analysis for decision-making and therefore only the CMA results are presented.

Medicine acquisition costs for all treatments were included within the analysis for year 1 and subsequent years. For certolizumab pegol, the maintenance dose was 200mg (after a 400mg starting dose at weeks 0, 2 and 4) Administration costs were included for all SC and IV treatments. For SC treatments, the cost of training patients to self-administer at the start of therapy was included. Monitoring costs for both the initial phase and maintenance phase were also included and consisted of full blood count, liver function tests, urea and electrolytes, chest x-rays, tuberculosis tests. Treatment- related adverse events were not included in the model.

Utility values for certolizumab pegol and all other biologics were derived from the certolizumab studies. For SoC, utility values were derived from the placebo arm of the pivotal certolizumab pegol phase III studies. Within these studies EQ-5D-3L data were collected and the company used

a published risk equation to estimate values for each PASI health state which accounted for key variables including age, sex, BMI, PASI response.

A patient access scheme (PAS) was submitted by the company and was assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. PAS discounts are in place for secukinumab and ixekizumab and these were included in the results used for decision-making by SMC by using estimates of the comparator PAS prices.

Table 2: Cost minimisation analysis results for subgroup 1 (inadequate responders to standard non-biologic systemic therapy). Results are presented over 5 years at list prices for all comparators.

Medicine	Incremental costs/savings
certolizumab pegol	-
Adalimumab	£1,065.02
ustekinumab 90mg	-£373.54
ustekinumab 45mg	-£373.54
secukinumab	-£30,454.42
ixekizumab	-£31,202.50

A negative figure denotes incremental savings

Table 3: Base case cost- utility analysis results for subgroup 2 (patients who are candidates for non-biologic systemic therapy) at list price

Medicine	Incremental Cost Effectiveness Ratio (ICER)
standard of care (SoC)	-
certolizumab pegol	£20,019.28

The results presented do not take account of the PAS for secukinumab and ixekizumab or the PAS for certolizumab pegol but these were considered in the results used for decision-making at SMC. SMC is unable to present the results provided by the company which used an estimate of the PAS price for certolizumab pegol, secukinumab and ixekizumab due to commercial confidentiality and competition law issues.

There were a number of weaknesses with the analysis which include the following;

- Patients in the placebo arm within the pooled pivotal studies were not receiving systemic active treatment for psoriasis. As such, there is considerable uncertainty surrounding the clinical efficacy (PASI response) for SoC patients within the subgroup (2) economics. SMC clinical experts consider that the place in therapy for certolizumab pegol is in patients who have previously tried non-biologic therapy. Use of biologic TNFs as an alternative to non-biologic therapies represents a significant change in the treatment pathway. Following the New Drugs Committee meeting, the submitting company requested that SMC should consider certolizumab pegol for use only in subgroup (1) i.e. patients who are inadequate responders to standard non-biologic systemic therapy.
- Given the positioning proposed by the company noted above, this meant that the relevant analysis for decision- making was the CMA reported in table 2 above. The cost minimisation results may be subject to some uncertainty due to the possibility of dose escalation for

certolizumab pegol. It is anticipated that a proportion of patients will continue on certolizumab pegol 400mg as maintenance treatment. The submitting company provided some additional analysis to test the effects of assuming a proportion of patients would receive the higher dose of certolizumab pegol and also threshold analysis to show the percentage of patients who would be required to have the higher dose for cost-minimisation not to be met. These analysis provided some reassurance regarding this source of uncertainty.

Despite these issues, the economic case was considered demonstrated for inadequate responders to standard non-biologic systemic therapy.

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

Summary of patient and carer involvement

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

- We received patient group submissions from the Psoriasis and Psoriatic Arthritis Alliance (PAPAA) and The Psoriasis Association, both organisations are registered charities.

- PAPAA has not received any pharmaceutical company funding in the past two years. The Psoriasis Association has received 4.1% pharmaceutical company funding in the past two years, including from the submitting company.

- Psoriasis is a relentless, visible condition which affects all areas of an individual's life. People with moderate to severe disease can have unsightly red, scaly skin that is not only visible to others, but is also itchy and painful. Owing to the highly visible nature of psoriasis, people can often adopt negative coping mechanisms such as avoiding social situations making the condition both isolating and lonely. It also impacts on employment, participation in education and has effects on the wider family.

- Although there have been advancements in therapy and people are now well served with a range of treatments, there will always be individuals who fail to achieve an adequate response.

- Patient Groups highlighted that certolizumab pegol offers a further option for individuals in whom current standard therapies have failed. This may help patients to live a 'normal' life, which is not restricted by the impact of both the physical and mental aspects of psoriasis. In addition, they suggested that certolizumab pegol may be used in women of childbearing potential,, allowing women to consider raising a family without the risk of destabilising their disease.

Additional information: guidelines and protocols

In October 2010 the Scottish Intercollegiate Guidelines Network (SIGN) issued publication number 121, diagnosis and management of psoriasis and psoriatic arthritis in adults. It recommends that patients with psoriasis who do not respond to topical therapy should be offered narrow band UVB (NBUVB) phototherapy. Psoralen UVA (PUVA) photochemotherapy should be considered for those patients who do not respond to NBUVB. Patients with severe or refractory psoriasis should be considered for systemic therapy with ciclosporin, methotrexate or acitretin, following discussion of benefits and risks. Patients with severe psoriasis who fail to respond to, or have a contraindication to, or are intolerant of phototherapy and systemic therapies including ciclosporin and methotrexate, should be offered biologic therapy unless they have contraindications or are at increased risk of hazards from these therapies. For severe psoriasis, the guideline recommends biologic treatment options in alphabetical order: adalimumab, etanercept, infliximab or ustekinumab .[6]

In September 2017 the National Institute of Health and Care Excellence (NICE) updated clinical guideline number 153, psoriasis: assessment and management. This did not review evidence for use of a first biological agent because guidance on this is available in existing NICE technology appraisals and reference is made to those in adults for adalimumab, etanercept, infliximab, ixekizumab, secukinumab and ustekinumab. The guideline makes a recommendation to consider changing to an alternative biological drug in adults if the psoriasis does not respond adequately to a first biological drug as defined in NICE technology appraisals[39] (at 10 weeks after starting treatment for infliximab, 12 weeks for etanercept, ixekizumab and secukinumab, and 16 weeks for adalimumab and ustekinumab; primary failure) or the psoriasis initially responds adequately but subsequently loses this response, (secondary failure) or the first biological drug cannot be tolerated or becomes contraindicated.[7]

In April 2017 the British Association of Dermatologists (BAD) published Guidelines for biologic therapy for psoriasis. This recommends that biologic therapy be offered to people with psoriasis requiring systemic therapy if methotrexate and ciclosporin have failed, are not tolerated or are contraindicated and the psoriasis has a large impact on physical, psychological or social functioning (for example, a DLQI or cDLQI of >10 or clinically relevant depressive or anxiety symptoms) and one or more of the following disease severity criteria apply: the psoriasis is extensive (defined as BSA >10%, or a PASI ≥10) or the psoriasis is severe at localised sites and associated with significant functional impairment and/or high levels of distress (for example nail disease or involvement of high-impact and difficult-to-treat sites such as the face, scalp, palms, soles, flexures and genitals). It is also recommended to consider biologic therapy earlier in the treatment pathway (for example, if methotrexate has failed, is not tolerated or is contra-indicated) in people with psoriasis that fulfils the disease severity criteria and who also have active psoriatic arthritis or who have psoriasis that is persistent (that is psoriasis that relapses rapidly off a therapy that cannot be continued long-term). The choice of first-line biologic therapy should be tailored to the needs of the person and take into account the psoriasis and patient factors. Initial response to

biologic therapy should be assessed at time points appropriate for the drug in question, and then on a regular basis during therapy (for example, every 6 months). Consider changing to an alternative therapy, including another biologic therapy, if any of the following applies: the psoriasis does not achieve the minimum response criteria (primary failure), the psoriasis initially responds but subsequently loses this response (secondary failure) or the current biologic therapy cannot be tolerated or becomes contraindicated. The choice of second-line biologic therapy may include any of the currently licensed biologic therapies. Consideration should be given to reserving infliximab for use in people with very severe disease or where other available biologic agents have failed or cannot be used. Consider escalating the dose of biologic therapy in adults, where this is feasible and funded when an inadequate primary response may be due to insufficient drug dosing (for example, in people who are obese or whose psoriasis relapses during the treatment cycle). Take into account that this may be associated with an increased risk of infection, and, depending on the drug, off-licence.[8]

Additional information: comparators

Other biologic medicines licensed for the treatment of adults with moderate to severe plaque psoriasis, including adalimumab, brodalumab, etanercept, guselkumab, infliximab, ixekizumab, secukinumab and ustekinumab.

Cost of relevant comparators

Medicine	Dose Regimen	Cost per year (£)
Certolizumab pegol	**400mg SC at weeks 0, 2 and 4, then 200mg or 400mg every two weeks**	**10,010 to 18,590 (year 1: 9,295 to 18,590)**
Brodalumab	210 mg SC at weeks 0, 1, and 2, then every 2 weeks.	16,640 (year 1: 17,280)
Ixekizumab	160mg SC at week 0, then 80mg at weeks 2, 4, 6, 8, 10 and 12, then 80mg every four weeks	14,625 (year 1: 20,250)
Secukinumab	300mg SC at weeks 0, 1, 2, 3 and 4 and then monthly	14,625 (year 1: 19,500)
Guselkumab	100mg SC at weeks 0 and 4, then every 8 weeks	14,625 (year 1: 18,000)
Infliximab	5mg/kg IV at weeks 0, 2 and 6, then every 8 weeks	9,048 (year 1: 12,064)
Ustekinumab	45mg (or 90mg*) SC at weeks 0 and 4, then every 12 weeks	9,304 (year 1: 12,882)

Etanercept	25mg SC twice weekly	8,366
Adalimumab	80mg SC at week 0, then 40mg SC every two weeks	8,237 (year 1: 8,554)

Doses are for general comparison and do not imply therapeutic equivalence. Costs from BNF online on 18 December 2018. Costs calculated using the full cost of vials/ampoules assuming wastage. Costs do not take any patient access schemes into consideration.

Additional information: budget impact

The company assumed that the number of patients eligible for treatment was 1,953 in year 1 rising to 1,977 in year 5. The market share was assumed to be 1.2% in year 1 (23 patients), rising to 5% in year 5 (105 patients). A 20% discontinuation rate was applied in each year resulting in 19 patients being treated in year 1 and 84 patients in year 5.

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

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

References

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This assessment is based on data submitted by the applicant company up to and including 15 February 2019.

**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*

Medicine 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.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a

patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

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.