SMC Scottish Medicines Consortium
Advising on new medicines for Scotland
www.scottishmedicines.org.uk
NHS SCOTLAND
Delta House • 50 West Nile Street • Glasgow • G1 2NP • Tel 0141 225 6999 • Chairman: Dr Alan G MacDonald

Re-Submission

brodalumab 210mg solution for injection in pre-filled syringe (Kyntheum®)

SMC No 1283/17

Leo Laboratories Ltd

6 April 2018

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 resubmission

brodalumab (Kyntheum®) is accepted for restricted use within NHS Scotland.

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

SMC restriction: for 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.

Brodalumab was superior to placebo and to an alternative interleukin inhibitor at improving symptoms in adults with moderate to severe plaque psoriasis.

This advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of brodalumab. It is contingent upon the continuing availability of the Patient Access Scheme in NHS Scotland or a list price that is equivalent or lower.

Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium

Indication

For the treatment of moderate to severe plaque psoriasis in adults patients who are candidates for systemic therapy.[1]

Dosing Information

Brodalumab 210mg subcutaneously at weeks 0, 1 and 2 followed by 210mg every two weeks. Consideration should be given to discontinuing treatment in patients who have shown no response after 12 to 16 weeks of treatment. Some patients with an initial partial response may subsequently improve with continued treatment beyond 16 weeks.

Brodalumab should not be injected into areas where the skin is tender, bruised, red, hard, thick, scaly, or affected by psoriasis.

Brodalumab is intended for use under the guidance and supervision of a physician experienced in the diagnosis and treatment of psoriasis.[1]

Product availability date

July 2017

Summary of evidence on comparative efficacy

Brodalumab is a biologic medicine for the systemic treatment of psoriasis. It is a human monoclonal antibody which selectively binds to and blocks interleukin 17 receptor A (IL-17RA) which inhibits IL-17 cytokine-induced responses resulting in normalisation of inflammation in the skin.[1,2] The submitting company has requested that SMC considers brodalumab when positioned in line with the positioning for biologics in Scotland i.e. for use in patients who have failed to respond to standard systemic therapies (including ciclosporin, methotrexate and phototherapy), are intolerant, or have a contra-indication to these treatments.

Evidence to support the marketing authorisation for brodalumab comes from three double-blind, placebo-controlled, phase III studies (AMAGINE-1, -2 and -3).[2-4] All three studies comprised a 12-week induction phase, a double-blind treatment phase up to 52 weeks and an open-label, long-term extension phase. Both the AMAGINE-2 and -3 studies also included an active control group, ustekinumab. Eligible patients were aged 18 to 75 years with a history of at least six months of stable moderate to severe plaque psoriasis affecting at least 10% of body surface area. Patients also had a static Physician Global Assessment (sPGA) score of ≥3, and Psoriasis Area and Severity Index (PASI) score ≥12 at screening and at baseline.

In the identical AMAGINE-2 and -3 studies (n=1,831 and 1,881, respectively), patients were randomised during the induction phases in a 2:2:1:1 ratio to receive brodalumab subcutaneously (SC) 210mg (licensed dose) or 140mg (on day 1 and weeks 1, 2, 4, 6, 8 and 10), ustekinumab SC (45mg for those weighing ≤100kg and 90mg for those >100kg, on day 1 and week four and then every 12 weeks) or placebo. Randomisation was stratified by baseline bodyweight (≤100kg; >100kg), previous biologic use (which was capped at 50%), and geographical area.[2, 3]

At week 12, patients originally randomised to brodalumab were re-randomised to receive brodalumab 210 mg every 2 weeks or 140 mg every 2 weeks, every 4 weeks or every 8 weeks during the maintenance phase to week 52. Re-randomisation was stratified according to body weight at week 12 (≤100kg; >100kg), induction regimen, and week 12 response (i.e. sPGA 0 or ≥1). Patients originally randomised to placebo received brodalumab 210mg every 2 weeks and those initially randomised to ustekinumab continued to receive ustekinumab during maintenance. At week 16, any patient with an inadequate response (defined as a single sPGA ≥3 or persistent sPGA ≥2 over at least a 4-week period) could receive rescue treatment with brodalumab 210mg every two weeks. Patients not responding to rescue treatment discontinued study medication.

AMAGINE-2 and -3 had two co-primary outcomes that compared both doses of brodalumab with placebo at week 12: PASI 75 (≥75% reduction in PASI from baseline) and sPGA success (a score of 0/1 [clear/almost clear]). The primary outcome of PASI 100 (100% reduction in PASI from baseline) at week 12 was assessed for the comparison of brodalumab with ustekinumab. Key secondary outcomes at week 12 versus placebo included PASI 100, sPGA score of 0 and Psoriasis Symptom Inventory (PSI) response (total score ≤8 with no item scores >1). The key secondary outcome versus ustekinumab was PASI 75 response at week 12. The co-primary outcomes were met for both studies versus placebo as well as the primary outcome versus ustekinumab. In both studies, the median time to PASI 75 response was significantly shorter with brodalumab than ustekinumab. Results for the licensed dose of brodalumab (210mg every two weeks) and comparators are presented in table 1. Since each set of comparisons (brodalumab versus placebo or ustekinumab) used sequential statistical testing, in AMAGINE-2, because PASI 100 between the lower dose of brodalumab (140mg every two weeks) and ustekinumab did not reach statistical significance, further formal statistical testing was stopped.[2, 3]

Table 1: primary and key secondary outcomes at week 12 for brodalumab 210mg, ustekinumab and placebo from the AMAGINE-2 and -3 studies.[2, 3]

	AMAGINE-2			AMAGINE-3		
	Brodalumab	Ustekinumab	Placebo	Brodalumab	Ustekinumab	Placebo
Baseline PASI	20.3	20.0	20.4	20.4	20.1	20.1
PASI 75	86%*[a] (528/612)	70% (210/300)	8.1% (25/309)	85%*[b] (531/624)	69% (217/313)	6.0% (19/315)
sPGA 0/1	79%*† (481/612)	61% (183/300)	3.9% (12/309)	80%*† (497/624)	57% (179/313)	4.1% (13/315)
PASI 100	44%*† (272/612)	22% (65/300)	0.6% (2/309)	37%*† (229/624)	19% (58/313)	0.3% (1/315)
sPGA 0	45%*† (274/612)	22% (65/300)	0.6% (2/309)	37%*[c] (229/624)	19% (58/313)	0.3% (1/315)
PSI response	68%* (414/612)	55% (166/300)	6.8% (21/309)	61%* (382/624)	52% (162/313)	6.3% (20/315)

*p-value versus placebo <0.001; [a] p-value versus ustekinumab =0.08; [b] p-value versus ustekinumab =0.007; † p-value versus ustekinumab <0.001; [c] p-value versus ustekinumab =0.004. PASI 75 = ≥75% reduction in PASI from baseline; sPGA = static Physician Global Assessment 0/1 (clear/almost clear); PSI response = Psoriasis Symptom Inventory. PSI responder: total score ≤8 with no item scores >1.

Quality of life was assessed using the Dermatology Life Quality Index (DLQI) which is a validated, patient-reported, dermatology-specific outcome measure (range of 0 to 30, with higher scores indicating greater impairment of quality of life). At week 12, 61% and 59% of brodalumab patients in AMAGINE-2 and -3 achieved DLQI scores of either 0 or 1 (indicating no impact on quality of life) compared with 44% in both ustekinumab groups and 4.5% and 7% of placebo groups. Of study patients with a DLQI of ≥5 at baseline, an improvement of ≥5 points to week 12 was achieved by 88% of brodalumab, 83% of

ustekinumab and 30% of placebo patients in AMAGINE-2, and by 87%, 85% and 31% of patients respectively in AMAGINE-3.[1, 2]

During the maintenance phase, the key outcome of sPGA success at week 52 was significantly higher in patients re-randomised to the licensed dose of brodalumab (210mg every two weeks) compared with other doses. Pooled analysis of AMAGINE-2 and 3 found that 65% of brodalumab 210mg and 45% of ustekinumab patients achieved sPGA success at week 52.[1] Of patients originally randomised to ustekinumab, who received rescue treatment with brodalumab at week 16, 91% (40/44) patients in AMAGINE-2 and 82% (49/60) patients in AMAGINE-3 achieved PASI 75 at week 52.[3]

In AMAGINE-1, patients were randomised equally during the induction phase to receive brodalumab SC 210mg or 140mg or placebo (on day 1 and weeks 1, 2, 4, 6, 8 and 10), stratified as for AMAGINE-2 and -3. At week 12, patients originally randomised to brodalumab, who achieved sPGA 0 or 1, were re-randomised equally to receive brodalumab (at previous dose) or placebo, stratified by body weight at week 12 (≤100kg; >100kg) and sPGA response (0 or 1). All other patients received brodalumab 210mg every two weeks until week 52. Patients who experienced a return of their disease (defined as sPGA ≥3) between weeks 16 and 52 were retreated with their original dose of brodalumab. AMAGINE-1 had two co-primary outcomes: the proportion of patients who achieved PASI 75 and sPGA success (0 or 1) at week 12 and these were both significantly greater with brodalumab compared with placebo. PASI 75 was achieved by 83% (185/222) of brodalumab patients (licensed dose) and 2.7% (6/220) of placebo patients and sPGA success by 76% (168/222) and 1.4% (3/220) of patients respectively. Key secondary outcomes also significantly favoured brodalumab over placebo, including PASI 100 (42% versus 0.5%) and sPGA score of 0 (42% versus 0.5%) at week 12.[1, 2, 4] Quality of life was significantly improved with brodalumab versus placebo in terms of DLQI (score of 0 or 1 in 56% and 5% of patients respectively at week 12). There were also significantly greater improvements in Hospital Anxiety and Depression Scale (HADS) depression and anxiety scores in brodalumab compared with placebo patients at week 12.[4]

In the withdrawal and re-treatment phase, of those initially randomised to brodalumab 210mg every two weeks, 167 patients were re-randomised at week 12 (84 to placebo and 83 to brodalumab). The key outcome at week 52 of sPGA success was achieved by 83% of brodalumab and no placebo patients.[1, 2, 4]

Limited data from open-label, long-term extensions of AMAGINE-1, 2 and 3 indicate that treatment effects were maintained to five years.

Summary of evidence on comparative safety

Comparative safety data are available from the AMAGINE-2 and -3 studies and are reported in this document for the licensed dose of brodalumab. During the induction phase of AMAGINE-2 and -3 respectively, adverse events were reported by 58% (354/612) and 57% (353/622) of brodalumab patients, 59% (177/300) and 54% (168/313) of ustekinumab patients and 53% (165/309) and 49% (152/313) of placebo patients.[3] Serious adverse events were reported by 1.0% and 1.4% of brodalumab patients, 1.3% and 0.6% of ustekinumab patients and 2.6% and 1.0% of placebo patients in AMAGINE-2 and -3. An adverse event resulted in discontinuation of the study medication in 1.0% and 1.1% of brodalumab patients, 1.3% and 0.6% of ustekinumab patients and 0.3% and 1.0% of placebo patients in AMAGINE-2 and 3[3]

In both studies, the most commonly reported adverse events were nasopharyngitis, upper respiratory tract infection, headache, and arthralgia. *Candida* infections were more frequent in the brodalumab groups than either the ustekinumab or placebo groups. However all were graded as mild or moderate in severity and there were no systemic *Candida* infections. Neutropenia was more observed more

frequently in the brodalumab and ustekinumab groups than in the placebo groups. However, cases of neutropenia were not associated with serious infections, and most cases were mild, transient and reversible. There was one suicide attempt by a patient receiving brodalumab 210mg in AMAGINE-2.[3]

Table 2: adverse events reported during the induction phases of the AMAGINE-2 and -3 studies[3]

	AMAGINE-2			AMAGINE-3		
	Brodalumab (n=612)	Ustekinumab (n=300)	Placebo (n=309)	Brodalumab (n=622)	Ustekinumab (n=313)	Placebo (n=313)
Nasopharyngitis	7.4%	6.0%	4.5%	5.0%	5.1%	7.0%
Upper respiratory tract infection	5.4%	6.7%	7.4%	5.3%	5.1%	5.4%
Headache	5.1%	4.0%	2.9%	3.4%	3.5%	4.5%
Arthralgia	4.6%	3.0%	3.9%	5.8%	1.9%	3.2%
Injection site reactions	1.5%	0.7%	1.0%	1.4%	3.2%	1.9%
Candida infections	1.6%	0.7%	0.6%	1.3%	0.3%	0.3%
Serious infections	0.3%	0	0.3%	0.6%	0.6%	0.3%
Neutropenia	0.2%	0.7%	0	1.1%	0.3%	0
Depression	0.3%	0.7%	0.3%	0.3%	0.3%	0.6%

During the maintenance phase of AMAGINE-2 and AMAGINE-3, adverse events (reported by exposure adjusted event rate) were 403/100 patient years and 397/100 patient years with continuous brodalumab compared with 413/100 patients year and 376/100 patients year with continuous ustekinumab.

Summary of clinical effectiveness issues

Psoriasis is a chronic, immune-mediated, inflammatory condition of the skin with a relapsing-remitting clinical course. Plaque psoriasis is the most common type and is characterised by red, scaly patches, plaques and pustules that usually itch. The main types of treatment for psoriasis include topical therapy (e.g. corticosteroids), phototherapy, and systemic therapy with either conventional agents (e.g. methotrexate, ciclosporin) or biologic agents. Brodalumab, like secukinumab and ixekizumab, is a monoclonal antibody which targets IL-17. It differs from the others by blocking the IL-17A receptor but the significance of this difference is unclear. Secukinumab and ixekizumab have been accepted for restricted use by SMC (advice number 1054/15 in May 2015 and 1223/17 in March 2017, respectively). Other available biologics include the TNF antagonists (infliximab, etanercept and adalimumab) and the anti-IL-12/IL-23 (ustekinumab), which have all been accepted for restricted use by NHS Quality Improvement Scotland (QIS) or SMC. The submitting company has requested that SMC considers brodalumab when positioned as for other biologics in Scotland i.e. for 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.

Brodalumab, at the licensed dose (210mg every two weeks), was superior to placebo in three phase III, double-blind, randomised, controlled studies (AMAGINE-1, -2 and -3) measured by PASI 75 and sPGA (0,1) at week 12; and to ustekinumab (AMAGINE-2 and -3) measured by PASI 100 at week 12. Efficacy

of brodalumab continued during the maintenance phases of the studies up to week 52. The Committee for Medicinal Products for Human Use (CHMP) guidelines on clinical investigation of medicinal products for treatment of psoriasis recommends PASI and a physician global assessment scale (e.g. sPGA) to assess response to treatment. The response to treatment with brodalumab was faster than with ustekinumab (median time to PASI 75 of 4.1 weeks versus 8.1 weeks). Brodalumab was also associated with improvements in quality of life compared with ustekinumab and placebo.

The primary outcomes in the AMAGINE studies were assessed at week 12 (after induction) which is early for a chronic relapsing-remitting condition. However, evidence of efficacy and safety is available from maintenance treatment for up to 52 weeks followed by open-label extensions which terminated early. During the maintenance phases, brodalumab 210mg dose was only assessed when administered every two weeks. Although this is the licensed dose, the European Medicines Agency considered this to be a limitation of the studies since the maintenance effect of 210mg administered less frequently was not explored.[2]

AMAGINE study patients were not required to have failed, or been intolerant or had a contra-indication to conventional systemic therapies and so the study populations were broader than the company's positioning for brodalumab. In the AMAGINE-2 and -3 studies, 76% and 68% of patients respectively, had received previous treatment with systemic therapy or phototherapy. In addition, 25% and 29% of AMAGINE-2 and -3 patients respectively had received previous biologic therapy. The SMC clinical experts indicated that after conventional systemic therapy, TNF antagonists were the most commonly used first-line biologics followed by ustekinumab, secukinumab and ixekizumab. Subgroup analyses have indicated that the treatment effect of brodalumab was similar in both treatment-naïve patients and patients previously treated with systemic treatment or biologics. Limited data on the rescue use of brodalumab following failure of ustekinumab during the maintenance phase of AMAGINE-2 and -3 indicated that the majority of patients achieved PASI 75 at week 52.[2]

Subgroup analysis also found that the treatment effect of brodalumab was lower in patients weighing >100kg than in those ≤100kg. The European Public Assessment Report notes that the company will perform a post-authorisation clinical study to establish the optimal dose in patients with a very high weight.[2]

The withdrawal and retreatment phase of the AMAGINE-1 study provided controlled evidence, limited to those who achieved a response to induction treatment, on the decrease in response rate following treatment withdrawal and the effectiveness of retreatment. However initial responders, re-randomised to placebo at week 12, experienced an inadequate response within a median of 8.1 weeks and required a median of 4 weeks retreatment to regain response and therefore an on-demand treatment regimen was not considered a realistic option.[2,4] The summary of product characteristics (SPC) notes that consideration should be given to discontinuing treatment in patients with no response after 12 to 16 weeks of treatment but that some patients with an initial partial response may subsequently improve with continued treatment beyond 16 weeks.[1]

Since comparative data are limited to ustekinumab, the company presented results of a Bayesian network meta-analysis (NMA) of 54 studies (41 in base case) which compared brodalumab with other biologic treatments (adalimumab, etanercept, infliximab, ixekizumab, secukinumab and ustekinumab) and apremilast in patients with moderate to severe plaque psoriasis. The relative efficacies were compared using PASI response rates at different levels. The NMA indicated that brodalumab, at the licensed dose, was more effective than adalimumab, apremilast, etanercept and ustekinumab and of similar efficacy to infliximab, ixekizumab and secukinumab. There are a number of limitations which affect the validity of these results. The target population was broader than the proposed positioning within the company submission. The NMA limited comparison to induction treatment only and there was no comparison of safety or health-related quality of life data.

There was heterogeneity across the studies in the time points for assessment of PASI responses and in baseline characteristics, including duration of psoriasis, PASI score and prior use of previous treatments including biologics. A number of sensitivity analyses, performed to consider the impact of disease severity and previous biologic treatment, found similar results.

The availability of brodalumab would offer the service and patients another biologic treatment option for patients with moderate to severe plaque psoriasis who have failed to respond to conventional non-biologic systemic therapies. Brodalumab is administered SC every two weeks which is a shorter dosing interval, particularly during maintenance treatment, than is recommended for other biologics, including ustekinumab, secukinumab, ixekizumab and infliximab. The adverse event profile for brodalumab is characteristic of medicines within the class of immunomodulators. However, the SPC also notes that suicidal ideation and behaviour, including completed suicide, have been reported in patients treated with brodalumab.[1]

Clinical experts consulted by SMC considered that brodalumab is a therapeutic advancement due to its different mechanism of action compared with existing anti-IL-17A medicines and that its place in therapy was as an alternative anti IL-17A treatment option.

Summary of comparative health economic evidence

The submitting company presented a cost-utility analysis (CUA) comparing brodalumab to adalimumab, etanercept 50mg per week and ustekinumab with the licensed dosing; and a cost-minimisation analysis (CMA) comparing brodalumab to ixekizumab and secukinumab. SMC clinical experts indicated that the most relevant comparators were secukinumab, ixekizumab, and potentially also ustekinumab. All patients were assumed to have moderate to severe plaque psoriasis, had failed on prior systemic treatments or were intolerant to systemic therapies.

The cost-utility analysis was underpinned by a Markov state-transition model with 2 weeks cycles using a 5 year time horizon. The model consisted of four treatment related health states: induction phase, maintenance phase which was further divided by PASI response levels, best supportive care (BSC) and death. Patients entered the model in the induction stage at the end of which they were assigned to a particular PASI state based on their PASI response. Patients without an adequate response continued directly from the induction phase to the BSC state. In the base case, patients with a PASI response lower than 75% were considered non-responders to the treatment. Patients with an adequate response remained in the same PASI response state during the maintenance phase until treatment discontinuation or death. An annual discontinuation rate of 18.7% was applied whilst in the maintenance phase. After entering the BSC state patients reverted to the placebo responses from the NMA and received non-biologic supportive therapy until the end of the modelled time horizon or death. The cost-minimisation analysis was based on the same model but same efficacy inputs were assigned to all medicines.

In the absence of head-to-head studies of brodalumab to comparators other than ustekinumab and placebo, the company conducted an NMA as noted above. Outputs of this NMA were used to inform the clinical inputs of the model. Utility values were derived from responses to an EQ-5D questionnaire from the AMAGINE-1 study and valued using a UK dataset. These varied by PASI response. No costs or utility decrements were included for adverse events as similar safety profiles among therapies were assumed.

The costs included medicines acquisition costs, monitoring costs and costs associated with BSC. Use of medicines was consistent with that observed in the underlying clinical studies. The cost of biosimilar etanercept was used in the base case analysis. BSC was modelled using results of a retrospective

observational study. Costs of adverse events were included in a scenario analysis.

A patient access scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. 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.

Incremental cost effectiveness ratios (ICERs) were presented for a fully incremental cost-utility analysis of pairwise comparisons for brodalumab versus adalimumab, etanercept, and ustekinumab. Without the PAS, brodalumab had an ICER of £116,333 per QALY versus ustekinumab. All pairwise results of the cost-utility analysis are presented in table 1. SMC would wish to present the with-PAS cost-effectiveness estimates that informed the SMC decision. However, owing to the commercial in confidence concerns regarding the PAS, SMC is unable to publish these results. As such, only the without-PAS figures can be presented.

Table 1: Cost-effectiveness results for brodalumab against adalimumab, etanercept, and ustekinumab at list prices

Treatment	Incremental costs at list price	Incremental QALYs	Results at list price
Adalimumab	£22,544	0.252	£89,329
Etanercept	£26,664	0.447	£59,635
Ustekinumab	£20,609	0.177	£116,333

In the cost minimisation analysis, brodalumab was compared to secukinumab and ixekizumab which were considered the main comparators by the SMC clinical experts. The results using list prices for all medicines are shown in table 2.

Table 2: Cost-minimisation results for brodalumab against secukinumab and ixekizumab at list prices

Treatment	Acquisition drug costs	Monitoring costs	BSC costs	Total cost	Incremental cost (brodalumab versus comparator)
Brodalumab	£44,695	£686	£9,959	£55,340	
Secukinumab	£43,380	£686	£9,959	£54,025	£1,315
Ixekizumab	£43,206	£686	£9,959	£53,851	£1,489

The results presented do not take account of the PAS for secukinumab and ixekizumab or the PAS for brodalumab 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 secukinumab and ixekizumab due to commercial confidentiality and competition law issues.

The submitting company performed one-way sensitivity analyses and scenario analyses. Results from sensitivity analyses for brodalumab versus ustekinumab showed that the main inputs and assumptions influencing the cost-utility results were efficacy and utility variables as shown in table 3. Without the PAS, using the upper bound of the 95% credibility interval for efficacy of ustekinumab or assuming that 65% patients receiving BSC would reach PASI 50 resulted in ICERs of approximately £165k and £148k per QALY, respectively.

Table 3: Results of the CUA sensitivity analysis for brodalumab versus ustekinumab at list prices

	Scenario	ICERs at list prices
1	Lower bound of efficacy of ustekinumab	£91,341
2	Upper bound of efficacy of ustekinumab	£164,969
3	Lower bound of BSC annual cost	£122,145
4	PASI responses from NMA adjusted model	£117,719
5	Drug class-specific discontinuation rate	£113,866
6	No utility gains during induction	£111,758
7	Utility data from all patients with moderate to severe psoriasis	£145,803
8	Efficacy of BSC of 65% PASI 50	£147,964
9	Inclusion of adverse events	£116,356
10	Time horizon: 1 year	£108,889
11	Time horizon: 10 years	£117,058

Results from sensitivity analyses for brodalumab versus secukinumab and ixekizumab in the CMA are presented in table 4 below using list prices for medicines costs.

Table 4: Results of the CMA sensitivity analysis against secukinumab and ixekizumab at list prices

	Scenario	At list prices	
		Results versus secukinumab*	Results versus ixekizumab*
1	Annual discontinuation rate 14.9%	£1,750	£1,935
2	Annual discontinuation rate 22.4%	£917	£1,078
3	Time horizon: 2 years	−£1,072	−£899
4	Time horizon: 10 years	£2,869	£3,043

* A negative sign in the results column indicates that brodalumab is cost-saving against the comparator and therefore cost-minimisation is demonstrated.

The main weaknesses include:

- SMC clinical experts advised that clinical practice can vary depending on disease characteristics and that consequently some of the available biologic treatments may be used in a sequence. Secukinumab, ixekizumab and ustekinumab were indicated to be the preferred alternatives in the second or third line of treatment, i.e. after TNF inhibitors. Not assuming treatment sequences in the economic evaluation appears reasonable given the likely positioning of brodalumab and the other anti-IL17A treatment options towards the end of the treatment sequence.
- There is some uncertainty surrounding the generalisability of BSC as modelled to Scottish setting. However, as it was modelled for all comparators identically, this is unlikely to introduce large bias in the economic evaluation, particularly in cost-minimisation analysis.
- The cost-utility analysis was informed by the NMA that did not distinguish between patients relative to prior treatment experience and contained some weaknesses as noted above.

Despite these weaknesses, the economic case has 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.

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

- The Psoriasis Association has received 4.09% pharmaceutical company funding in the past two years, including from the submitting company. PAPAA has not received any pharmaceutical company funding in the past two years.

- Psoriasis is a lifelong, visible condition which can occur at any age. It can be a debilitating disease that impacts all aspects of life, physically and psychologically. Owing to the highly visible nature of psoriasis, patients often avoid social situations and it can affect career choice. It can also have a significant impact on the wider family and on personal relationships.

- Although there have been advances in therapy there will always be individuals with an unmet need where current therapies do not work or begin to fail.

- To help psoriasis sufferers lead as satisfying a life as those without the condition, patients and their carers welcome access to a range of treatments in the pathway for different grades of severity, with a wide choice of options available if initial treatments fail. Brodalumab would offer an alternative biologic therapy with the opportunity to increase quality of life.

Additional information: guidelines and protocols

The British Association of Dermatologists (BAD) guidelines for biologic therapy for psoriasis has recently been updated in 2017.[6] This recommends offering biologic therapy to patients requiring systemic therapy, when methotrexate and ciclosporin have failed, are not tolerated or are contra-indicated, and when the psoriasis has a large impact on physical, psychological and social functioning as well as having extensive disease (BSA >10% or PASI ≥10 or at least moderate on PGA) and/or severe disease in localised sites and associated with significant functional impairment and/or high levels of distress. Biologic therapy can be considered earlier in the treatment pathway (e.g. if methotrexate has failed, is not tolerated or is contra-indicated) in patients who meet the disease severity criteria and also have psoriatic arthritis or have persistent psoriasis. The guideline makes recommendations on choice of biologic, including the following first-line agents: offer ustekinumab, or (particularly in patients with psoriatic arthopathy) adalimumab and consider (in patients with or without psoriatic arthritis) secukinumab. For those not responding to first-line treatment, any licensed biologic can be considered for second-line use, giving consideration to disease and patient factors. The guideline also recommends that infliximab should be reserved for patients with very severe disease (PASI ≥20 or DLQI ≥18). This predates the availability of brodalumab.

Several other European and British guidelines exist regarding systemic treatment of psoriasis; these predate the availability of secukinumab, ixekizumab and brodalumab.

The Scottish Intercollegiate Guidelines Network (SIGN) guideline on Diagnosis and management of psoriasis and psoriatic arthritis in adults was published in 2010.[7] This recommends that patients with severe psoriasis who have failed 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. Adalimumub, etanercept, ustekinumab and infliximab are recommended:

- Adalimumab loading regimen followed by 40mg every other week is recommended in the treatment of severe psoriasis.
- Etanercept 25mg twice weekly or 50mg weekly is recommended in the treatment of severe psoriasis.
- Infliximab 5mg/kg at weeks 0, 2, 6 and repeated as maintenance treatment every two months is recommended in the treatment of severe psoriasis, especially when rapid disease control is required.
- Ustekinumab 45mg for patients weighing under 100kg and 90mg for patients weighing over 100kg given at weeks 0 and 4 then every 12 weeks as maintenance is recommended in the treatment of severe psoriasis.

Good practice points note that the use of biologic treatments should conform to the BAD guidelines (2009). The comparative long-term safety of systemic and biologic treatments for severe psoriasis is currently being investigated in a five-year treatment register, the British Association of Dermatologists Biologic Interventions Register (BADBIR) (www.badbir.org). Patients on biologic therapies should be offered the opportunity to join the long term safety register BADBIR.[7]

The National Institute for Health and Care Excellence (NICE) published a clinical guideline on the assessment and management of psoriasis in 2012, which was updated in September 2017.[8] The guideline makes broadly similar recommendations as the SIGN guideline regarding the use of biologics.

Additional information: comparators

Other biologic agents (adalimumab, infliximab, etanercept, ustekinumab, secukinumab and ixekizumab).

Cost of relevant comparators

Medicine	Dose Regimen	Cost per year (£)
Brodalumab	**210mg SC at weeks 0, 1 and 2 and then every two weeks**	**First year: 17,280 Subsequent years: 16,640**
Ixekizumab	160mg SC at week 0, followed by 80mg SC at weeks 2, 4, 6, 8, 10 and 12, then maintenance dosing of 80mg every four weeks	First year: 20,250 Subsequent years: 14,625
Secukinumab	300mg SC at weeks 0, 1, 2, 3 and 4 and then monthly	First year: 19,500 Subsequent years: 14,625
Ustekinumab	45mg (or 90mg*) SC at weeks 0 and 4 and then every 12 weeks	First year: 12,882 Subsequent years: 9,304
Infliximab	5mg/kg IV at weeks 0, 2 and 6, then every 8 weeks	First year: 12,064 Subsequent years: 9,802
Adalimumab	80mg SC at week 0, then 40mg SC every two weeks	First year: 9,860 Subsequent year: 9,156
Etanercept	25mg SC twice weekly or 50mg SC weekly**	8,528

*Doses are for general comparison and do not imply therapeutic equivalence. Costs for adalimumab from eVadis on 3 January 2018. Costs for brodalumab, etanercept, infliximab, ixekizumab, secukinumab and ustekinumab from electronic medicines compendium (eMC) dictionary of medicines and devices on 31 January 2018. Costs calculated using a bodyweight of 70kg and the full cost of vials/ampoules assuming wastage. * ustekinumab 90mg*

*given if bodyweight >100kg. **if necessary, etanercept 50mg SC twice weekly may be given for 12 weeks then 25mg twice weekly or 50mg weekly. SC=subcutaneous. IV=intravenous. Costs do not take any patient access schemes into consideration.*

Additional information: budget impact

The submitting company estimated there would be 1,863 patients eligible for treatment with brodalumab in year 1 rising to 1,907 patients in year 5 to which confidential estimates of treatment uptake were applied.

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 commercially confidential.**

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This assessment is based on data submitted by the applicant company up to and including 16 March 2018.

**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*

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 drug 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 NHS Scotland 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 NHS Scotland 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.