Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
www.scottishmedicines.org.uk
Delta House 50 West Nile Street Glasgow G1 2NP Tel 0141 225 6999 Chairman: Dr Alan G MacDonald

baricitinib 2mg and 4mg film-coated tablet (Olumiant®) SMC No 1265/17

Eli Lilly and Company Ltd.

4 August 2017

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

baricitinib (Olumiant®) is accepted for restricted use within NHS Scotland.

Indication under review: treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drugs (DMARDs). Baricitinib may be used as monotherapy or in combination with methotrexate.

SMC restriction: In patients with severe disease (a disease activity score [DAS28] greater than 5.1) that has not responded to intensive therapy with a combination of conventional DMARDs. In patients with severe disease inadequately controlled by a TNF antagonist, it may be used in patients ineligible to receive rituximab.

Baricitinib, compared with placebo and with a tumour necrosis factor (TNF) antagonist, significantly improved signs and symptoms of RA in patients with an inadequate response to conventional DMARDs and, compared with placebo, in patients who had an inadequate response to a TNF antagonist.

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

Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium

Published 11 September 2017

Indication

Treatment of moderate to severe active RA in adult patients who have responded inadequately to, or who are intolerant to one or more DMARDs. Baricitinib may be used as monotherapy or in combination with methotrexate.[1]

Dosing Information

4mg orally once daily with or without food. A dose of 2mg once daily is appropriate for patients such as those aged at least 75 years and may be appropriate for those with a history of chronic or recurrent infections or those who have achieved sustained control of disease activity with 4mg once daily and are eligible for dose tapering.[1]

Treatment should be initiated by physicians experienced in the diagnosis and treatment of rheumatoid arthritis.[1]

Product availability date

4 April 2017

Summary of evidence on comparative efficacy

Baricitinib reversibly inhibits JAK1 and JAK2 enzymes, which transduce intracellular signals from cell surface receptors for several cytokines and growth factors involved in haematopoiesis, inflammation and immune function. Baricitinib modulates these signalling pathways and reduces serum immunoglobulin, lymphocytes and C-reactive protein (CRP). It also inhibits some intracellular signals induced by interleukin-6 (IL-6), i.e. it inhibits IL-6 induced signal transducers and activators transcription (STATs) phosphorylation.[1]

Three double-blind phase III studies (RA-BEAM, RA-BUILD and RA-BEACON)[2-5] recruited adults with moderate to severe active RA, defined by at least six tender joints (of 68 examined) and six swollen joints (of 66 examined) plus an elevated c-reactive protein (CRP) concentration. RA-BEAM also required that patients have at least three joint erosions in hand, wrist, or foot joints based on central radiographs or at least one erosion in these joints and be rheumatoid factor (RF) or anti-citrullinated peptide antibody (ACPA) antibody positive. In RA-BEAM and RA-BUILD patients were biologic-naive and were intolerant to or had inadequate response, in RA-BEAM, to at least 12 weeks (at stable doses for at least eight weeks) of methotrexate 7.5mg to 25mg per week (clinical rationale provided if <15mg) and, in RA-BUILD, to conventional DMARDs. In RA-BEACON patients received at least 12 weeks of conventional DMARD and were intolerant to or had an inadequate response to three months treatment with a tumour necrosis factor (TNF)-antagonist. In RA-BEAM patients were randomised in a 3:3:2 ratio to baricitinib 4mg once daily, placebo,or adalimumab 40mg subcutaneously every other week for 52 weeks, with patients in the placebo group switched, without their knowledge, to baricitinib 4mg once daily from week 24. In the other studies patients were randomised equally to once daily baricitinib 4mg, 2mg or placebo for 24 weeks. Patients could continue to receive concomitant treatment with stable doses of conventional DMARDs, non-steroidal anti-inflammatory drugs (NSAIDs), analgesics and glucocorticoids (≤10mg prednisolone daily or equivalent). In all studies the primary outcome was proportion of patients achieving at least 20% improvement on American College of Rheumatology criteria (ACR20) response at 12 weeks and the primary comparison was versus placebo, with a

secondary comparison versus adalimumab in RA-BEAM. This was assessed in the modified intention-to-treat population, which comprised all randomised patients who received at least one dose of study drug.[2-5]

Across the studies the proportion of patients achieving an ACR20 response at week 12 was significantly greater with baricitinib (both doses) compared with placebo and with baricitinib 4mg compared with adalimumab, as summarised in table 1 below.There were also significant improvements with baricitinib (both doses), compared with placebo, for the secondary outcomes ACR50 and ACR70 responses and low disease activity (defined by 28-joint disease activity score [DAS28-ESR] ≤3.2). In the RA-BEAM and RA-BUILD studies of patients with inadequate response to conventional DMARDs, the proportion of patients in remission (defined by simplified disease activity index [SDAI] ≤3.3) was also significantly increased with baricitinib.[2-5]

Table 1: Primary and secondary endpoints at week 12.[1-5]

	ACR20	ACR50	ACR70	SDAI ≤3.3	DAS28-ESR≤3.2
RA-BEAM (unresponsive or intolerant of methotrexate)					
Baricitinib 4mg (n=487)	70%**#	45%**#	19%**#	8%**	24%**
Placebo (n=488)	40%	17%	5%	2%	7%
Adalimumab (n=330)	61%**	35%**	13%**	7%**	21%**
RA-BUILD (unresponsive or intolerant of conventional DMARDs)					
Baricitinib 4mg (n=227)	62%**	34%**	18%**	9%**	22%**
Baricitinib 2mg (n=229)	66%**	33%**	18%**	9%**	21%**
Placebo (n=228)	39%	13%	3%	1%	7%
RA-BEACON(unresponsive or intolerant of at least one TNF antagonist)					
Baricitinib 4mg (n=177)	55%**	28%**	11%*	5%	12%*
Baricitinib 2mg (n=174)	49%**	20%*	13%**	2%	13%*
Placebo (n=176)	27%	8%	2%	2%	4%

*p≤0.01; **p≤0.001 versus placebo; #p≤0.05 versus adalimumab; ACR20, ACR50 and ACR70 = 20%, 50% and 70% improvement in American College of Rheumatology criteria; SDAI = simplified disease activity index; DAS28-ESR = disease activity score on 28 joints; DMARDs = disease modifying anti-rheumatic drugs; TNF = tumour necrosis factor.

In RA-BEAM and RA-BUILD baricitinib, compared with placebo, significantly reduced the progression of joint damage as measured by least square (LS) mean increase in modified total Sharp score **(**mTSS), erosion score and joint space narrowing and increased the proportion of patients with no radiographic progression at week 24 and 52 as detailed in table 2.

Table 2: Radiographic endpoints in RA-BEAM and RA-BUILD.[1,3,4]

	LS Mean change from baseline:			Proportion of patients with no radiographic progression
	mTSS	Erosion Score	Joint Space narrowing	
RA-BEAM (unresponsive or intolerant of methotrexate) 24 weeks				
Baricitinib 4mg (n=487)	0.41***	0.29***	0.12**	81%***
Placebo (n=488)	0.9	0.61	0.29	70%
Adalimumab (n=330)	0.33***	0.24***	0.10**	83%***
RA-BEAM (unresponsive or intolerant of methotrexate) 52 weeks				
Baricitinib 4mg (n=487)	0.71***	0.51***	0.21***	79%**
Placebo (n=488)	1.80	1.23	0.58	70%
Adalimumab (n=330)	0.60***	0.42***	0.19**	81%**

RA-BUILD (unresponsive or intolerant of conventional DMARDs) 24 weeks				
Baricitinib 4mg (n=227)	0.15**	0.11**	0.04*	80%
Baricitinib 2mg (n=229)	0.33*	0.30	0.03*	72%
Placebo (n=228)	0.70	0.47	0.23	74%

******* p<0.001, ** p≤0.01, *p≤0.05 versus placebo. LS = least square; mTSS = modified total Sharp score; DMARDs = disease-modifying anti-rheumatic drugs

Baricitinib, compared with placebo, significantly increased the proportion of patients achieving the minimum clinically important change on HAQ-DI (decrease of at least 0.30) and significantly improved LS mean change from baseline to 12 weeks for this outcome and the quality of life outcomes, short-form 36 (SF-36) physical component summary score, and functional assessment of chronic illness therapy – fatigue (FACIT-F).[1,6-8]

Patients who completed the treatment period of RA-BEAM, RA-BUILD or RA-BEACON were eligible to enter the ongoing long-term extension study, RA-BEYOND. Patients received oral baricitinib 4mg or 2mg daily as a continuation of their dose in the preceding study.[2] A subgroup of patients who had sustained low disease activity or remission (Clinical Disease Activity Index [CDAI]≤10) after at least 15 months of baricitinib 4mg daily were re-randomised to double-blind baricitinib 4mg or 2mg daily. There were significant differences between the group continuing on the 4mg dose and the group reduced to the 2mg dose for maintenance of low disease activity based on CDAI score: 93% (234/251) versus 82% (207/251) at 12 weeks; 85% (163/191) versus 76% (144/189) at 24 weeks; and 78% (57/73) versus 59% (51/86) at 48 weeks, in the respective groups. The majority of patients who lost their low disease activity or remission status after dose reduction could regain disease control after the dose was returned to 4mg.[1]

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

Summary of evidence on comparative safety

It was noted by the European Medicines Agency (EMA) that baricitinib has a complex safety profile. Therefore, it is recommended in the summary of product characteristics (SPC) that it should only be used under supervision of an experienced specialist.[2]

Across the clinical studies (RA-BEAM, RA-BUILD and RA-BEACON plus three phase II studies) data through 24 weeks or up to rescue indicated that significantly more patients in the baricitinib 4mg group, compared with placebo, reported infections: 36% versus 28%. However, rates of serious infections were similar 1.5% and 1.6%, respectively. The most commonly reported infections were upper respiratory tract infections, herpes zoster and herpes simplex. Due to its mode of action, baricitinib can cause viral reactivation and herpes zoster and herpes simplex were more frequently reported for baricitinib than for placebo. It is noted in the SPC that herpes zoster was reported more commonly in patients ≥65 years of age who had previously been treated with both biologic and conventional DMARDs. If a patient develops herpes zoster, baricitinib treatment should be temporarily interrupted until the episode resolves. Baricitinib induces low density lipoprotein (LDL) and high density lipoprotein (HDL) cholesterol, the LDL/HDL ratio remained unchanged after baricitinib treatment. Weight and waist circumference were also increased, however, baricitinib has so far not been associated with a higher incidence of cardiovascular events. Baricitinib can interfere with haematopoiesis and across the clinical studies the rate of anaemia was marginally increased with baricitinib 4mg. The SPC recommends monitoring of haemoglobin as part of routine patient management. Baricitinib has also been associated with

increased liver enzymes and, possibly by reducing renal excretion, it increases serum creatinine. It was also associated with increases in creatine phosphokinase, but these were not clearly accompanied by clinical symptoms of muscle damage. The SPC also advises monitoring for possible increased risk of malignancy, including lymphoma, in patients with rheumatoid arthritis receiving immunomodulatory medicines.[2]

In RA-BEAM there were similar rates of adverse events with baricitinib and adalimumab, 71% versus 68%. There were low rates of serious adverse events, 4.7% and 1.8%, and withdrawals due to adverse events, 4.9% and 2.1%, respectively. The pattern of adverse events with baricitinib and adalimumab was generally similar. For some laboratory analysis (e.g. serum creatinine, creatine phosphokinase, LDL and HDL-cholesterol), changes with baricitinib and adalimumab were in the same direction, but larger with baricitinib.[3]

Summary of clinical effectiveness issues

Baricitinib is the first JAK inhibitor licensed in the UK for the treatment of RA.

RA is a chronic systemic inflammatory disease primarily affecting the joints. Patients with moderate to severely active disease have persistent systemic inflammation with elevated acute phase proteins and pro-inflammatory cytokines. Joint inflammation directly affects the synovial membrane and bone resulting in permanent joint damage that can lead to disability. Patients can have symptoms of fatigue, pain and joint stiffness and may have associated co-morbidities of cardiovascular disease, infections, mental health disorders and malignancies.[2]

Scottish Intercollegiate Guidelines Network (SIGN) guidance recommends that all patients with moderate to severe disease activity should receive DMARDs, adjusted to achieve remission or a low disease activity score.[9] Treatment is usually initiated with a conventional DMARD. For patients with severe disease not adequately controlled by conventional DMARDs Healthcare Improvement Scotland (HIS) has endorsed National Institute of Health and Care Excellence (NICE) technology assessment TA375 which recommends the following biologic medicines (in combination with methotrexate) as treatment options: adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept. Adalimumab, etanercept, certolizumab pegol and tocilizumab can be used as monotherapy for people who cannot take methotrexate because it is contraindicated or because of intolerance. For patients with severe disease not adequately controlled by conventional DMARDs and a TNF-antagonist, HIS has endorsed NICE TA195, which recommends rituximab and, for rituximab-ineligible patients, the following biologic medicines (in combination with methotrexate) are treatment options: adalimumab, etanercept, infliximab and abatacept.[10-13]

Clinical experts consulted by SMC note that there is an unmet need for effective therapies for patients who have RA not adequately controlled by currently available conventional DMARDs and biologic medicines.

In the three pivotal studies the primary outcome was ACR20 response. This has been the primary outcome in many studies of DMARD. However, regulatory advice on the appropriate outcomes for studies of DMARD may be changing towards the use of outcomes that measure low disease activity or remission.[14] It was noted by the EMA that ACR20, which represents a change from baseline in signs and symptoms of at least 20%, was a low target in view of the efficacy of available DMARDs, may not be appropriately sensitive to detect a treatment effect due to high

placebo response rates, and 20% change may represent a small absolute difference in patients with at least moderately severe RA. Low disease activity and remission outcomes were considered to have clearer clinical relevance and were taken into account during the EMA review of efficacy. As these outcomes were achieved throughout the baricitinib studies, issues around choice of primary outcome were not raised.[2]

It was noted by the EMA that for DMARDs, such as baricitinib, which target acute phase reactants (e.g. CRP), the DAS28-CRP outcomes may overestimate clinical response, and that there may be silent residual inflammation in the joints even though CRP is low. SDAI and CDAI scores, which are less influenced by CRP, were included in the EMA review. In general, the conclusions for DAS28-CRP outcomes of low disease activity were congruent with estimates using SDAI and CDAI. However, DAS28 remission rates were higher for DAS28-CRP. The SDAI (and Boolean remission by ACR-EULAR) was more conservative.[2]

In the three pivotal studies baricitinib significantly increased the proportion of patients achieving an improvement in signs and symptoms of RA, compared primarily with placebo, as measured by the primary outcome, ACR20, at week 12 and by secondary outcomes including ACR50 and ACR70.[2-5] Particularly relevant in view of the proposed new EMA guidance on investigation of medicines for RA[14], were the benefits in rates of low disease activity, assessed by DAS-28-hsCRP and DAS28-ESR and remission, that was assessed by these outcomes and by SDAI and CDAI. Baricitinib also improved physical function and quality of life. In the two studies that recruited patients with an inadequate response to conventional DMARDs baricitinib, compared with placebo, significantly delayed progression of radiographically-assessed joint damage.[2-5]

There was no radiographic assessment of joint damage in the study (RA-BEACON) of patients who had an inadequate response to TNF-antagonists.[5] Therefore, there is no evidence of an effect of baricitinib on progression of joint damage in this group of patients. There are limited data on use of baricitinib as monotherapy; this is only available from a subgroup of 48 patients from the RA-BUILD study.

In RA-BEAM, which recruited patients with an inadequate response to methotrexate, baricitinib, compared with adalimumab, was associated with significantly increased ACR20, ACR50 and ACR70 response rates at week 12. However, there were no significant differences in remission rates, progression of joint damage, physical function or quality of life.[3] There was no direct comparative evidence relative to other relevant comparators therefore two indirect comparisons were presented using Bayesian network meta-analyses (NMA) comparing effects on ACR20, ACR50, ACR70 and European League Against Rheumatism (EULAR) response.

The first NMA compared baricitinib plus conventional DMARD versus biologic medicines (tocilizumab, abatacept, adalimumab, infliximab, etanercept, rituximab, golimumab, certolizumab pegol and tofacitinib) plus conventional DMARD and versus biologic medicines alone (tocilizumab, adalimumab, etanercept, infliximab and rituximab) in patients with moderate to severe RA not adequately controlled by conventional DMARDs. The second compared baricitinib plus conventional DMARD with biologic medicines (golimumab, tocilizumab, abatacept and rituximab) in combination with conventional DMARD in patients with moderate to severe RA not adequately controlled by a TNF antagonist. The NMAs included 48 and six studies, respectively. They suggested that overall, there were no clear differences between baricitinib and comparators. Weaknesses identified included; issues with study selection, heterogeneity in study design, including background DMARD, use of rescue medication and analysis of ACR response rates, baseline disease severity, outcomes across the common conventional DMARD control group, failure to include any outcomes for radiographic disease progression, functional impairment,

quality-of-life or safety and use of an algorithm to estimate much of the EULAR data. Despite the weaknesses it was felt that the NMA supported the conclusion that baricitinib and the comparators were broadly similar.

The EMA noted in that in subgroup analyses of pooled data from four phase III studies (RA-BEAM, RA-BUILD, RA-BEACON and RA-BEGIN) there were no relevant trends for gender, age groups, race, disease duration and baseline disease activity. However, there was a lower response for patients weighing >100kg (8.8% of the study population) and/or high body mass index, including low disease activity and HAQ-DI endpoints. For example, the odds ratio to obtain the low disease activity outcome, DAS28-CRP <3.2 response, versus placebo was 6.56 for patients <60kg, 3.75 for patients ≥60 and <100kg and 2.32 for patients ≥100kg. This was only partly explained by reduced plasma levels at higher bodyweight, since the reduction in plasma exposure was marginal in those with high body weight. Also patients with a high bodyweight who achieved target pharmacokinetic levels still responded less than the general population. It was also noted that patients with high bodyweight had higher disease activity at baseline. The EMA concluded that considering these factors and the risks of higher baricitinib doses no dose adjustment are required for this population.

Clinical experts consulted by SMC consider that baricitinib is a therapeutic advance due to its novel mechanism of action and oral route of administration, which may have advantages for the patient and service compared with biologic medicines, which are administered parenterally by intravenous or subcutaneous injection. They suggest that it may be used initially as a third or later-line biologic therapy, but may be used earlier in the treatment pathway in the future.

Summary of comparative health economic evidence

The submitting company presented a range of economic analyses of baricitinib in combination with methotrexate as follows:

- Cost- minimisation analyses (CMA) of baricitinib in patients with severe disease inadequately controlled by conventional DMARDs (severe cDMARD-IR) and also in patients ineligible for rituximab who have severe disease inadequately controlled by aTNF-antagonist (severe rituximab-ineligible TNF-antagonist IR). The comparator treatments in both CMAs were abatacept, adalimumab, certolizumab pegol, biosimilar etanercept, biosimilar infliximab, golimumab and tocilizumab. The analyses were presented at 2, 5 and 10 year time horizons.
- Cost- utility analysis (CUA) of baricitinib in patients who have moderate disease inadequately controlled by conventional DMARDs (moderate RA cDMARD-IR) IR patients. The comparator treatment for this analysis was best supportive care consisting of treatment with a combination of conventional DMARDs and a 45 year time horizon was used.

The submitting company also presented a CUA of baricitinib versus a sequence of treatments including rituximab in patients who are TNF-antagonist insufficient responders but eligible to receive rituximab, however the company indicated that they would not expect baricitinib to be used in this population. No economic analysis was presented for use of baricitinib as monotherapy.

For the CMAs, NMA were used to support the assumption of similar efficacy. The analyses only included medicines acquisition costs; no costs for administration or monitoring were included, which the company considered to be conservative given that baricitinib is an oral treatment.

For the cost-utility analysis, a discrete event simulation model was used and was based directly on the model used in the recent NICE MTA (TA375).[12]This used treatment sequences to reflect the pathways patients may follow in clinical practice. Patients entering the model started their treatment and were assigned an initial EULAR response based on the findings of the meta analyses. If the patient did not respond to the treatment, this was terminated and subsequent treatment was initiated. Patients remained in the model until treatment discontinuation or death. The subsequent therapies were identical between baricitinib and comparators if possible. A rate of disease progression as measured by changing HAQ scores, was incorporated into the model and utility values were also calculated using information on HAQ. Adverse events were not taken into account in the base case.

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. The results for the cost-minimisation analysis are shown in table 3 and table 4 show the cost-utility analysis results.

Table 3: Cost minimisation analysis- results without PAS for baricitinib and comparators: severe RA cDMARD-IR and rituximab-ineligible TNF-antagonist-IR patients; cost differences at 2, 5 and 10 years.

Medicine	2 year cost difference versus baricitinib (without baricitinib PAS)	5 year cost difference versus baricitinib (without baricitinib PAS)	10 year cost difference versus barictinib (without baricitinib PAS)
Abatacept	-£10,271	-£24,411	-£44,964
Adalimumab	£2,645	£6,287	£11,581
Certolizumab	£1,299	£4,563	£9,309
Etanercept	£3,879	£9,220	£16,983
Golimumab	£2,645	£6,287	£11,581
Infliximab	£4,468	£12,958	£25,300
Tocilizumab	-£2,693	-£6,400	-£11,788

The results presented do not take account of the PAS for tocilizumab, golimumab, certolizumab pegol and abatacept, or the PAS for baricitinib 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 prices due to commercial confidentiality and competition law issues.

Table 4: Cost utility analysis results versus best supportive care; moderate RA cDMARD-IR and rituximab-eligible TNF agonist IR populations

Analysis	Incremental cost-effectiveness ratio (ICER)
Base case Moderate RA cDMARD- IR	£48,223 without baricitinib PAS
Sensitivity analysis moderate RA cDMARD-IR: linear progression in HAQ	£28, 385 without baricitinib PAS
Sensitivity analysis moderate RA cDMARD-IR: include adverse events	£47,689 without baricitinib PAS
Base case rituximab-eligible TNF agonist IR	Baricitinib dominated (more expensive, less effective) without PAS

There are a number of issues with the analyses presented:

- Given a lack of direct clinical trial evidence against most of the comparator treatments, the CMA and CUA analyses are based on the findings of the NMA, and as noted above, these are associated with some weaknesses. The cost-effectiveness analysis presented above show the results for patients according to the severity of disease however the NMA results were not stratified according to disease severity, with the results assumed applicable to both populations. It should also be noted that in the case of the results based on the CUAs, the credible intervals for the EULAR response rates were overlapping with all interventions but the numerical differences in the responses were used to generate quality adjusted life year (QALY) differences in the analyses.
- For the CUA in moderate RA cDMARD-IR and rituximab-eligible TNF-antagonist IR populations, baricitinib would not be judged cost-effective by conventional standards.
- In the CUA in the moderate cDMARD-IR population, the results were sensitive to the method used to model the rate of HAQ progression; the base case analysis used the method used in the current NICE MTA but use of methods used in other appraisals gave variation in the ICERs. It is also noted that the company did not provide one-way sensitivity analysis due to the model structure, which makes it more difficult to easily ascertain the key drivers of the results.
- No analyses were provided for baricitinib monotherapy. However, it is noted that NICE MTA 375 accepted that biologic therapies could, in general, be used as monotherapy in situations where methotrexate use was inappropriate.

Given these findings, the economic case has been demonstrated for the following two populations on the basis of the CMA:

- Patients who have severe disease inadequately controlled by conventional DMARDs.
- Patients who are ineligible for rituximab who have severe disease inadequately controlled by a TNF-antagonist.

However, given the comparatively high or dominated ICERs from the CUAs, the economic case has not been demonstrated for the following populations:

- Patients who have moderate disease inadequately controlled by conventional DMARDs.
- Patients who are eligible to receive rituximab and who have disease inadequately controlled by a TNF-antagonist.

Summary of patient and public involvement

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

- We received a patient group submission from the National Rheumatoid Arthritis Society, which is a registered charity.

- The National Rheumatoid Arthritis Society has received 15% pharmaceutical company funding in the past two years, including from the submitting company.

- Being diagnosed with an incurable, painful disease like RA can be extremely distressing, as it is life-changing. RA impacts on every area of life and has effects on emotional and physical well-being. It can be very distressing for the partner of someone with RA to witness their loved-one in severe pain and suffering the debilitating effects of fatigue, so this disease does very

much impact on the whole family. As ¾ of people are diagnosed when of working age, anxiety over job-loss due to their disease is a significant factor.

- The combination of conventional disease modifying anti-rheumatic drugs (DMARDS) and biologic/biosimilar DMARDS currently available provide a range of options for people living with RA. However, there remains unmet need due to the heterogeneity of RA. Carers often have to help patients with their biologic therapy and with an oral medicine like baricitinib, the patient becomes more independent in taking their medication.

- Baricitinib is a new class of therapy not previously available to RA patients. It will add to the therapeutic options available to clinicians and patients. As an oral medication it is better for patients as they are very likely to prefer this over having to have a regular infusion or inject themselves.

Additional information: guidelines and protocols

The Scottish Intercollegiate Guidelines Network (SIGN) published guideline 123 Management of early rheumatoid arthritis in February 2011. All patients with moderate to severe disease activity should receive treatment with DMARDs, adjusted with the aim of achieving remission or a low disease activity score (DAS)/28-joint disease activity score (DAS28). Use of TNF antagonists for the treatment of severe, active and progressive RA in adults not previously treated with methotrexate or other DMARDs is not recommended.[9]

The National Institute for health and Care Excellence (NICE) updated its guideline CG79 in December 2015, which refers to MTA advice for the use of biologics (TA375 and TA195).[15]

The European League Against Rheumatism (EULAR) guidelines published in 2016 state that in patients with unfavourable prognostic factors (autoantibodies, high disease activity, early erosions, failure of two conventional DMARDs), for whom conventional DMARDs have failed to produce an adequate response, biologics or targeted synthetic DMARDS (JAK inhibitors) should be used upon failure of conventional DMARDs, irrespective of disease severity.[16]

Additional information: comparators

Baricitinib is likely to be used in place of biologic medicines for RA.

Cost of relevant comparators

Medicine	Dose Regimen	Cost per year (£)
baricitinib	**2 to 4mg orally once a day**	**10,473**
abatacept	125mg SC once a week	15,725
tocilizumab	162 mg SC once a week	11,871
tocilizumab	8mg/kg IV every four weeks	9,984
certolizumab pegol	400mg SCat weeks 0, 2, 4 then 200mg SC every two weeks	9,295 (10,368 in year 1)
etanercept	50 mg SC once a week or 25mg twice a week	9,295
adalimumab	40mg SC every two weeks	9,156
golimumab	50 mg SC once a month	9,156
infliximab	Initially 3 mg/kg by IV infusion at weeks 0, 2, 6, then every eight weeks	6,786 10,179 (in year 1)

Doses are for general comparison and do not imply therapeutic equivalence. Costs are from eVadis on 16 May 2017, except infliximab (MIMS). Dose assumes weight of 70kg. Costs calculated using the full cost of vials/ampoules assuming wastage. Costs do not take any patient access schemes into consideration. IV = intravenous; SC = subcutaneous

Additional information: budget impact

The submitting company estimated there would be 5,826 patients eligible for treatment with baricitinib in year 1 rising to 5,943 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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*6. Commercial in Confidence**

*7. Commercial in Confidence**

*8. Commercial in Confidence**

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10. National Institute of Health and Care Excellence (NICE). Technology assessment TA195,

11. Healthcare Improvement Scotland. Advice on NICE TA375.

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14. European Medicines Agency. Committee for Medicinal Product for Human Use (CHMP) Guideline on clinical investigation of medicinal products other than NSAIDs for treatment of rheumatoid arthritis – Draft, CHMP/EWP/556/95 Rev.2. 20 March 2015.

15. National Institute of Health and Care Excellence (NICE). Clinical guideline 79.

16. Smolen JS, Landewe R, Bijlsma G, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. Ann Rheum Dis 2017;76:960-977.

This assessment is based on data submitted by the applicant company up to and including 14 July 2017.

**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.