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

Re-submission

belimumab, 120mg and 400mg powder for concentrate for solution for infusion (Benlysta®) SMC No. (775/12)

GlaxoSmithKline UK Ltd

07 April 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 resubmission

belimumab (Benlysta®) is accepted for restricted use within NHS Scotland.

Indication under review: Add-on therapy in adult patients with active, autoantibody-positive systemic lupus erythematosus (SLE) with a high degree of disease activity (e.g. positive anti-dsDNA and low complement) despite standard therapy.

SMC restriction: patients with evidence of serological disease activity (i.e. positive anti-dsDNA and low complement) and a Safety of Estrogens in Lupus Erythematosus National Assessment-Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) score ≥10.

Belimumab, in addition to standard of care, modestly improved disease control in patients with SLE in two phase III studies.

This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of belimumab. 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

Indication

Add-on therapy in adult patients with active, autoantibody-positive systemic lupus erythematosus (SLE) with a high degree of disease activity (e.g. positive anti-double stranded DNA [anti-dsDNA] and low complement) despite standard therapy.[1]

Dosing Information

The recommended dose regimen is 10mg/kg by intravenous infusion over one hour on days 0, 14 and 28 and at four-week intervals thereafter. The patient's condition should be evaluated continuously. Discontinuation of treatment should be considered if there is no improvement in disease control after six months of treatment.[1]

Treatment should be initiated and supervised by a qualified physician experienced in the diagnosis and treatment of SLE. Infusions should be administered by a qualified healthcare professional trained to give infusion therapy. Administration of belimumab may result in severe or life-threatening hypersensitivity reactions and infusion reactions. Patients have been reported to develop symptoms of acute hypersensitivity several hours after the infusion has been administered. Recurrence of clinically significant reactions after initial appropriate treatment of symptoms has also been observed. Therefore, it should be administered in an environment where resources for managing such reactions are immediately available. Patients should remain under clinical supervision for a prolonged period of time (for several hours), following at least the first two infusions, taking into account the possibility of a late onset reaction. Premedication including an antihistamine, with or without an antipyretic, may be administered before the infusion of belimumab.[1]

Product availability date

19 September 2011

Summary of evidence on comparative efficacy

Belimumab is a human IgG1λ monoclonal antibody specific for soluble human B Lymphocyte Stimulator protein (BLyS). Belimumab binds to BLyS and inhibits the survival of B cells. Levels of BLyS are elevated in patients with SLE and there is an association between plasma BLyS levels and SLE disease activity.[1] SLE is a chronic auto-immune disease clinically characterised by arthralgia, arthritis, skin rashes, serositis, haematological abnormalities, central nervous system dysfunction and renal inflammation.[2]

The submitting company has requested that SMC considers belimumab when positioned for use in patients with evidence of serological disease activity (i.e. low complement, positive anti-dsDNA) and a Safety of Estrogens in Lupus Erythematosus National Assessment-Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) score ≥10. (The SELENA-SLEDAI index ranges from 0 to 105, with a score of 0 indicating no disease activity, scores >10 indicating high activity and ≥20, indicating very high activity).[2, 3] The marketing authorisation for belimumab requires patients to be reviewed at six months and states that treatment should be discontinued unless there is a reduction in SELENA-SLEDAI score of ≥4 points at this time.

Evidence comes from two similar phase III multi-centre, randomised, double-blind, placebo-controlled studies, BLISS-76 and BLISS-52, that evaluated the efficacy and safety of belimumab with standard of care versus standard of care alone in patients with SLE.[4, 5]Eligible patients were aged at least 18 years

with an SLE diagnosis according to the American College of Rheumatology criteria, active disease (SELENA-SLEDAI ≥6) at screening, sero-positivity and a treatment regimen that was stable for at least 30 days. Patients with severe active lupus nephritis or severe active central nervous system lupus were excluded from the studies.[4, 5]

Patients were centrally stratified according to SELENA-SLEDAI score, proteinuria and race, then randomised equally to receive belimumab 10mg/kg, 1mg/kg or placebo by intravenous infusion over one hour on days 0, 14 and 28 and every 28 days through to week 72 in BLISS-76, and to week 48 in BLISS-52. All study medication was administered with standard of care, a stable treatment regimen, which could include prednisone (or equivalent) up to 40mg daily with antimalarials, non-steroidal anti-inflammatory drugs (NSAIDs), and/or immunosuppressants. Initiation of immunosuppressants was prohibited during the study but addition of a new antimalarial drug and dosage increases of concomitant immunosuppressive or antimalarial drugs were permitted until week 16. After week 16, the maximum dose of immunosuppressive or antimalarial drug could not be increased above the baseline or the week 16 dose, whichever was greater.[4, 5]

In both studies, the primary efficacy endpoint was response at week 52, evaluated using the SLE Responder Index (SRI). This is a composite measure, combining three validated tools for estimating SLE activity: SELENA-SLEDAI, Physician's Global Assessment (PGA) and the British Isles Lupus Assessment Group (BILAG) index. Response was defined as a reduction of ≥4 points in the SELENA-SLEDAI score and no new BILAG A organ domain score or no more than one new BILAG B organ domain score and no worsening in PGA score (increase <0.3) at week 52 compared with baseline. The results for the belimumab 10mg/kg, the licensed dose of belimumab, and placebo are presented.[4, 5]

The BLISS-76 study was conducted at 136 centres in Europe, North and Central America and treated 819 patients. SRI response at week 52 was 43% (118/273) and 34% (93/275) for patients in the belimumab 10mg/kg and placebo groups respectively, odds ratio 1.52 (95% confidence interval [CI]: 1.07 to 2.15), p=0.021.[2, 4]

Not all the secondary endpoints were met. SRI response at week 76 was not statistically different between the treatment groups: 38% (105/273) and 32% (89/275) in the belimumab 10mg/kg and placebo groups respectively. Change in quality of life from baseline to week 24, measured using the short form 36 version 2 physical component summary score, was not significantly different between the groups. There was no significant difference in steroid-sparing in patients taking at least 7.5mg prednisolone daily at baseline; the proportion of patients with an average reduction in prednisolone dose of ≥25% to ≤7.5mg daily during weeks 40 to 52 was 18% (21/120) versus 13% (16/126) for 10mg/kg versus placebo.[2, 4]

BLISS-52 was conducted at 90 centres in Latin America, Asia-Pacific and Eastern Europe and treated 865 patients. The primary outcome, SRI response rate at week 52, was significantly higher in the belimumab 10mg/kg group compared with placebo: 58% (167/290) versus 44% (125/287) respectively, odds ratio 1.83 (95% CI: 1.30 to 2.59) p=0.0006. [2, 5]

The Summary of Product Characteristics includes a subgroup analysis of pooled data from the BLISS-76 and BLISS-52 studies within those patients with low complement and positive anti-dsDNA at baseline. The SRI response rate was significantly higher in patients receiving belimumab 10mg/kg compared with placebo; 52% (157/305) versus 32% (91/287), p<0.0001. This subgroup comprised 53% (592/1125) of ITT patients in the belimumab 10mg/kg and placebo groups and is larger than the proposed positioning target group which further restricts to SELENA-SLEDAI score ≥10.[1]The submitting company presented unpublished evidence to support the use of belimumab in the target population within the proposed positioning, using data pooled from both studies. SRI response rate at week 52 in this target population was reported as 63% (121/193) in the belimumab 10mg/kg group and 38% (77/203) in the placebo group corresponding to an odds ratio of 2.7 (95% CI: 1.8 to 4.1), p<0.0001. The

difference in steroid reduction (% achieving ≤7.5mg daily) during weeks 40 to 52 was statistically significant; 16% (20/126) and 7% (9/126) for patients in the belimumab 10mg/kg and placebo groups respectively, odds ratio 2.43 (95% CI: 1.05 to 5.65).

Supportive data come from a phase III randomised, double-blind, placebo-controlled study, NCT01484496, that recruited adult patients with positive antinuclear antibody and/or anti-dsDNA and SELENA-SLEDAI score ≥8 (mean score at baseline was 10.5 in the belimumab group and 10.3 in the placebo group). Patients with severe lupus kidney disease or severe central nervoussystem disease were excluded. A total of 839 patients were randomised in a 2:1 ratio to receive belimumab 200mg administered subcutaneously every week for 52 weeks. The dose and route of administration are unlicensed. A significantly higher proportion of patients receiving belimumab than placebo achieved the primary outcome of SRI response (defined as for the pivotal studies), at week 52: 61% versus 48%; odds ratio 1.68 (95% CI: 1.25 to 2.25), p=0.0006.[6]

There are some long-term data supporting sustained benefit. Of 449 patients enrolled in a phase II study, 296 patients entered the continuation phase and 31% (92/296) of these patients were still receiving belimumab and maintaining a response at seven years.[7]

Summary of evidence on comparative safety

In a pooled safety analysis of all belimumab studies, the incidence of adverse effects was similar between the belimumab and placebo treatment groups. At least one treatment-emergent adverse event was experienced by the majority of patients. The most frequently reported adverse events were headache, upper respiratory tract infections, arthralgia, nausea, urinary tract infections, diarrhoea, fatigue and pyrexia. [2]

The main adverse events of special interest were infections, infusion reactions and malignancy. The incidence of infections across the studies was 70% and 67% in the belimumab 10mg/kg and placebo groups respectively. Severe infections occurred in 3.3% and 3.7% of patients respectively. Most infusion-related reactions occurred during either the first or second infusion and the incidence declined over subsequent infusions. Serious infusion or hypersensitivity reactions occurred in 0.9% and 0.4% of belimumab and placebo treated patients respectively. Belimumab is an immunomodulator so the potential risk for malignancy may be a concern. The malignancy rate reported during the relatively short duration of the studies was similar to the background rate for SLE patients.

Progressive multifocal leukoencephalopathy has been reported with belimumab treatment for SLE.[1]

Summary of clinical effectiveness issues

SLE is a chronic, autoimmune, multisystem disorder with a relapsing-remitting clinical course.[2, 8] It is associated with a high risk of permanent organ damage and a significant impact on mortality. The disease mainly affects young women who often require treatment over many years. The current standard of care includes the use of antimalarials, NSAIDs, corticosteroids and immunosuppressants. There is some off-label use of rituximab despite a lack of robust evidence in the treatment of SLE. Belimumab is the first biological agent to show benefit in patients with SLE. It has been developed as a targeted therapy for a specific aspect of SLE pathology associated with immune response in SLE, the BLyS pathway. [2]Clinical experts consulted by SMC considered that there is unmet need in this therapeutic area, namely patients who have failed on current standard treatments. The experts noted that safety and tolerability issues associated with existing treatment options such as corticosteroids and

immunosuppressants present a particular therapeutic challenge in patients affected by SLE, many of whom are women of childbearing potential. [2]

The submitting company has requested that SMC considers belimumab when positioned for use in patients with significant disease activity: patients with evidence of serological disease activity (i.e. low complement, positive anti-dsDNA) and a SELENA-SLEDAI score ≥10. The company also proposes within the base case economic analysis that the maximum duration of treatment should be restricted to six years after which patients would return to best supportive care.

In the two pivotal studies, belimumab demonstrated a modest benefit in the treatment of SLE as measured by the SRI response rate. This was primarily assessed at week 52 and longer term controlled data are limited. Many of the secondary endpoints in BLISS-76 were not met, including the SRI response rate measured at week 76. While there was no significant difference in quality of life between the treatment groups, the European Medicines Agency (EMA) noted that data for belimumab suggests a beneficial effect on fatigue. The improvement in fatigue scores was more pronounced in the subgroups of patients with higher disease activity. The BLISS-52 study, with patients recruited from Asia-Pacific, Latin America and Eastern Europe had more positive results but the results may be less generalisable to the Scottish population.[2, 4, 5] The EMA requested additional analyses of the two studies because of the modest benefit found. A more stringent endpoint, requiring a reduction of at least 6 points, or a score less than 2 on the SLEDAI component, found a greater benefit associated with belimumab. Additional analyses also suggested that patients with higher disease activity (SELENA-SLEDAI ≥10) responded better to belimumab.[2]

The pivotal studies had a number of limitations. The duration was short for this chronic disease and may have been inadequate to measure clinically detectable organ damage. Patients with central nervous system manifestations and lupus nephritis were excluded from the clinical studies and belimumab is not recommended for use in these patients.[2] The baseline SELENA-SLEDAI score in BLISS-76 and BLISS-52 was ≥10 for 52% of patients. Prednisone (or equivalent) was taken daily by 96% of patients; 67% to 71% of patients were taking more than 7.5mg daily at baseline. Less than half of the patients studied were taking an immunosuppressant, such as azathioprine, methotrexate or mycophenolate mofetil. Antimalarials were used by 64% to 70% of patients. It is unclear if the target population in the company's proposed positioning had been maximally treated.[4, 5]The target population corresponds to 34% of the pooled BLISS-76 and BLISS-52study population. Only 45% (177/396) of patients in the target subgroup were from the BLISS-76 study which was more relevant to Scottish practice.

There are no data relating to an active comparator. An unpublished systematic review of treatments for SLE, commissioned by the submitting company, concluded that a meta-analysis was not feasible because of the heterogeneity of the reported outcomes. In the economic analysis provided, the submitting company assumed that belimumab and rituximab would have equivalent clinical efficacy. However as rituximab is mainly used in patients with renal or central nervous system SLE, and belimumab is not recommended for these patients, it is not considered to be a relevant comparator. This view is endorsed by clinical experts contacted by SMC.

Clinical experts consulted by SMC consider that belimumab is a therapeutic advancement in that it is the only treatment licensed for patients with highly active SLE despite standard therapy. They consider that belimumab could be used in some patients who continue to have highly active symptomatic disease despite maximum tolerated therapy, but who do not have renal or central nervous system involvement. Hypersensitivity reactions can occur with belimumab so facilities and staff to manage these would be required. Patients should remain under clinical supervision for a prolonged period of time (for several hours), following at least the first two infusions.[1]

Summary of comparative health economic evidence

The company submitted a cost-utility analysis comparing belimumab to standard care in adults with active autoantibody-positive SLE with evidence for serological disease activity (low complement, positive anti-dsDNA) and SELENA-SLEDAI ≥10. A comparison with rituximab was also provided as a sensitivity analysis. The data from the pooled BLISS studies were selected specifically for this subgroup.

A decision-analytic model was used in the form of a micro-simulation incorporating the interaction between patient characteristics, disease activity, medication (corticosteroid use), risk of organ damage development (a patient with SLE could potentially develop damage in 12 different organ systems) and mortality. The time horizon used in the analysis was a lifetime.

The pooled BLISS clinical studies were an important source of data in the model, including the patient's baseline characteristics, the likelihood of response at week 24 (based on a patient demonstrating a SELENA-SLEDAI score decrease of 4), the change in SELENA-SLEDAI score up to week 52, likelihood of discontinuation, and the effect of SELENA-SLEDAI score on utility (without organ damage) and SLE treatment costs.[4, 5] The analysis used subgroup data for patients with low complement and positive anti-dsDNA at baseline.

Belimumab treatment was assumed to continue for a maximum of six years in the base case. However, patients were first assessed after week 24 and treatment was assumed to stop if they did not have an improvement in SELENA-SLEDAI score of 4 points or more. The annual discontinuation rate in those responding to treatment was estimated to be 8% in year 1 and 11.7% in subsequent years.

A second model based on data from the American cohort was used to predict the long-term impact of changes in SELENA-SLEDAI on organ damage.[9] Because the baseline characteristics from the American cohort were different from the patient characteristics in the pooled BLISS trials, the submitting company adjusted the constant in the regression to obtain a better fit to the data; for example, the American patients had less severe disease than those in the belimumab studies. The submitting company also developed a survival model using the American cohort,[9] adjusting it by standardised mortality ratios from the literature. Adverse events were not included in the model.

The baseline quality of life assumed in the analysis was determined by a regression equation (which accounted for age, family origin and SELENA-SLEDAI score), which was derived from the BLISS studies. Disutility multiplier values for each type of organ damage were identified from a search of the literature. These disutility multipliers were applied to the utility score if a patient developed organ damage in the model cycle.

NHS costs included medicines and administration, costs of managing SLE and costs of treating organ damage. Resource use varied according to disease severity and was determined using a linear regression analysis. A literature search was conducted to identify the cost of organ damage.

The model predicted lower disease activity for patients on belimumab than in patients on standard care only, which led to decreased steroid dose and decreased risk of organ damage and contributed to a difference in mortality risk. The model predicted that patients on belimumab live longer than those on standard care. Although a decreased duration of damage was shown for organs on which belimumab has a large effect (cardiovascular, pulmonary and renal), the duration of damage for other organ systems was increased because of the prolonged life expectancy.

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. Under the PAS a simple discount is offered on the cost of the medicine.

With the PAS belimumab plus standard of care resulted in an incremental cost effectiveness ratio (ICER) of £26,756 per QALY compared to standard of care alone, based on an incremental cost of £18,332 and an incremental QALY gain of 0.685. The company provided both one-way and scenario sensitivity analyses. The most sensitive results are provided in the table below.

Table: Key sensitivity analysis results

Sensitivity analysis scenario	**ICER (with the PAS)**
Effectiveness of belimumab at reducing SELENA-SLEDAI at week 52 reduced for responders	£41,356
Effectiveness of belimumab at reducing SELENA-SLEDAI at week 52 reduced for all patients	£38,621
Costs and benefits discounted at 6%	£34,988
Treatment duration increased from 6 years to lifetime (for responders)	£34,535
Patient mean age is increased to 65 years	£33,130

The submitting company also provided a simple cost minimisation analysis versus rituximab. This comparison was based on an assumption of equivalence of outcomes between belimumab and rituximab; a formal indirect comparison was not undertaken. Based on this analysis belimumab (with the PAS) was estimated to be a cost-effective treatment option. Medicine costs were based on using a mean patient weight of 65.4kg and included administration costs.

There were a number of weaknesses in the analysis as follows:

- There is uncertainty about the long-term significance of short-term changes in SELENA-SLEDAI score. The company has undertaken modelling using an American cohort but this raises further issues about the relevance of these data to Scotland and the adequacy of matching the definitions used between data sources (e.g. cohort study versus studies used for utility values). The impact of this is to introduce uncertainty, but the overall direction of bias is unclear.
- The base case model assumed a maximum treatment duration of six years, however sensitivity analysis was presented to show the impact of assuming longer treatment durations. If a lifetime treatment duration was used, the cost per QALY increased to £34,535 with the PAS. The duration of treatment in clinical practice remains unclear and thus this remains a source of potential upward uncertainty in the cost per QALY.
- There is a lack of evidence available on the effectiveness of belimumab compared to rituximab leading to difficulties in being able to perform an appropriate comparison. The results of the cost-minimisation analysis versus rituximab should be interpreted with caution given the lack of evidence to support the assumption of comparable efficacy. Furthermore, the comparison versus rituximab may not be relevant as belimumab is not recommended for renal and central nervous system involvement, and this is where rituximab is currently used.
- Medicine costs were based on the weight distribution of patients within the studies as opposed to the mean patient weight of 65.4kg. As the use of the mean patient weight is considered to be a more appropriate, the company was asked to provide a sensitivity analysis whereby belimumab drug costs were based on a mean patient weight of 65.4kg. Based on this analysis, the ICER increased slightly to £27,877 with the PAS.
- In the model, costs of organ damage assume the figures from the literature apply at the first incidence of disease. However, if SLE patients are under constant surveillance for illness they

may be treated at an earlier stage and costs may be lower. Lower initial costs of organ damage would raise the cost per QALY.

Despite the weaknesses outlined above, the economic case has been demonstrated.

Summary of patient and public involvement

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

- We received a patient group submission from Lupus UK, which is a registered charity.
- Lupus UK has received 0.07% pharmaceutical company funding in the past two years, with none from the submitting company.
- Patients find the most challenging aspects of living with lupus to be the symptoms (particularly fatigue and joint and muscle pain), loss of independence and inability to work. Most require support for day-to-day living and a significant number experience mental health problems such as anxiety and depression.
- Standard treatments cannot always control symptoms and side effects from current treatments can have a significant impact. In addition, not all patients can tolerate current standard treatments.
- Belimumab is important to patients and carers due to an absence of options for the group of lupus patients with high disease activity who do not respond to standard treatment. In addition, trials have demonstrated that when used alongside standard therapy, it can produce a modest statistically significant reduction in disease activity compared to standard care alone.
- Belimumab is the first medicine to be licensed specifically for lupus in at least 50 years and is therefore significant to the lupus community.

Additional information: guidelines and protocols

The British Society for Rheumatology updated their guideline for the management of systemic lupus erythematosus in adults in May 2016. It states that rituximab or belimumab may be considered for the management of moderate SLE that is refractory to other drugs. It notes that rituximab can be prescribed and reimbursed in England according to the NHS England 2013 interim clinical commissioning policy statement for rituximab in adult SLE patients. For severe SLE, rituximab or belimumab may be considered on a case by case basis where patients have failed on other immunosuppressive drugs due to inefficacy or intolerance.[10]

The European League Against Rheumatism (EULAR) task force published recommendations for the management of SLE in 2008 based on evidence and expert consensus. Patients who do not have major organ manifestations should receive antimalarials and/or corticosteroids. NSAIDs may also be useful. In patients whose disease is non-responsive, immunosuppressants such as azathioprine, mycophenolate mofetil or methotrexate can be considered. Biological agents were on the research agenda.[11]

Additional information: comparators

Treatments used off-label in some patients who have not responded to conventional therapy include cyclophosphamide and rituximab.

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
Belimumab	**By intravenous infusion, 10mg/kg on day 0, 14 and 28 and at 4 week intervals thereafter.**	**9,072 to 10,773 in first year then 8,424 to 10,004 in subsequent years**

Doses are for general comparison and do not imply therapeutic equivalence. Costs from Dictionary of medicines and devices on 01 February 2017. Mean patient weight in the economic analysis was 65.4kg, therefore the cost range for belimumab is based on patients weighing 60 to 76kg.

Additional information: budget impact

The submitting company estimated there would be 474 patients eligible for treatment with belimumab in year 1 increasing to 631 patients in year 5. The estimated uptake rate was 10% in year 1 (28 patients) rising to 58% in year 5 (178 patients) with a discontinuation rate of 36% applied in year 1 and 51% applied in year 5.

SMC clinical expert responses indicate the number of patients treated with belimumab in practice may be lower than estimated by the submitting company.

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 17 March 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*

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

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.