Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2330

ravulizumab 300mg/3mL and 1,100 mg/11mL concentrate for solution for infusion (Ultomiris®)

Alexion Pharma UK Limited

9 April 2021

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

ADVICE: following a full submission under the orphan equivalent medicine process

ravulizumab (Ultomiris®) is accepted for restricted use within NHSScotland.

Indication under review: for the treatment of patients with a body weight of 10kg or above with atypical haemolytic uremic syndrome (aHUS) who are complement inhibitor treatment-naïve or have received eculizumab for at least 3 months and have evidence of response to eculizumab.

SMC restriction: under the advice of the national renal complement therapeutics service

Two single-arm, phase III studies demonstrated the beneficial treatment effect of ravulizumab on complete thrombotic microangiopathy (TMA) response, defined as normalisation of haematological parameters and improvement in renal function.

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a PAS / list price that is equivalent or lower.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

Chairman
Scottish Medicines Consortium

Indication

For the treatment of patients with a body weight of 10kg or above with atypical haemolytic uremic syndrome (aHUS) who are complement inhibitor treatment-naïve or have received eculizumab for at least 3 months and have evidence of response to eculizumab.[1]

Dosing Information

The recommended dosing regimen consists of a loading dose followed by maintenance dosing, administered by intravenous infusion, and is based on patient's bodyweight. See Table 1 for details. For patients switching from eculizumab to ravulizumab, the loading dose of ravulizumab should be administered 2 weeks after the last eculizumab infusion, and then maintenance doses are administered once every 8 weeks, starting 2 weeks after loading dose administration, as shown in Table 1.[1]

Table 1. Ravulizumab weight-based dosing regimen.[1]

Body weight range (kg)	Loading dose	Maintenance dose*	Dosing interval
≥40 to <60	2,400mg	3,000mg	Every 8 weeks
≥60 to <100	2,700mg	3,300mg	Every 8 weeks
≥100	3,000mg	3,600mg	Every 8 weeks

*Maintenance dose is administered 2 weeks after loading dose

In aHUS, ravulizumab treatment to resolve thrombotic microangiopathy (TMA) manifestations should be for a minimum duration of 6 months, beyond which length of treatment needs to be considered for each patient individually. Patients who are at higher risk for TMA recurrence, as determined by the treating healthcare provider (or clinically indicated), may require chronic therapy.[1]

Paediatric patients with aHUS with body weight ≥40 kg are treated in accordance with the adult dosing recommendations. The weight-based doses and dosing intervals for paediatric patients ≥10 kg to <40 kg are shown in Table 2.[1]

Table 2. Ravulizumab weight-based dosing regimen for paediatric patient below 40 kg.[1]

Body weight range (kg)	Loading dose	Maintenance dose*	Dosing interval
≥10 to <20	600mg	600mg	Every 4 weeks
≥20 to <30	900mg	2,100mg	Every 8 weeks
≥30 to <40	1,200mg	2,700mg	Every 8 weeks

*Maintenance dose is administered 2 weeks after loading dose

Product availability date

March 2021

Ravulizumab meets SMC orphan equivalent criteria.

Summary of evidence on comparative efficacy

Ravulizumab is a monoclonal antibody that specifically binds to the complement protein C5, which preserves the early components of complement activation that are essential for opsonisation of microorganisms and clearance of immune complexes.[1] Ravulizumab is a re-engineered version of eculizumab which extends the circulating half-life.

The evidence to support the efficacy and safety of ravulizumab comes from two open-label, single-arm, phase III studies. ALXN1210-aHUS-311 (study 311) recruited adult patients with aHUS who were complement inhibitor treatment naïve and ALXN1210-aHUS-312 (study 312) recruited children and adolescents aged <18 years with aHUS and consisted of two cohorts: treatment naïve (Cohort 1) and eculizumab-experienced (Cohort 2). Patients in study 311 and Cohort 1 of study 312 were required to have evidence of TMA (including thrombocytopenia, evidence of haemolysis and kidney injury) based on a platelet count at screening of <150,000/µL, lactate dehydrogenase (LDH) ≥1.5 upper limit of normal (ULN) at screening, baseline haemoglobin ≤lower limit of normal (LLN) for age and gender, baseline serum creatinine ≥ULN (≥97.5th percentile for age in Cohort 1), and bodyweight ≥40kg (≥5kg for study 312). Patients in Cohort 2 of study 312 were required to have a diagnosis of aHUS, including platelet count <LLN at screening, LDH >ULN at screening at the time of the TMA event, and were clinically stable following ≥90 days treatment with eculizumab.[2]

In both studies, during the 26-week initial evaluation periods, patients received a weight-based loading dose of intravenous (IV) ravulizumab on day 1, followed by maintenance treatment on day 15 and every 8 weeks thereafter for patients weighing ≥20kg, or every 4 weeks for patients weighing <20 kg. In study 311 (n=56), an IV loading dose of 2400mg, 2700mg, and 3000mg was administered in patients weighing ≥40 to <60kg, ≥60 to <100kg, and ≥100kg, respectively, on day 1 and maintenance doses of 3000mg, 3300mg, and 3600mg, respectively, on day 15, and then every 8 weeks thereafter. In study 312, the loading and maintenance doses were based on the patient's body weight recorded on dose regimen decision days. Following the 26-week initial evaluation period patients were eligible to enter an extended treatment period for up to 4.5 years.[2-4]

The primary outcome was complete TMA response during the 26-week initial evaluation period, as evidenced by normalisation of haematological parameters (platelet count and LDH) and ≥25% improvement in serum creatinine from baseline. Patients had to meet all complete TMA response criteria at two separate assessments obtained at least 28 days apart, and any measurement in between to be considered a responder. In study 312, the primary outcome was evaluated in Cohort 1 only (n=18).[2] See Table 3 for results.

Table 3. Efficacy results from Study 311 and Study 312. 26-week initial evaluation period (FAS population).[2, 4-6]

	Study 311 Ravulizumab (n= 56)	Study 312 Cohort 1 Ravulizumab (n= 18)
Complete TMA response	54%	78%
Platelet count normalisation	84%	94%
LDH normalization	77%	89%
≥25% improvement in serum creatinine	59%	83%
Haematologic normalisation[a]	73%	89%
Haemoglobin response (≥20 g/L increase)	71%	89%
Time to complete TMA response	86.0 days	30.0 days
Discontinuation of dialysis from baseline	59%	83%
CKD stage improvement	68%	88%
Median change in FACIT-Fatigue score[b]	20.0	10.0
≥3-point improvement in FACIT-Fatigue score[b]	84%	-

a = platelet count and LDH normalization, b = paediatric FACIT-Fatigue questionnaire used to assess HRQL in patients ≥5 years of age in ALXN1210-aHUS-312. The FACIT-Fatigue score ranges from 0–52, with higher score indicating less fatigue. ≥3 point improvement can be considered clinically meaningful.

CKD = chronic kidney disease; FACIT = Functional Assessment of Chronic Illness Therapy; LDH = lactate dehydrogenase; TMA = thrombotic microangiopathy;

In the extension period of study 311, four additional patients achieved a complete TMA response beyond those who had achieved the primary endpoint during the 26-week initial evaluation period.[2, 5] In study 312 (Cohort 1), three additional patients achieved a complete TMA response beyond those who achieved the primary endpoint during the initial evaluation period.[6]

In Cohort 2 of study 312 (n=10), efficacy outcomes included: dialysis requirement status; observed value and change from baseline in estimated glomerular filtration rate (eGFR); CKD stage (as evaluated by eGFR at select target days and classified as improved, stable [no change], or worsened compared with baseline); observed value and change from baseline in haematologic parameters (platelets, LDH, haemoglobin); change from baseline in quality of life, as measured by paediatric FACIT-Fatigue scale; and TMA parameters in patients who discontinued treatment in the extension period but remained in the study.[4]

At a median duration of 50.3 (range, 49.4 to 58.7) weeks, all 10 patients were still enrolled in the study. None of the 10 patients were undergoing dialysis at baseline and no patients required dialysis at any point post ravulizumab treatment during the study. Kidney function, haematologic parameters, and FACIT-Fatigue scores remained stable throughout the 26-week initial evaluation period and extension period up to one year.[4]

Three indirect comparisons using individual patient level data were presented by the company comparing ravulizumab with eculizumab in three populations with aHUS: adult patients without prior kidney transplant; adult patients with kidney transplant; and paediatric patients without

prior kidney transplant. All of the analyses performed were unanchored (as the included studies were all single arm). A pooled dataset of all patients from the eligible studies was developed and propensity score weighting was applied to adjust for differences between the pooled treatment groups. Multiple outcomes were assessed for each population, including complete TMA response. The company concluded that no statistically significant or clinically relevant differences were observed between the two treatments.

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

Summary of evidence on comparative safety

In study 311 and study 312, nearly all patients reported at least one treatment-emergent adverse event (TEAE). The most commonly reported TEAE (≥20%) in study 311 and Cohort 1 of study 312 were headache (34%), diarrhoea (28%), vomiting (26%), hypertension (23%), nausea (20%) and pyrexia (20%). Most TEAEs were of grade 1 or grade 2; 46% and 20% were grade 3 and grade 4 respectively. Serious adverse events were reported by approximately 50% of patients, most commonly related to infections and infestations (20%). The most commonly reported SAE were hypertension (5.4%), abdominal pain (4.1%), and pneumonia (4.1%). The main risk identified with ravulizumab by the European Medicines Agency (EMA) was an increased susceptibility to infections caused by Neisseria spp., especially Neisseria meningitidis. No meningococcal infections were reported in studies 311 and 312. Four patients discontinued treatment due to an adverse event (3 adult patients and 1 paediatric patient). The safety profile in paediatric patients appears to be similar to the adult population, except for a higher incidence of pyrexia, nasopharyngitis and constipation in children. Serious infections were also more frequent in paediatric patients. In Cohort 2 of study 312, no unexpected safety findings or new safety signals were identified; no serious AEs were treatment related or required treatment discontinuation.[2, 4]

Summary of clinical effectiveness issues

Atypical haemolytic uremic syndrome (aHUS) is a rare disease which develops due to dysregulation of the alternative complement pathway, resulting in uncontrolled complement activation. It can occur in adults and children and, in approximately half of patients, mutations in complement regulatory genes and/or the presence of neutralising antibodies have been identified. The estimated incidence of aHUS is 0.4 patients per million population per annum.[7] The disease is characterised by a chronic thrombotic and inflammatory state resulting from platelet and endothelial cell activation which increases the risk of sudden blood clotting, renal insufficiency with ensuing dialysis, and other severe complications of TMA which frequently lead to premature death.[2] Eculizumab was the only treatment with a marketing authorisation for aHUS, but is not recommended for use by SMC (SMC 767/12). Individual patients in Scotland may receive treatment with eculizumab under the guidance of the National Renal Complement Therapeutics Service. Ravulizumab is structurally similar to eculizumab but has an increased antibody half-life, which would reduce the burden of administration from every 2 weeks to every 8 weeks during maintenance. Clinical experts consulted by SMC considered that ravulizumab fills an unmet need

in this therapeutic area, namely due to the more convenient frequency of administrations than eculizumab. Ravulizumab meets SMC orphan equivalent criteria.

In study 311, complete TMA response was observed in 54% of patients during the 26-week initial evaluation period. Platelet normalisation, LDH normalisation and renal function improvement were achieved in 84%, 77% and 59% of patients respectively. Four additional patient achieved complete TMA response during the extension period. In study 312 (Cohort 1), complete TMA response was achieved by 78% of patients and platelet normalisation, LDH normalisation and renal function improvement were achieved 94%, 89% and 83% of patients respectively. Changes in renal function in paediatric patients should be interpreted with caution since glomerular filtration rate (GFR) values change substantially within the first 5 to 10 years of life. Data taken from the latest data-cut show that response was overall maintained in both studies up to and beyond one year. In Cohort 2 of study 312, all patients that had previously responded to eculizumab remained stable after switching to ravulizumab. Together, these results can be considered clinically meaningful.[2, 4]

Studies 311 and 312 were small, single-arm, open-label studies which are prone to various biases and is a key limitation of the evidence. Consequently, some uncertainties remain over the efficacy and safety of ravulizumab, and quality of life outcomes are difficult to interpret because of the open-label and non-comparative nature of the studies. A randomised controlled trial would have been preferable but in practice due to the rarity and severity of the condition the EMA considered that approach to be prohibitive.[2]

There were some issues with the generalisability of the results. Most patients in the collective evidence were treatment naïve and had a reasonably short history of disease, which may not fully reflect the population in Scotland.[2] Only 10 patients had previously received treatment with eculizumab, all of whom were aged <18 years.[4] In addition to these 10 patients, the EMA considered evidence from a phase III study in paroxysmal nocturnal haemoglobinuria (study PNH-302) which enrolled eculizumab-stable adult patients.

Reasons for discontinuing treatment of ravulizumab may differ in clinical practice compared with the studies. Discontinuation due to lack of renal recovery, due to stabilisation or normalisation of renal function, or due to presenting with aHUS too late and treatment being considered futile are reasons that the submitting company maintain were not specified in the study protocols for discontinuation but occur in clinical practice. Investigators were allowed to discontinue treatment in the best interests of the patient. At present it is not clear if complement inhibitors should be discontinued when renal function normalises; research is ongoing.[12] Secondly, there is no experience of concomitant plasmapheresis, plasma exchange, or fresh frozen plasma infusion use with ravulizumab. Administration of plasma exchange/plasma infusion may reduce ravulizumab serum levels.[1]

A number of limitations may affect the validity of the indirect treatment comparisons presented by the company. The analyses were unanchored and used individual patient level data for both treatments. However, unknown prognostic factors may not have been balanced between the pooled treatment groups which introduces uncertainty into the analyses. The analyses included a

relatively small number of eligible patients before adjustment (because aHUS is a relatively rare condition), which reduced the power of the comparisons. In order to achieve a match, the effective sample size was further reduced to enable the assessment of some outcomes via the models, which may have resulted in a lack of statistical power for some comparisons. Given the aforementioned limitations, the results of the indirect comparisons are uncertain. However, since both medicines share an identical mechanism of action, and ravulizumab has been shown to be non-inferior to eculizumab in comparative phase III studies of patients with paroxysmal nocturnal haemoglobinuria,[13, 14] the company's conclusion of similar efficacy between both complement inhibitors seems reasonable.

Clinical experts consulted by SMC considered that ravulizumab is a therapeutic advancement due to likely similar efficacy with eculizumab but with less frequent administrations. If accepted for use ravulizumab would likely be used instead of eculizumab.

Patient and clinician engagement (PACE)

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of ravulizumab, as an orphan equivalent medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- aHUS is a very rare and serious condition where small abnormal blood clots can affect various organs in the body, most commonly the kidneys. aHUS can have a substantial impact on patients' day-to-day activities and participation in leisure activities. Patients have to live with chronic kidney disease, including end stage kidney disease for some, which greatly impacts on quality of life.

- The availability of eculizumab revolutionised aHUS treatment, markedly improving clinical outcomes for many patients. However, the 2-weekly IV infusions are time-consuming, emotionally draining and the frequent IV infusions can put patients' veins at risk of long-term damage. Therefore, there is an unmet need for more convenient treatments.

- Clinician representatives acknowledged the uncertainties in the clinical evidence for ravulizumab. Given the mode of action of the medicine, ravulizumab is predicted to be as safe and as effective eculizumab.

- The main advantage of ravulizumab over eculizumab is the less frequent dosing, with infusions being every 8 weeks instead of every 2 weeks. This may make it easier for patients to gain or maintain employment, plan holidays, and enjoy life with friends and family. It would also reduce the burden of care for family members/carers. Patient group representatives highlighted how highly valued this additional time would be for patients, family and carers.

Additional Patient and Carer Involvement

We received patient group submissions from aHUS alliance Global Action and Kidney Research UK. aHUS alliance Global Action is a charitable incorporated organisation and Kidney Research UK is a registered charity. aHUS alliance Global Action has not received any pharmaceutical company funding in the past two years. Kidney Research UK has received 20% pharmaceutical company funding in the past two years, including from the submitting company. Representatives from both organisations participated in the PACE meeting. The key points of their submissions have been included in the full PACE statement considered by SMC.

Summary of comparative health economic evidence

The company submitted a cost minimisation analysis comparing ravulizumab with eculizumab for the treatment of atypical haemolytic uremic syndrome (aHUS). Results were presented separately for the adult and paediatric populations. A cost-utility analysis was provided as a scenario analysis. Note that the economic analysis was based only on the higher strength 300mg/3mL and 1,100 mg/11mL vials available for use in NHSScotland.

A state transition model was used with a 100-year lifetime horizon and tracked disease progression through four main mutually exclusive health states (initiate treatment, discontinuation, relapse and reinitiate treatment) and eight sub states describing aHUS progression (CKD Stages 0–2, 3a–3b, 4, 5/ESRD, transplant, transplant success, excess death and background death).

The clinical evidence for ravulizumab was obtained from the study 311 (adults) and study 312 (children).[2-4] As no direct data are available the relative effectiveness of ravulizumab compared to eculizumab was estimated from the indirect treatment comparison. For eculizumab the data were taken from the relevant eculizumab studies.[15-17] The indirect treatment comparison showed comparable efficacy between ravulizumab and eculizumab and therefore justified the cost-minimisation analysis approach. Treatment duration in the model assumes lifetime use of ravulizumab and eculizumab by patients initiated on treatment but also includes discontinuation data from the clinical studies plus other factors that may affect treatment duration not captured in the studies. For the base case analysis, patient characteristics are from the pooled eculizumab and ravulizumab study data applying the adult and children population weighting.

Quality-adjusted life-years (QALYs) were not included in the base case due to the cost minimisation analysis, which assumes equal efficacy between ravulizumab and eculizumab. A scenario analysis was provided where QALYs were calculated due to numerical differences in efficacy from the indirect treatment comparison. In this scenario the numerical differences in terms of CKD stage efficacy were applied which resulted in more patients in the ravulizumab arm being predicted to transition to the CKD 5 health state (which has higher mortality rates, an increased possibility of transplants and lower utilities). The company states that these differences

are not plausible based on the evidence of no statistical differences and on the expert opinion they received of expected similarities between the treatments.

The analysis included acquisition costs, administration costs, meningococcal vaccine, treatment monitoring, discontinuation costs, costs of relapse, costs of reinitiating treatment and CKD health state unit costs and resource use.

Ravulizumab and eculizumab are administered intravenously with an infusion time for eculizumab of 25-45 minutes whereas for ravulizumab infusion time is dependent on patient weight (ranging from 25-75 minutes). The weight distributions from the associated clinical studies were used to calculate the average costs of treatment per cycle. In order to account for changing weight over time in the paediatric population (adult patient weights remain constant over the model time horizon), the average weight of children in the UK per age is used to calculate the average growth rate per 6 months, assuming a linear increase.

The base-case results of the analysis are summarised in table 4. 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 NHS Scotland. Under the PAS, a simple discount is offered on the list price of the medicine. 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 list price results can be presented.

Table 4. Base-case results (list price)

Costs	Eculizumab	Ravulizumab
Total costs	£4,454,269	£4,608,240
Incremental costs	£153,971	

A cost-utility analysis was also provided as a scenario analysis. Due to the use of numerical differences in efficacy from the indirect treatment comparison, the cost-utility analysis scenario is considered to be conservative.

Key results of one-way sensitivity analyses and scenario analyses are shown in Table 5. The parameters with the largest impacts were the relapse rates, length of aHUS diagnosis period and treatment discontinuation. The conclusion remained unchanged for all scenarios tested.

Table 5. Selected sensitivity analyses (list price)

Scenario	Change(s) made to model	Incremental Cost
	Base case	£153,971
1	ECU: Relapse rate (adults) (+/- 95% CI)	£158,564 - £149,983
2	Length of diagnosis period (months) – Ecu (+/- 95% CI)	£221,673 - £152,690
3	Proportion of patients who discontinue for mis-diagnosis (+/- 95% CI)	£202,420 - £118,668

PAS = patient access scheme, ECU = eculizumab, CI = confidence interval

The key limitations with the analysis are:

- Clinical expert responses indicate eculizumab is the appropriate comparator. However, it is important to note that eculizumab was not recommended by SMC, and is not considered cost-effective.
- There is no direct evidence available comparing ravulizumab with the key comparator eculizumab in this indication and the evidence for ravulizumab is from single-arm, open-label studies meaning the evidence base is uncertain. An indirect treatment comparison was provided as the basis for the comparable efficacy assumption underpinning the cost-minimisation analysis and while the conclusion of comparable efficacy is reasonable, there are some limitations with the indirect comparison as noted above.
- The results of the cost-minimisation analysis were also provided according to body weight ranges, which showed some uncertainty in the paediatric population in the ≥ 10 to < 20kg weight group. While this analysis is of note, particularly as a large proportion of patients in study 312 were in this weight range, paediatric patients would continue on treatment and move to the higher doses over the model time horizon; the base case result in table 4 is therefore the relevant estimate of overall cost-effectiveness of ravulizumab. The company highlighted that a patient will only spend a small proportion of time in this weight group over a lifetime.
- The model includes treatment-naïve patients only with an assumption applied that outcomes will generalise to eculizumab-experienced patients who are stable on treatment. This raises questions about the generalisability of the evidence to patients currently receiving eculizumab treatment.

The Committee considered the benefits of ravulizumab in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that as ravulizumab is an orphan equivalent medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, the Committee accepted ravulizumab for restricted use in NHSScotland.

Additional information: guidelines and protocols

The National Renal Complement Therapeutics Centre (NRCTC) provide guidance on the treatment of aHUS on their website: https://www.atypicalhus.co.uk/ahus/eculizumab-in-the-treatment-of-ahus/ (date accessed: 22 December 2020). The guidance states that eculizumab has replaced plasma exchange as the gold standard in the management of complement mediated primary aHUS in adults and children, and should be offered to all patients with a potential new diagnosis of complement mediated primary aHUS. Although all investigations on the NRCTC diagnostic checklist must be undertaken at initial presentation in adults, only the ADAMTS13 activity must be available prior to authorisation of eculizumab. Until this is available plasma therapy is recommended where appropriate. In children due to the rarity of thrombotic thrombocytopaenic purpura (TTP) and the difficulty of plasma exchange, kidney disease: improving global outcomes (KDIGO) recommended that eculizumab can be commenced prior to the ADAMTS13 result with the caveat that clinical deterioration on eculizumab should necessitate immediate plasma therapy. The website also provides guidance for eculizumab in patients with aHUS requiring renal transplantation; eculizumab is authorised for use on a case-by-case basis.

Additional information: comparators

Eculizumab.

Additional information: list price of medicine under review

Medicine	Dose Regimen	Cost per year (£)
Ravulizumab	2,700mg loading dose by IV infusion, then 3,300mg by IV infusion 2 weeks later and every 8 weeks	389,838 for year 1 299,178 to 349,041 for subsequent years

Costs from emc med data on 31 March 2021. Costs calculated for adult weighing 70kg, (relevant to weight band ≥60 to <100kg), costs for children will be lower. Costs do not take patient access schemes into consideration.

Additional information: budget impact

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

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

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This assessment is based on data submitted by the applicant company up to and including 11 February 2021.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy*

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

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

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

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the

considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.