SMC2526

# pembrolizumab concentrate for solution for infusion (Keytruda®)

## Merck Sharp & Dohme (UK) Ltd

10 March 2023

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

**pembrolizumab (Keytruda®)** is accepted for use within NHSScotland.

**Indication under review:** as monotherapy for the adjuvant treatment of adults and adolescents aged 12 years and older with Stage IIB or IIC melanoma and who have undergone complete resection.

Recurrence-free survival was significantly longer with pembrolizumab compared with placebo in a phase III study of adolescent and adult patients with completely resected, Stage IIB or IIC melanoma.

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.

Pembrolizumab has previously been accepted for use as monotherapy for the adjuvant treatment of patients with Stage III melanoma and lymph node involvement who have undergone complete resection (SMC2144).

**Chair**
**Scottish Medicines Consortium**

# 1. Clinical Context

### 1.1. Medicine background

Pembrolizumab is a humanised monoclonal antibody that binds to the programmed cell death-1 (PD-1) receptor found in T-cells and blocks its interaction with ligands PD-L1 and PD-L2. This blockade potentiates T-cell responses resulting in immune mediated anti-tumour activity.[1]

Pembrolizumab has already been accepted by SMC as monotherapy for the adjuvant treatment of adults with Stage III melanoma and lymph node involvement who have undergone complete resection (SMC2144). The licence has now been extended to include patients with stage IIB or IIC melanoma. The dose in adults is 200mg every three weeks or 400mg every six weeks administered as an intravenous infusion. For the adjuvant treatment of melanoma, it should be administered until disease recurrence, unacceptable toxicity, or for a treatment duration of up to one year.[1]

### 1.2. Disease background

Melanoma is a malignant tumour that arises from melanocytes and primarily involves the skin. For Stage IIB and IIC melanoma, surgical resection represents the first-line treatment, followed by active surveillance for recurrence.

### 1.3. Treatment pathway and relevant comparators

Patients with Stage IIB or IIC melanoma, who undergo complete resection, are currently managed through routine surveillance; there is no standard adjuvant treatment in current practice.

# 2. Summary of Clinical Evidence

### 2.1. Evidence for the licensed indication under review

Evidence to support the efficacy and safety of pembrolizumab for patients with Stage IIB or IIC melanoma and who have undergone complete resection comes from the ongoing KEYNOTE-716 study. Study details are summarised in Table 2.1.

**Table 2.1. Overview of the relevant study**

| Criteria | KEYNOTE-716 [2, 4-8] |
|---|---|
| Study Design | International, randomised, double-blind, parallel-group, phase III study |
| Eligible Patients | • ≥12 years of age.<br>• Surgically resected and histologically/pathologically confirmed, newly diagnosed Stage IIB or IIC cutaneous melanoma (tumour stage of T3b, T4a, or T4b) with pathologically confirmed negative sentinel lymph node biopsy.<br>• Not previously treated for melanoma beyond complete surgical resection.<br>• No more than 12 weeks between final surgical resection and randomisation, with complete surgical wound healing.<br>• No evidence of metastatic disease on imaging as determined by investigator assessment.<br>• ECOG Performance Status of 0 or 1 at the time of enrolment, LPS score ≥50 (for patients ≤16 years old), or a KPS score ≥50 (for patients >16 and <18 years old).<br>• No prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an |

| | |
|---|---|
| | agent directed to another stimulatory or co-inhibitory T-cell receptor. |
| Treatments | The treatment phase consisted of two parts: an adjuvant phase (part 1) and a crossover/rechallenge after first recurrence phase (part 2); this submission only focusses on efficacy and safety from part 1.<br>In part 1, patients were randomised equally to receive IV pembrolizumab (adult dose: 200mg; paediatric dose: 2mg/kg up to a maximum of 200mg) every 3 weeks (n=487) or placebo every 3 weeks for 17 cycles (~1 year) (n=489). Treatment continued until recurrence, unacceptable toxicity, withdrawal or for the duration of up to one year. |
| Randomisation | Randomisation was stratified by T cancer staging (T3b, T4a, or T4b) for adults with a separate stratum for paediatric patients (aged 12 to 17 years). |
| Primary outcome | Recurrence-free survival (RFS), defined as the time from randomisation to any recurrence (local or regional, or distant) as assessed by the investigator or to death due to any cause. This was assessed in the ITT population. |
| Secondary outcomes | • Distant metastasis-free survival (DMFS), defined as the time from randomisation to appearance of a distant metastasis as assessed by the investigator. A distant metastasis refers to cancer that has spread from the original (primary) tumour to distant organs or distant lymph nodes.<br>• Overall survival, defined as the time from randomisation to death due to any cause. |
| Statistical analysis | The study used the graphical method of Maurer and Bretz to control multiplicity. Study hypotheses could be tested more than once, and when a particular null hypothesis was rejected, the alpha allocated to that hypothesis could be reallocated to other hypothesis tests. The multiplicity strategy was applied to the primary hypothesis (testing superiority of pembrolizumab to placebo with respect to RFS) and two secondary hypotheses (testing superiority with respect to DMFS [first re-allocation] and overall survival [second re-allocation]). The overall Type-I error among the three hypotheses was strongly controlled at 2.5% (one-sided), with 2.5% initially allocated to the RFS hypothesis. The study was to be considered a success if RFS was statistically significant at either an interim analysis or the final analysis under multiplicity control. |

Abbreviations: ECOG = Eastern Cooperative Oncology Group; ITT = intention-to-treat; IV = intravenous; KPS = Karnofsky performance status; LPS = Lansky-Play Performance Scale.

At the first interim analysis (data cut-off: 04 December 2020; median follow-up of 14.4 months in the pembrolizumab group and 14.2 months in the placebo group), pembrolizumab significantly reduced the risk of disease recurrence or death versus placebo (hazard ratio [HR]: 0.65 [95% CI 0.46 to 0.92]; p=0.007). At the second interim analysis (data cut-off: 21 June 2021; median follow-up of 20.9 months in both groups), descriptive results were consistent (HR: 0.61 [95% CI 0.45 to 0.82]). At the third interim analysis (not pre-specified for RFS analysis; data cut-off: 04 January 2022; median follow-up of 27.4 months in the pembrolizumab group and 27.3 months in the placebo group), descriptive results were also consistent with the first interim analysis.[6, 7]

At the third interim analysis (planned interim analysis for DMFS), pembrolizumab demonstrated a statistically significant improvement in DMFS compared with placebo. Insufficient events had occurred to enable analysis of overall survival to be conducted. [6] See Table 2.2 for primary and selected secondary outcomes results.

**Table 2.2. Primary and selected secondary outcomes of KEYNOTE-716 at the third interim analysis (data cut-off 04 January 2022)[6]**

| | Pembrolizumab n=487 | Placebo n= 489 |
|---|---|---|
| **Recurrence-free survival assessed by the investigator** | | |
| **Patients with event, n (%)** | 95 (20%) | 139 (28%) |
| **Median RFS, months (95% CI)** | 37.2 (NR, NR) | NR (NR, NR) |
| **Stratified HR (95% CI)** | 0.64 (0.50 to 0.84) | |
| **RFS Rate at 24 months (%) (95% CI)** | 81% (77 to 85) | 73% (68 to 77) |
| **Distant metastasis-free survival assessed by the investigator** | | |
| **Patients with event, n (%)** | 63 (13%) | 95 (19%) |
| **Median DMFS, months (95% CI)** | NR (NR, NR) | NR (NR, NR) |
| **HR (95% CI), p-value** | 0.64 (0.47 to 0.88), p=0.0029[a] | |
| **DMFS Rate at 24 months (%) (95% CI)** | 88% (84 to 91) | 82% (78 to 86) |

Abbreviations: CI = confidence interval; DMFS = Distant metastasis-free survival; HR = hazard ratio; n = number of patients; NR = not reached; RFS = recurrence-free survival

[a]met the boundary for superiority (one-sided α 0·0128)

### 2.2. Health-related quality of life outcomes

Health-Related Quality of Life (HRQoL) was assessed using the European Organisation for Research and Treatment of Cancer (EORTC) quality of life 30 item questionnaire (QLQ-C30, only administered for adults) and the European Quality of Life 5 Dimensions (EQ-5D). These instruments were administered at baseline, every 12 weeks during treatment in the first 2 years then every 6 months in the third year, at the discontinuation visit and at the 30-day follow-up visit.

There were no clinically meaningful differences between the pembrolizumab and placebo groups in HRQoL outcomes from baseline.[2, 4]

## 3. Summary of Safety Evidence

In the KEYNOTE-716 study at data cut-off 4th January 2022, any treatment-emergent adverse event (AE) was reported by 96% (462/483) of patients in the pembrolizumab group and 92% (445/486) in the placebo group and these were considered treatment-related in 83% and 64% respectively. In the pembrolizumab and placebo groups respectively, patients reporting a grade 3 or higher treatment-related AE were 17% versus 4.9%, patients with a reported serious treatment-related AE were 10% versus 2.3%, patients and patients discontinuing therapy due to a treatment-related AE was 16% versus 2.5%.[6, 8]

The most frequently reported treatment-related AEs of any grade with an incidence ≥15% were in the pembrolizumab group versus the placebo group: pruritus (25% versus 11%), fatigue (21% versus 19%) diarrhoea (19% versus 12%), arthralgia (17% versus 8.0%), rash (16% versus 6.9%), and hypothyroidism (16% versus 2.7%). Immune-mediated events and infusion reactions occurred in 38% and 9.2% of patients. [5]

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

## 4. Summary of Clinical Effectiveness Considerations

The key strengths and uncertainties of the clinical case are summarised below.

### 4.1. Key strengths

- In KEYNOTE-716, at the first interim analysis, pembrolizumab significantly reduced the risk of disease recurrence in comparison to placebo, in adolescent and adult patients with completely resected, Stage IIB or IIC melanoma. This result was considered clinically relevant. [2] Results from the second and third interim analyses were consistent with the results of the first interim analysis.
- At the third interim analysis, pembrolizumab had also significantly reduced the risk of distant metastasis in comparison to placebo.

### 4.2. Key uncertainties

- Overall survival data for pembrolizumab are currently immature. Regulators noted it remains to be excluded that pembrolizumab as adjuvant therapy merely delays disease relapse with no benefit on the overall survival compared to a delayed treatment at recurrence. In addition, the median follow-up was only about 2.3 years at the latest interim analysis. Additional results with longer follow-up and for clinically relevant outcomes, such as overall survival, are needed to confirm pembrolizumab benefits. The marketing authorisation holder was requested to submit results from the future analyses of DMFS and overall survival.[2]
- Patients aged 12 years and older were eligible for inclusion, but only two adolescents were enrolled. There is some uncertainty about the generalisability of KEYNOTE-716 data to adolescents. However, regulators considered that based on the similarity in terms of disease biology between adults and adolescents and based on the pharmacology of drug effect, extrapolation from adults to adolescents was supported. With regard to safety, the long-term toxicities of checkpoint inhibitors in the adolescent population are unknown; the marketing authorisation holder was requested to prospectively collect post-authorisation efficacy and safety data on paediatric/adolescent treated patients in the licensed indication.[2]
- Statistical significance was demonstrated for RFS at the first interim analysis, however, results were highly immature with only 11% and 17% of events in the pembrolizumab and control groups, respectively. Descriptive results from subsequent interim analyses did consolidate the initial RFS results, though only 20% and 28% of events had occurred at the third interim analysis, in the pembrolizumab and placebo group, respectively. DMFS results from the third interim analysis were also immature (with only 13% and 19% of events, respectively). [2]
- The impact of the use of pembrolizumab as adjuvant therapy on subsequent treatment in the advanced setting is unknown. The best treatment sequencing is also unknown.

### 4.3. Clinical expert input

Clinical experts consulted by SMC considered that pembrolizumab fills an unmet need in this therapeutic area, namely as there are currently no adjuvant treatment offered for adults and adolescents aged 12 years and older with Stage IIB or IIC melanoma and who have undergone complete resection. They considered that pembrolizumab is a therapeutic advancement as data

suggest that recurrence-free survival and distant metastasis-free survival are improved in patients treated with pembrolizumab compared to placebo.

### 4.4. Service implications

Clinical experts consulted by SMC considered that the introduction of this immunotherapy will have an impact on oncology services delivering this treatment.

## 5. Summary of Patient and Carer Involvement

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

- We received patient group submissions from Melanoma Action and Support Scotland (MASScot) and Melanoma Focus. MASScot is a Scottish charitable incorporated organisation (SCIO) and Melanoma Focus is a registered charity.
- MASScot has not received any pharmaceutical company funding in the past two years. Melanoma Focus has received 20% pharmaceutical company funding in the past two years, including from the submitting company.
- Melanoma incidence is related to age, however, compared with other cancer types, melanoma occurs relatively frequently in younger age groups. There is therefore a growing population of melanoma patients who are younger in age with the majority of their life ahead of them; they want to increase the possibility of seeing their children grow up and reaching important milestones. The biggest fear is stage 4 disease. As with all cancer diagnoses, being told that there is spread, even into local lymph glands causes fear and alarm especially for parents of dependent children.
- Pembrolizumab is the first adjuvant treatment to be licensed for high-risk stage IIB/IIC melanoma. Many patients are young with young families, explanation that the alternative would be 'Watch and Wait', does help to put treatment into perspective. Being told that the melanoma has spread can scare patients more than the risk of having treatment.
- Patients would rather have treatment when they are fit and healthy and have single agent immunotherapy rather than combination immunotherapy if they were diagnosed with metastatic disease. The patient groups expressed strong support for pembrolizumab as a treatment option for stage IIB/IIC melanoma.

## 6. Summary of Comparative Health Economic Evidence

### 6.1. Economic case

The submitting company provided an economic case as described in Table 6.1.

**Table 6.1 Description of economic analysis**

| Criteria | Overview |
|---|---|
| Analysis type | Cost utility analysis |
| Time horizon | Lifetime – 40.7 years based on an assumed starting age of 59.3 years |
| Population | Patients with stage IIB or IIC melanoma and who have undergone complete resection |
| Comparators | Routine surveillance |

| | |
|---|---|
| Model description | A 4 state Markov model was used. The included states were recurrence-free (RF), locoregional recurrence (LRR), distant metastases (DM), and death. |
| Clinical data | The main source of clinical data was the KEYNOTE-716 study, which provided information on the efficacy of pembrolizumab in reducing the rate of recurrence and the outcomes in the LRR state. [2, 4-8] Outcomes once a patient entered the DM state came from the KEYNOTE-006 study.[9] |
| Extrapolation | Survival modelling was applied to estimate the specific transition probabilities between one state and another, adjusted for competing risks. To model the probabilities of moving from the RF state to the LRR and DM state independent log-normal curves were fitted to KEYNOTE-716 data. For the transition from RF to death an exponential function was used. All of those curves were adjusted based on an assumption that the risk of recurrence reduced naturally over time. Independent exponential functions were used to model the transition between the LRR and the DM state. In the absence of data on deaths in the LRR state, the mortality rate in the LRR state was assumed equal to that in the RF state, which is likely conservative. Finally, the mortality rate in the DM state was dependent upon the assumed treatment received at that stage. An exponential curve was fitted to the progression free and overall survival curves for patients receiving pembrolizumab in the KEYNOTE-006 study. Survival for alternative treatments were estimated by applying hazard ratios, which themselves were estimated from a network meta analysis, to the pembrolizumab survival curves. |
| Quality of life | The EQ-5D-5L questionnaire was completed by participants in the KEYNOTE-716 study. Those values were mapped to 3L values using the algorithm developed by van Hout et al. 2012.[10] A linear mixed-effects model with patient-level random effects was used to estimate the utility values for patients in the RF, LRR and DM states (up to the point of progression. The utility value for patients in the DM state following progression was based on data from Beusterien et al (2009), and was valued at 0.59.[11] A one off disutility derived from the regression of KEYNOTE-716 data was applied to account for adverse events. |
| Costs and resource use | Medicine costs covered the acquisition and administration costs of pembrolizumab. Additional costs were applied for adverse events in both arms. Costs were also included for subsequent treatment lines at the LRR stage, and for first and second line treatment in the DM state.<br>Each health state was associated with an assumed level of resource use. Those resource costs were estimated from clinical visits, imaging, salvage surgery and outpatient visits and inpatient stays. Patients dying in the DM state were assumed to accrue a terminal care cost of £8,486 based on Georghiou and Bardsley (2014).[12] |
| PAS | A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a discount was offered on the list price.<br><br>The results presented do not take account of the PAS discounts for nivolumab, ipilimumab, dabrafenib, trametinib, vemurafetinib, encorafenib and binimetinib, which were used in subsequent treatment lines, but these were considered in the results used for decision-making. SMC is unable to present the results provided by the company which used an estimate of the PAS price for nivolumab, ipilimumab, dabrafenib, trametinib, vemurafetinib, encorafenib and binimetinib due to commercial confidentiality and competition law issues. |

### 6.2. Results

The base case results are presented in Table 6.2. Use of pembrolizumab was projected to increase adjuvant treatment costs, while also leading to reduction in the cost of subsequent treatment. The estimated QALY gains in the pembrolizumab arm are a result of an increased time spent in the RF state, with a reduction in time spent in the LRR and DM states.

**Table 6.2 Base case analysis (inclusive of PAS on pembrolizumab only)**

| Technologies | Incremental cost-effectiveness ration (ICER) (£/QALY) |
|---|---|
| Pembrolizumab versus Routine Surveillance | 16,207 |

### 6.3. Sensitivity analyses

The company provided sensitivity analysis and scenario analysis exploring areas of uncertainty in the model. Those analyses showed that a large driver of the results was the assumptions made on the costs and outcomes of the LRR and DM health states. A selection of illustrative scenarios are presented in the Table below.

**Table 6.3 Selected scenario analysis results (inclusive of PAS on pembrolizumab only)**

| # | Base case | Scenario | ICER (£/QALY) |
|---|---|---|---|
| 1 | Alternative functions for modelling of transitions from RF state<br><u>Base case:</u><br>RF→LRR: Lognormal<br>RF→DM: Lognormal | RF→LRR: Log-logistic<br>RF→DM: Lognormal | 18,996 |
| 2 | | RF→LRR: Log-logistic<br>RF→DM: Exponential | 7,749 |
| 3 | Alternative approaches for modelling transitions from RF state<br><u>Base case:</u><br>Independent modelled curves | <u>Dependent models with time-constant HR:</u><br>RF→LRR: Exponential<br>RF→DM: Exponential | 10,075 |
| 4 | | <u>Dependent models with time-varying HR:</u><br>RF→LRR: Exponential<br>RF→DM: Exponential | 15,155 |
| 5 | Alternative risk reduction assumptions<br><br><u>Base case:</u><br>For patients in the RF state, a 95% risk reduction is applied at 10 years, with linear decrease starting from 7 years | For patients in the RF state, an 80% risk reduction is applied at 10 years, with linear decrease starting from 7 years | 18,070 |
| 6 | | For patients in the RF state, the 95% risk reduction is applied at 10 years, with linear decrease starting from 5 years | 15,201 |
| 7 | Subsequent treatment costs:<br><br><u>Base case:</u><br>All subsequent treatment costs included | Costs of second line therapies in the DM state are excluded, as the model does not consider the efficacy of 2L agents | 12,045 |
| 8 | Alternative dosing schedule for pembrolizumab | Pembrolizumab administered as 200mg every 3 weeks in adult population | 17,161 |

| # | Base case | Scenario | ICER (£/QALY) |
|---|---|---|---|
| | Base case: pembrolizumab administered as 400mg every 6 weeks in adult population | | |
| 9 | Vial sharing not permitted | Vial sharing is permitted | 15,166 |
| 10 | Time horizon = 40.7 years (starting age 59.3) [Generated by SMC Assessment Team] | Time horizon = 50 years (starting age 50) | 12,554 |
| 11 | | Time horizon = 30 years (starting age 70) | 27,728 |

Abbreviations: RF = recurrence-free, LRR = locoregional recurrence, DM = distant metastases, HR = hazard ratio, 2L = second line, mg = milligrams, QALYs = quality adjusted life years, ICER = incremental cost-effectiveness ratio

### 6.4. Key strengths

- The economic analysis was aligned with the extension of the target population to people with stage IIB and IIC melanoma following complete resection and the comparator is appropriate.
- The model structure is closely matched to those used in previous SMC submissions in similar clinical areas, such as pembrolizumab for melanoma at stage III disease.
- Clinical evidence for the comparison of pembrolizumab and routine surveillance came from a large randomised controlled study.

### 6.5 Key uncertainties

- The study data from KEYNOTE-716 were quite immature meaning extrapolation into the future was extensive. While the company has validated its approach and conclusions with clinical experts, there were a number of key assumptions utilised in regard to the long-term efficacy of treatment, the reducing risk of recurrence over time and future treatment patterns. The nature of adjuvant treatment means that it generates value by avoiding costly health issues in the future, and so these assumptions about long-term treatment patterns and outcomes were highly impactful on the economic case.
- Similarly, very few deaths were observed in the KEYNOTE-716 study, and no statistical difference in overall survival was demonstrated. While the company presented secondary evidence which suggested a strong correlation between recurrence–free and overall survival, there was no direct evidence to demonstrate a survival benefit from the use of pembrolizumab. Despite this, the modelling concluded that pembrolizumab would lead to a longer life span.
- The results of the probabilistic sensitivity analysis suggested that the model had some non-linear elements which pushed the probabilistic mean above the deterministic mean. The company stated a belief that this discrepancy was generated by the sampling of the parameters used to estimate the transitions between the RF and LRR and DM states.
- Clinicians consulted by SMC highlighted the service implications that would result from use of pembrolizumab in Scotland within the patient population. The costs included in the model may not reflect the current capacity constraints in place.

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

## 7. Conclusion

Despite these limitations, the case was felt sufficiently robust to gain acceptance by SMC.

## 8. Guidelines and Protocols

A national clinical guideline SIGN 146 - Cutaneous melanoma was published in January 2017. See here (hyperlinked). [13]

A NICE guideline Melanoma: assessment and management [NG14] was published in July 2015 and last updated in July 2022. See here (hyperlinked).[14]

ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up on Cutaneous Melanoma were published in 2019. See here (hyperlinked). [15]

## 9. Additional Information

### 9.1. Product availability date

25 July 2022

### 9.2. Summary of product characteristics

pembrolizumab 25mg/mL concentrate for solution for infusion (Keytruda®)

**Table 9.1 List price of medicine under review**

| Medicine | Dose regimen | Cost per year (£) |
|---|---|---|
| **pembrolizumab** | **Administered as an intravenous infusion over 30 minutes, for up to a maximum of 12 months.**<br>- **Adult: 200mg every 3 weeks or 400mg every 6 weeks**<br>- **Adolescent (12 years and above): 2mg/kg bodyweight, up to a maximum of 200mg, every 3 weeks** | **94,680** |

*Costs from BNF online on 13 January 2023. Costs calculated using the full cost of vials assuming wastage. Costs do not take any patient access schemes into consideration.*

## 10. Company Estimate of Eligible Population and Estimated Budget Impact

The submitting company estimated there would be 147 patients eligible for treatment with pembrolizumab in each year 1 rising to 175 patients in year 5 to which confidential estimates of treatment uptake were applied. Information from SMC clinical experts suggest that the patient numbers predicted by the company may be an underestimate.

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. This template does not incorporate any PAS discounts associated with comparator medicines.

*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 17 February 2023.

**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:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

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.