Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2394

nivolumab 10mg/mL concentrate for solution for infusion (Opdivo®)

Bristol-Myers Squibb Pharmaceuticals Ltd

05 November 2021

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

ADVICE: following a full submission

nivolumab (Opdivo®) is accepted for use within NHSScotland.

Indication under review: in combination with ipilimumab for the treatment of adult patients with mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H) metastatic colorectal cancer after prior fluoropyrimidine-based combination chemotherapy.

In a single-arm cohort of a phase II study, nivolumab in combination with ipilimumab was associated with clinically relevant overall response rates in adults with dMMR or MSI-H metastatic colorectal cancer who had received prior fluoropyrimidine-based chemotherapy.

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

Chairman
Scottish Medicines Consortium

Indication

Nivolumab in combination with ipilimumab for the treatment of adult patients with mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H) metastatic colorectal cancer after prior fluoropyrimidine-based combination chemotherapy.[1]

Dosing Information

Nivolumab 3mg/kg in combination with ipilimumab 1mg/kg both by 30 minute intravenous (IV) infusion every 3 weeks for the first 4 doses. Nivolumab should be administered before ipilimumab. This is followed by a second phase in which nivolumab monotherapy 240mg every 2 weeks is administered by 30 minute IV infusion, with the first dose given 3 weeks after the last dose of the combination of nivolumab and ipilimumab. Dose escalation or reduction is not recommended. Dosing delay or discontinuation may be required based on individual tolerability as detailed in the summary of product characteristics (SPC).

Treatment should be continued as long as clinical benefit is observed or until treatment is no longer tolerated. Atypical responses (an initial transient increase in tumour size or small new lesions within the first few months followed by tumour shrinkage) have been observed. It is recommended to continue treatment for clinically stable patients with initial evidence of disease progression until progression is confirmed. Treatment must be initiated and supervised by physicians experienced in the treatment of cancer.[1]

Product availability date

24 June 2021

Nivolumab in this indication meet SMC orphan equivalent and end-of-life criteria.

Summary of evidence on comparative efficacy

Nivolumab is a monoclonal antibody that targets the programmed death (PD)-1 receptor and blocks interaction with its ligands, PD-L1 and PD-L2 leading to potentiation of T-cell responses, including anti-tumour responses. Ipilimumab is a monoclonal antibody that targets cytotoxic T-lymphocyte antigen-4 (CTLA-4) leading to enhanced T-cell responses towards the tumour. Dual blockade of PD-1 and CTLA-4 is considered to have synergistic anti-tumour activity.[1]

A cohort of an ongoing open-label phase II study (cohort 2 of Checkmate-142) includes adults with dMMR/MSI-H metastatic colorectal cancer who had received at least one previous line of therapy for metastatic disease that included a fluoropyrimidine and oxaliplatin or irinotecan, with patients progressing on or within 6 months of adjuvant oxaliplatin also included. Patients had measurable disease on Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 and an Eastern Co-operative Oncology (ECOG) performance status of 0 or 1. All patients received IV infusions of nivolumab 3mg/kg over 60 minutes and ipilimumab 1mg/kg over 90 minutes every three weeks for four doses then nivolumab 3mg/kg IV infusion every two weeks until disease progression or unacceptable toxicity. A strict stopping rule was not specified, but patients could discontinue

treatment after a minimum of two years if all criteria for investigator-assessed maximum clinical benefit had been achieved. The primary outcome was investigator-assessed overall response rate (ORR), defined as complete or partial response on RECIST version 1.1. This was assessed in all patients within the cohort who received at least one dose of study drug.[2,3]

Within cohort 2 (n=119) the median follow-up was 13.4 and 31.5 months at data cut-offs on 18 August 2017and19 February 2019, respectively, with 63% (75/119), and 43% (51/119) of patients still on treatment. Additional data are available with median follow up 51.1 months at data cut off October 2020. The primary outcome, investigator-assessed ORR, increased over the three time-points as detailed in Table 1 below.[2-4]

Table 1: Outcomes of CheckMate-142 study.[2,4]

	August 2017 (N=119)	**February 2019 (N=119)**	**October 2020 (N=119)**
Best overall response (Investigator-assessed, RECIST v1.1)			
ORR (investigator), % (n), 95% confidence interval	55% (65) 45% to 64%	60% (72) 51% to 69%	65% (77) 55% to 73%
Complete response, % (n)	3.4% (4)	7.6% (9)	13% (15)
Partial response, % (n)	51% (61)	53% (63)	52% (62)
Stable disease, % (n)	31% (37)	25% (30)	21% (25)
Progressive disease, % (n)	12% (14)	12% (14)	12% (14)
Not evaluable, % (n)	2.5% (3)	2.5% (3)	2.5% (3)
Time to response, median	2.76 months	2.76 months	-
Duration of response, median	NR	NR	NR
Progression free survival (Investigator-assessed, RECIST v1.1)			
Events	33	48	51
Median	NR	41.5 (32.8, 41.6)	-
Overall survival			
Deaths	23	33	35
Median	NR	NR	NR
Estimate at 12 months	85%	85%	85%
Estimate at 24 months	-	74%	75%
Estimate at 48 months	-	-	70%

NR = not reached; ORR = overall response rate, defined as complete or partial response; RECIST v 1.1 = response evaluation in solid tumours version 1.1.

Health Related Quality of Life was assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 (EORTC QLQ-C30) questionnaires and Euroqol 5 dimension 3 level (EQ-5D-3L). At the data cut-off August 2017, there were sustained improvements versus baseline in some symptoms and global quality of life on the EORTC QLQ-C30 and in the EQ-5D visual analogue scale (VAS).[2]

Unanchored matching adjusted indirect comparison (MAIC) compared nivolumab-ipilimumab (data from cohort 2 of CheckMate 142, October 2020 cut-off)[2,4] versus folinic acid, 5-fluorouracil (5-FU) plus oxaliplatin (FOLFOX) (data from CONFIRM 2)[5]; folinic acid, 5-FU plus irinotecan (FOLFIRI) (data from VELOUR and RAISE)[6,7]; trifluridine-tipiracil (data from RECOURSE EU and US

subgroups)[8,9] and best supportive care (BSC) (data from RECOURSE EU and US subgroups)[8,9] in adults with metastatic colorectal cancer for the outcomes: progression-free survival (PFS) and overall survival (OS). The results, which suggest that nivolumab-ipilimumab is superior to the comparators, were applied to the economic analyses.

Summary of evidence on comparative safety

The European Medicines Agency (EMA) review concluded that the safety profile of nivolumab-ipilimumab in patients with dMMR/MSI-H metastatic colorectal cancer appears consistent with that in renal cell carcinoma and with the recognised safety profile of the individual medicines.[2]

At the latest data cut-off (October 2020), almost all patients, 99% (118/119), had an adverse event, which were treatment-related in 85%. Serious adverse events were reported by 56%, including 23% which were treatment-related. Adverse events led to study drug discontinuation in 18% of patients and these were treatment-related in 13%. Common adverse events included diarrhoea (58%), pyrexia (44%), cough (35%), pruritus (35%), anaemia (34%), fatigue (34%), abdominal pain (32%), nausea (30%), asthenia (29%) and back pain (28%). Adverse events of special interest were mainly immune-related events, including pneumonitis or interstitial lung disease, colitis, hepatitis, nephritis, adverse reactions and endocrinopathies. These data from CheckMate 142 were combined with data from a study of nivolumab-ipilimumab in renal cell carcinoma to update the SPC (see SPC for further details).[2]

Summary of clinical effectiveness issues

About 5% of patients with metastatic colorectal cancer have dMMR/MSI-H and they may have poorer responses to the chemotherapies typically used for metastatic colorectal cancer. First and second line treatment of metastatic colorectal cancer is usually with fluoropyrimidine-based combination chemotherapies such as FOLFOX and FOLFIRI. Some targeted treatments are also licensed for this disease. However, the benefits of current conventional chemotherapy (with or without biologics) after first-line therapy are modest in patients with metastatic colorectal cancer. In the subgroup with dMMR/MSI-H the benefits are not well defined due to limited data, but there may be a reduced response to cytotoxic chemotherapy. There is an unmet need for effective therapies in this patient group.[2] Clinical experts consulted by SMC confirmed that there is an unmet need for effective therapies in second-line and later treatment of metastatic colorectal cancer, particularly a need for immunotherapies.

Nivolumab-ipilimumab is the first immunotherapy regimen licensed for second-line and later treatment of metastatic colorectal cancer, for the subgroup of patients with dMMR/MSI-H. In this indication it meets SMC orphan equivalent and end-of-life criteria.

In cohort 2 of CheckMate 142 nivolumab-ipilimumab produced substantial responses that have increased as the study progresses from an investigator-assessed ORR of 55% in August 2017 to 65% in October 2020. These responses are durable, with median duration of response (DOR) not reached at the latest analysis (October 2020). At this cut-off, median follow-up was 51 months

(minimum follow-up was nearly four years, 46.9 months), median investigator-assessed PFS and OS had not been reached and 71% of patients were alive. The EMA concluded that these results were clinically meaningful.[2]

The EMA also concluded that outcomes with nivolumab-ipilimumab were superior to currently available therapies based on additional analyses performed during the review, including within patient analysis of response to previous therapy versus response in CheckMate 142 and a MAIC of PFS and OS using data from a retrospective cohort study (CA2097XM) of patients who received conventional second- or third-line treatment for dMMR/MSI-H metastatic colorectal cancer.[2]

To address the limitations in estimating relative treatment benefit which arise from the single-arm design of cohort 2 of CheckMate 142, the submission included several MAICs to inform economic analyses. These support the assumption that OS and PFS with nivolumab-ipilimumab are superior to that with the comparators, although the estimate of magnitude of benefit has limitations. That is, all available reference sources of data for comparators were not used. The rationale for this was to reduce heterogeneity. All patients in the nivolumab-ipilimumab study had dMMR/MSI-H, but this was not quantified in the comparator studies and it is not clear how many patients in those studies had dMMR/MSI-H. However, as outcomes with chemotherapy in dMMR/MSI-H patients tend to be poorer, the inclusion of patients without dMMR/MSI-H in comparator studies may bias in favour of the comparators. The matching process did not adjust for all differences across the studies in other baseline demographic and disease characteristics due to limitations of data. In several comparisons effective sample sizes were reduced to small numbers despite matching a limited number of criteria. Also, it is possible that unknown treatment-effect modifiers were not matched. One of the main limitations was that it was not possible to adjust for differences across the studies in maturity of data with a much lower proportion of patients in the nivolumab-ipilimumab study having events compared with comparator studies. The MAIC did not consider ORR, safety or quality of life outcomes.

The evidence from CheckMate 142 is limited by immaturity of data for PFS and OS. At the latest data cut-off (October 2020) 43% of patients had a PFS event and 29% of patients had died. It is likely that estimates of median PFS and OS may change as data mature. Further evidence may be provided in the future by an ongoing open-label phase III study, CA2098HW (CheckMate 8HW), which is comparing nivolumab monotherapy, nivolumab-ipilimumab and investigator's choice of chemotherapy in patients with MSI-H/dMMR metastatic colorectal cancer. The first interim analysis is expected in the last quarter of 2022.[2]

In cohort 2 of CheckMate 142 the majority of patients (76%) had received at least two prior lines of therapy, including 24% and 16% who had received three and at least four lines, respectively. Analyses at the February 2019 cut-off indicated that ORR may be lower with later lines: 63% for second-line, 58% for third-line, 52% for fourth-line and 37% for fifth or later line. At the October 2020 cut-off the ORR was 68% in patients receiving treatment at second-line.[2] This may affect the estimate of benefits in practice if nivolumab-ipilimumab is routinely used at second-line.

In cohort 2 of CheckMate 142 the ORR at the latest cut-off in patients aged at least 75 years was 36% and 45%, when assessed by blinded independent central review (BICR) and investigator, respectively. Analyses of baseline characteristics within this subgroup were conducted, but no

conclusions can be drawn from this small sample of 11 patients. Subgroup analyses indicated that ORR were consistent irrespective of PD-L1 status.[2]

In September 2021, SMC issued advice (SMC2375) that another immunotherapy (which is a PD-1 receptor inhibitor), pembrolizumab, is accepted for restricted use as monotherapy for the first-line treatment of dMMR/MSI-H metastatic colorectal cancer in adults, with a two-year clinical stopping rule restriction. Clinical experts advised that people who progress on pembrolizumab first-line would be unlikely to receive another medicine in this class at second-line. This could reduce the population eligible for nivolumab-ipilimumab in second-line or later settings. Nivolumab-ipilimumab is licensed for use in patients with dMMR/MSI-H, which would require a diagnostic test to confirm. Contact local laboratory for information.

Clinical experts consulted by SMC advised that nivolumab-ipilimumab in the treatment of adults with dMMR or MSI-H metastatic colorectal cancer after prior fluoropyrimidine-based combination chemotherapy is a therapeutic advance due to its superior efficacy. They believe that it would be used in place of current standard of care with an alternative fluoropyrimidine-based combination chemotherapy.

Summary of comparative health economic evidence

The submitting company presented a cost-utility analysis evaluating the use of nivolumab-ipilimumab within its full licensed indication. The analysis compared nivolumab-ipilimumab with BSC, trifluridine-tipiracil, FOLFOX and FOLFIRI through unanchored MAIC. Clinical experts indicated that FOLFOX and FOLFIRI were the most appropriate comparators.

A partitioned survival model was used to represent three health states; pre-progression, post-progression and death. The progression (pre and post) health states were divided into sub-health states of on and off treatment. A cycle length of one week was used in the model with a time horizon of fifty years.

PFS, OS and time on treatment (ToT) for nivolumab-ipilimumab were extrapolated using a semi-parametric approach. Kaplan-Meier data were applied until 6.44 months (at data cut-off) followed by parametric extrapolation. Background mortality was incorporated in the OS projections. For PFS the exponential function was selected, for OS the log-normal function was selected and for ToT the Gompertz function was selected. The comparator PFS and OS were based on the indirect treatment comparison, and ToT was derived from literature.

Utilities were estimated from EQ-5D-3L data collected from CheckMate 142 and valued using standard methods. The comparator health state utilities and the off treatment health state utility for nivolumab-ipilimumab were sourced from the National Institute for Health and Care Excellence (NICE) technology assessment TA242[10] which were measured using the Health Utility Index (HUI). Utilities were applied by on- and off- treatment status for nivolumab-ipilimumab and pre- and post-progression for comparators (0.75 and 0.69 respectively). It was assumed that adverse event disutilities were reflected by on treatment utility values and utility values were age-adjusted.

The medicine costs included were acquisition costs, administration costs and subsequent treatment costs. Patient Access Schemes (PAS) were submitted by the company for nivolumab and ipilimumab 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 of nivolumab and ipilimumab. A PAS discount is also in place for trifluridine-tipiracil and this was included in the results used for decision-making by using estimates of the comparator PAS price. SMC is unable to present the results provided by the company which used an estimate of the PAS price for trifluridine-tipiracil due to commercial confidentiality and competition law issues. The base case results with PAS are shown below in Table 2 versus BSC, FOLFOX and FOLFIRI. The main driver of quality-adjusted life years (QALY) gains is due to the significant difference in projected survival for nivolumab-ipilimumab.

For the comparison versus trifluridine- tipiracil, as noted above, SMC is unable to present the results using PAS prices and the submitting company has indicated the results at list prices cannot be presented. As such, SMC is unable to present any results for this comparison.

Table 21. Base case analysis results versus BSC, FOLFOX and FOLFIRI (PAS applied)

	Cost-effectiveness, nivolumab-ipilimumab versus comparator		
	BSC	**FOLFOX**	**FOLFIRI**
ICER (Cost/QALY)	**£16,456**	**£17,184**	**£17,973**
BSC: best supportive care; FOLFIRI: 5-FU, folinic acid and irinotecan; FOLFOX: 5-FU, folinic acid and oxaliplatin; ICER: incremental cost-effectiveness ratio; LY: life year; QALY: quality-adjusted life year			

A number of key scenarios are reproduced from the company submission below in Table 3. Additional scenarios requested from the submitting company are presented in the same table. Key sensitivities were time horizon and increase in baseline age. Overall the incremental cost-effectiveness ratio (ICER) remained stable with all scenarios falling below £30,000 per QALY.

Table 3. Scenario analyses versus BSC, FOLFOX and FOLFIRI (with PAS) – Summary results

		Cost-effectiveness, nivolumab-ipilimumab versus comparator		
Number	**Scenario**	**BSC**	**FOLFOX**	**FOLFIRI**
	Base case	**£16,456**	**£17,184**	**£17,973**
1	Alternative extrapolations – PFS – SP 6.44 exponential	**£16,456**	**£17,184**	**£17,973**
2	Alternative extrapolations – PFS – SP 6.44 Weibull	**£16,404**	**£17,128**	**£17,915**
3	Alternative extrapolations – OS – SP 6.44 exponential	**£19,553**	**£20,816**	**£22,027**
4	Alternative extrapolations – ToT – SP 6.44 log-logistic	**£18,974**	**£19,908**	**£20,802**
5	Alternative sources of comparator efficacy – unadjusted	**£16,351**	**£17,090**	**£17,072**
6	Alternative sources of comparator efficacy – pooled outcomes	**£16,718**	**£17,144**	**£17,295**
7	BICR-assessed PFS	**£16,571**	**£17,308**	**£18,103**
8	Remission in a proportion of patients	**£13,492**	**£13,875**	**£14,399**
9	10-year time horizon	**£31,575**	**£26,162**	**£29,089**
10	20% increase in baseline age	**£23,757**	**£20,890**	**£22,380**
11	10% increase in risk of progression and death for NIVO+IPI	**£18,782**	**£17,109**	**£17,926**
12	10% reduction in mean OS for NIVO+IPI	**£20,127**	**£18,178**	**£19,152**

BSC: best supportive care; FOLFIRI: 5-FU, folinic acid and irinotecan; FOLFOX: 5-FU, folinic acid and oxaliplatin; OS: overall survival; PFS: progression-free survival; BICR: blinded independent central review; ToT: time on treatment; IPI: ipilimumab; NIVO: nivolumab

There were a number of weaknesses with the analysis:

- As discussed in the clinical effectiveness section, median PFS and OS were not reached, and the PFS and OS are therefore uncertain. The extrapolations applied in the model had good statistical and visual fit. The alternative extrapolations were explored in scenarios and did not change the ICER drastically. Further, as noted above, there were limitations associated with the indirect treatment comparisons upon which the economic evaluation was based.
- Health Utility Index HUI values were used to derive the comparator health effects and it may not be appropriate to compare with EQ-5D-3L values for nivolumab-ipilimumab in order to reflect the true difference in health effects.
- The on treatment utility for nivolumab-ipilimumab may be unrealistically high, though the impact of the on treatment utility in sensitivity analyses is minimal. The company explored a scenario when applying equal utility values between nivolumab-ipilimumab and comparators. This resulted in a reduced ICER due to the differences in PFS between arms.
- Some subsequent treatments included are not available in NHS Scotland, though the impact of these would be minimal based on scenario analyses.

Despite these limitations, the economic case was demonstrated.

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

Summary of patient and carer involvement

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

- We received a patient group submission from Bowel Cancer UK, which is a registered charity.
- Bowel Cancer UK has received 1.8% pharmaceutical company funding in the past two years, including from the submitting company.
- A diagnosis of bowel cancer can be life-changing for those diagnosed, as well as their friends and family, and is even more acute for those at the metastatic stage of the disease when it is harder to treat and there is a low chance of survival.
- Current treatment options approved for use on the NHS for advanced bowel cancer are extremely limited with many patients unable to access a treatment that could prolong their life.
- Patients report that this treatment offers them greater hope, potentially added months and years of life, additional treatment choice and fewer side effects than chemotherapy, giving them better quality of life. They felt those who have bowel cancer with mismatch repair deficiency or similar, those newly diagnosed with the disease and younger people would benefit most from this treatment. It is important that patients have access to personalised, tailored treatment that is right for them. If outcomes for people with metastatic bowel cancer are to improve, a one-size fits all approach to treating people with the disease will not work.

Additional information: guidelines and protocols

The Scottish Intercollegiate Guidelines Network (SIGN) guideline number 126 on diagnosis and management of colorectal cancer was published in December 2011 and updated in August 2016. This recommends that all patients with metastatic colorectal cancer should be considered for chemotherapy. A combination treatment with 5-FU/leucovorin/oxaliplatin or capecitabine and oxaliplatin or 5-FU/ leucovorin/irinotecan are the preferred options in patients with good performance status and organ function. Consider raltitrexed for patients with metastatic colorectal cancer who are intolerant to 5-FU and leucovorin, or for whom these drugs are not suitable. Second line chemotherapy should be considered for patients with metastatic colorectal cancer with good performance status and adequate organ function. Irinotecan should be used as second line therapy following first line oxaliplatin (or vice versa). The choice of second line chemotherapy for patients with metastatic colorectal cancer will depend on patient fitness, comorbidity and previous chemotherapy exposure. There are no specific recommendation for patients with dMMR/MSI-H metastatic colorectal cancer.[11]

In January 2020 the National Institute for Health and Care Excellence published clinical guideline number 151: colorectal cancer. This refers to NICE advice issued for medicines licensed for second-line and subsequent treatment of metastatic colorectal cancer.[12]

European Society for Medical Oncology (ESMO) consensus guidelines for the management of patients with metastatic CRC published in 2016 recommend that in patients in whom the initial chemotherapy backbone has failed, the chemotherapy backbone should be changed. Following failure on 5-FU/leucovorin, patients who can tolerate it should be switched to an irinotecan or oxaliplatin-containing combination chemotherapy regimen such as FOLFIRI, FOLFOX or possibly irinotecan/oxaliplatin. Patients who receive FOLFIRI up front should receive FOLFOX and those patients who receive FOLFOX up front should receive an irinotecan-containing regimen, preferably FOLFIRI.[13] The guidelines also provide advice on combinations with targeted agents.[13]

Additional information: comparators

Nivolumab-ipilimumab would mainly be used in place of fluoropyrimidine-based combination chemotherapies such as FOLFOX and FOLFIRI and may be an alternative for trifluridine-tipiracil.

Additional information: list price of medicine under review

Medicine	Dose Regimen	Cost per year (£)
Nivolumab	3mg/kg IV infusion every three weeks for four doses then 240mg every two weeks	68,458 93,192 (year 1)
Ipilimumab	1mg/kg IV infusion every three weeks for four doses	

Costs from BNF online on 3 September 2021. Costs calculated using the full cost of vials/ampoules assuming wastage. Costs based on 70kg body weight. Costs do not take patient access schemes into consideration.

Additional information: budget impact

The submitting company estimated there would be 44 patients eligible for treatment with NIVO+IPI in each year to which confidential estimates of treatment uptake were applied.

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS. This template does not incorporate any PAS discounts associated with comparator medicines.

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

References

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11. Scottish Intercollegiate Guidelines Network (SIGN). Guideline number 126: diagnosis and management of colorectal cancer, updated August 2016.

12. National Institute for Health and Care Excellence (NICE). Clinical guideline number 151: colorectal cancer, January 2020.

13. Van Cutsem E, Cervantes A, Adam R, et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. Annal Oncol. 2016; 27(8): 1386-422.

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