Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2398

tucatinib 50mg and 150mg film-coated tablets (Tukysa®)

Seagen Inc

10 December 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 assessed under the end of life and orphan-equivalent process

tucatinib (Tukysa®) is accepted for use within NHSScotland.

Indication under review: in combination with trastuzumab and capecitabine for the treatment of adult patients with HER2-positive locally advanced or metastatic breast cancer who have received at least two prior anti-HER2 treatment regimens.

In a phase II study the addition of tucatinib to trastuzumab plus capecitabine was associated with a statistically significant improvement in progression-free survival.

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

In combination with trastuzumab and capecitabine for the treatment of adult patients with HER2-positive locally advanced or metastatic breast cancer who have received at least two prior anti-HER2 treatment regimens.[1, 2]

Dosing Information

The recommended dose of tucatinib is 300mg (two 150mg tablets) taken twice daily continuously in combination with trastuzumab and capecitabine. Treatment with tucatinib should be continued until disease progression or unacceptable toxicity. Tablets should be swallowed whole and should not be chewed, crushed, or split prior to swallowing. Tucatinib should be taken approximately 12 hours apart, at the same time every day, with or without a meal, and can be taken at the same time with capecitabine.

Treatment with tucatinib should be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products. For more information, including dosing of trastuzumab and capecitabine and management of adverse reactions, see Summary of product characteristics (SPC).[1, 2]

Product availability date

October 2021

Tucatinib meets SMC end of life and orphan equivalent criteria for this indication.

Summary of evidence on comparative efficacy

Tucatinib is a reversible, selective tyrosine kinase inhibitor (TKI) of human epidermal growth factor receptor 2 (HER2). Tucatinib inhibits phosphorylation of HER2, resulting in inhibition of downstream cell signalling and cell proliferation, and induces death in HER2 driven tumour cells.[1]

HER2CLIMB is a multicentre, randomised, double-blind, phase II study which evaluated the efficacy and safety of tucatinib compared with placebo, in combination with trastuzumab and capecitabine in adult patients with histologically confirmed HER2-positive locally advanced or metastatic breast cancer previously treated with trastuzumab, pertuzumab, and trastuzumab emtansine. Patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and patients with brain metastases were eligible for inclusion.[3, 4]

Patients were randomised 2:1 to receive tucatinib 300mg orally twice daily (n=410) or placebo (n=202), in combination with trastuzumab (6mg/kg intravenously once every 21 days, with an initial loading dose of 8mg/kg; subcutaneous administration was allowed) and capecitabine (1,000mg/m^2 orally twice daily on days 1 to 14 of each 21-day cycle). Treatment was to continue until unacceptable toxicity, disease progression, withdrawal of consent, or study closure. Randomisation was stratified according to whether brain metastases were present (yes or no),

ECOG performance status score (0 or 1) and geographic region (United States, Canada, or the rest of the world).[3, 4]

The primary outcome was progression free survival (PFS), defined as the time between date of randomisation to the date of documented disease progression (assessed by blinded independent central review [BICR] using response evaluation criteria in solid tumours criteria [RECIST] v1.1) or death due to any cause, whichever occurred first. The primary outcome analysis was performed in the first 480 patients who underwent randomisation. Key secondary outcomes, overall survival in the total study population and PFS in patients with brain metastases at baseline, were controlled for type I statistical error. If both of these outcomes achieved statistical significance objective response rate (ORR) was also formally tested.[3, 4]

The addition of tucatinib to treatment with capecitabine and trastuzumab was associated with a statistically significant improvement in PFS. Multiplicity-adjusted secondary outcomes also achieved statistical significance.[3, 4] See Table 1 for details.

Table 1. Primary and multiplicity-adjusted secondary outcome results of HER2CLIMB (data cut-off September 2019).[3, 4]

	Tucatinib*	**Placebo***
Median follow-up	14.0 months	
Progression-free survival as per BICR using RECIST 1.1 criteria (primary outcome population)		
n	320	160
Events	178	97
Median PFS	7.8 months	5.6 months
Hazard Ratio (95% CI)	0.54 (0.42 to 0.71) p<0.001	
PFS estimate at 12 months	35%	12%
Overall survival (total study population)		
n	410	202
Events	130	85
Median OS	21.9 months	17.4 months
Hazard Ratio (95% CI)	0.66 (0.50 to 0.88) p=0.005	
OS estimate at 24 months	45%	27%
Progression-free survival as per BICR using RECIST 1.1 criteria (patients with brain metastases at baseline)		
n	198	93
Events	106	51
Median PFS	7.6 months	5.4 months
Hazard Ratio (95% CI)	0.48 (0.34 to 0.69) p<0.001	
PFS estimate at 6 months	60%	34%

Objective response rate as per BICR using RECIST 1.1 criteria (total study population)		
n	410	202
Objective response rate	35%	19%
Complete response	1.7%	1.0%
Partial response	33%	18%

*Both treatment groups also received trastuzumab and capecitabine.
BICR = blinded independent central review; CI = confidence interval; OS = overall survival; PFS = progression-free survival; RECIST 1.1 = response evaluation criteria in solid tumours criteria version 1.1.

Additional secondary outcomes included duration of response (DOR) and clinical benefit rate. Duration of response was analysed in patients with measurable disease at baseline in the total study population. The median DOR as per BICR in the tucatinib group was 8.3 months (95% CI: 6.2 to 9.7 months) and 6.3 months (95% CI: 5.8 to 8.9) in the placebo group. Clinical benefit rate, defined as achieving stable disease or non-complete response/non-progression of disease for ≥6 months or a best overall response of complete or partial response as determined by BICR and by investigator using RECIST 1.1, was achieved in 60% of the tucatinib group and 38% of the placebo group.[3]

Health Related Quality of Life (HRQoL) was assessed using EuroQoL 5 Dimensions (EQ-5D-5L). The questionnaire was implemented after a protocol amendment and as a result only a subset of patients had baseline HRQoL data (n=330). No meaningful differences were observed in the 5 domains.[3]

The submitting company performed two network meta-analyses (NMA) using both frequentist and Bayesian methodologies to compare tucatinib in combination with trastuzumab and capecitabine with eribulin, capecitabine and vinorelbine monotherapy in adult patients with HER2-positive locally advanced or metastatic breast cancer who have received prior anti-HER2 treatment. Efficacy outcomes included PFS and overall survival. Seven studies (Yuan et al 2019[5], Study 301[6], EGF100151[7], CEREBEL[8], ELTOP[9], GBG 26[10] and HER2CLIMB[4]) were included in the network for PFS and six (Yuan et al 2019[5], Study 301[6], EGF100151[7], CEREBEL[8], ELTOP[9], and HER2CLIMB[4]) were included in the overall survival network. The submitting company concluded that the tucatinib combination demonstrated a superior overall survival and PFS benefit compared with eribulin, capecitabine and vinorelbine monotherapy.

Summary of evidence on comparative safety

In the HER2CLIMB study at data cut-off May 2020, the median duration of treatment in the tucatinib group was 7.4 months and in the placebo group was 4.4 months. Any treatment-emergent adverse event (AE) was reported by 99% (401/404) of patients in the tucatinib group and 97% (191/197) in the placebo group. In the tucatinib and placebo groups respectively, patients reporting a grade 3 or higher treatment-emergent AE were 59% versus 51%, patients with a reported serious treatment-emergent AE were 29% versus 29%, patients discontinuing any study treatment due to a treatment-emergent AE was 12% versus 10%.[3]

The most frequently reported treatment-emergent AEs of any grade with an incidence >10% in the tucatinib group versus the placebo group were: diarrhoea (82% versus 54%); palmar-plantar

erythrodysesthesia syndrome (65% versus 53%); nausea (60% versus 45%); fatigue (48% versus 44%); vomiting (37% versus 26%); decreased appetite (26% versus 21%); stomatitis (26% versus 14%); headache (23% versus 20%); aspartate aminotransferase increased (22% versus 11%); alanine aminotransferase increased (21% versus 6.6%); anaemia (21% versus 12%); blood bilirubin increased (20% versus 11%); hypokalaemia (17% versus 13%); constipation (16% versus 21%); abdominal pain (16% versus 16%); arthralgia (16% versus 6.1%); weight decreased (15% versus 6.1%); cough (15% versus 12%); blood creatinine increased (15% versus 1.5%).[3]

Overall, the safety profile of tucatinib is in accordance with what has been previously reported with TKIs that target HER2. The safety profile of tucatinib in combination with capecitabine and trastuzumab is considered overall acceptable and clinically manageable. Long-term safety data are awaited.[3]

Summary of clinical effectiveness issues

Breast cancer is the most common cancer in women in Scotland, with 4,711 new cases diagnosed in 2017. Around 15% to 30% of breast cancers have an overexpression of HER2, and once metastasised is associated with poor prognosis; 5-year overall survival rate ranges from 15% to 26%. First-line treatment for most patients with HER2-positive metastatic breast cancer is a combination of trastuzumab plus pertuzumab and chemotherapy. After progression on trastuzumab, pertuzumab and chemotherapy, standard of care treatment for patients with HER2-positive metastatic breast cancer is trastuzumab emtansine (SMC 990/14). In the third-line setting, there is no standard of care treatment and patients in Scotland typically receive single-agent chemotherapy, including but not limited to capecitabine, eribulin, or vinorelbine. These treatments have limited efficacy, and therefore, as confirmed by clinical experts consulted by SMC, there is a high unmet need for new targeted therapies. Tucatinib meets SMC end of life and orphan equivalent criteria for this indication.[3, 11]

In HER2CLIMB, the addition of tucatinib to trastuzumab plus capecitabine was associated with a statistically significant improvement of 2.2 months in PFS (as assessed by BICR). This gain in PFS can be considered clinically meaningful in a heavily pre-treated cohort with HER2-positive, metastatic breast cancer. Similar efficacy was demonstrated in patients with brain metastases at baseline. The key secondary outcome, overall survival, also favoured tucatinib (HR = 0.66 [95% CI: 0.50 to 0.88]), however, data were only partly mature; 32% and 42% of the tucatinib and placebo groups respectively had events. Further data are expected by the end of Q2 2023.[3, 4]

There were some limitations associated with the evidence that should be considered. The use of RECIST 1.1 criteria in patients with brain metastases is a limitation as brain metastases can frequently have a clinical impact at a much smaller size than specified in RECIST 1.1 criteria (1cm target lesions). Moreover, patients can experience multiple small lesions that represent notable disease burden but again do not meet measurable disease criteria as per RECIST 1.1. The secondary outcome, clinical benefit rate, is designed to encapsulate these patients by including patients with stable disease >6 months, which reflects better the overall treatment benefit in patients with unmeasurable disease. Clinical benefit rate results were positive.[3]

HER2CLIMB recruited patients with an ECOG performance status of 0 or 1, which could limit generalisability of study results to the wider population. This may be particularly relevant in patients with heavily pre-treated metastatic breast cancer.

The control treatment in HER2CLIMB was trastuzumab plus capecitabine, which differs from Scottish practice (chemotherapy monotherapy). Indirect treatment comparisons were presented to evaluate the benefit of the new treatment versus relevant comparators for NHS Scotland. There were some limitations affecting the validity of the NMA results. The population included within the analysis was broader than the licensed indication of tucatinib as it included patients with varying HER2 status and patients who had received at least one prior anti-HER2 therapy. A high proportion of studies were at a high risk of bias, which introduces additional uncertainty in the NMA results. The NMAs included a small number of studies, leading to uncertainty in how much heterogeneity exists within the network; safety outcomes were not evaluated and remain uncertain. Due to notable heterogeneity between studies, random effects should have been used instead of fixed effects. Random effects results have been presented in the appendices and it should be noted that credible intervals for overall survival using random effects cross 1. Therefore, the company's conclusion that tucatinib in combination with trastuzumab and capecitabine was superior in efficacy to eribulin, capecitabine, and vinorelbine, is associated with some uncertainty. However, the plausibility that tucatinib (plus trastuzumab and capecitabine) is superior to chemotherapy monotherapies is strengthened by the results of HER2CLIMB, which demonstrated superiority of tucatinib combination versus trastuzumab plus capecitabine.

Clinical experts consulted by SMC considered that tucatinib in combination with trastuzumab and capecitabine is a therapeutic advancement due to efficacy benefits reported in the key trial. It will likely be a preferred treatment option in third-line HER2-positive locally advanced or metastatic breast cancer as per the licensed indication.

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 tucatinib, as an orphan-equivalent/end of life medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- Metastatic breast cancer is an incurable progressive disease that is associated with poor prognosis. Patients who live with the disease face physical and psychological challenges that are substantial. Physically they have to cope with the effects of their cancer and its treatment. Symptoms are often severe and vary depending on site of metastases. Psychologically they have to live with the knowledge that their cancer cannot be cured, and that the time they have with friends and family is limited.
- There is an urgent need for new and clinically effective treatments for pre-treated patients who progress on current treatments. After progressing on at least two anti-HER2

treatment regimens, patients in Scotland would receive chemotherapy monotherapy, which has limited efficacy.

- Tucatinib (in combination with trastuzumab and capecitabine) is expected to help patients live progression-free for longer compared with currently available treatments. This benefit in progression-free survival would likely reduce symptoms of the disease, improve mental health, improve quality of life, and improve social functioning. These benefits will have a positive impact for family members and carers also, both physically and mentally.
- Other benefits of tucatinib combination are potential improvements in overall survival which are highly valued by patients, and possible advantages for patients with brain metastases. Tucatinib gives patients with brain metastases the hope that there is now a tolerable treatment that might reduce the need for radiotherapy or surgery on their brain.
- Although this treatment is associated with some increased side effects compared to trastuzumab with capecitabine alone, patients found them generally manageable and were prepared to tolerate them for the benefit the medicine could bring.

Additional Patient and Carer Involvement

We received patient group submissions from Breast Cancer Now and METUP UK. Breast Cancer Now is a registered charity and MET UP UK is a charitable incorporated organisation. Breast Cancer has received 4.25% pharmaceutical company funding in the past two years, including from the submitting company. METUP UK has not received any pharmaceutical company funding in the past two years. 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 submitting company provided a cost-utility analysis assessing tucatinib for use in adult patients with HER2-positive locally advanced or metastatic breast cancer who have received at least two prior anti-HER2 treatment regimens. The comparator used in the base case was eribulin, accepted for use by SMC for this indication, irrespective of HER2 status. Capecitabine and vinorelbine, as well as a blended comparator assuming different proportions of patients will receive one of the three comparator treatments, were also explored as comparators in scenario analysis. Clinical experts consulted by SMC noted that subcutaneous trastuzumab may also be relevant to Scottish clinical practice, which would influence both medicines acquisition costs and administration costs.

A partitioned survival model with three health states (progression free, progressed and dead) was used with a 1 week cycle length (a half-cycle correction was not applied) and a time horizon of 20 years. The time horizon was tested in sensitivity analysis upon request.

Clinical data to inform the model included the HER2CLIMB study of tucatinib provided in combination with trastuzumab and capecitabine, versus placebo with trastuzumab and capecitabine.[4] The NMA was also used to inform parameters as the various different NMA results

were used in scenario analysis. The method used to extrapolate survival data beyond the HER2CLIMB follow up period was provided upon request, as were the choices for the distributions fitted to both the progression-free and overall survival data (with AIC/BIC information to explore the comparative extent of goodness of fit). The submitting company also provided justification of their choice of study included in the network meta-analysis to produce the extrapolation [6]. The submitting company also provided details of the method used to extrapolate time to treatment discontinuation which is relevant as restricting mean treatment exposure in the scenario analysis has a considerable impact on the ICER results.

Utility scores used in the model were based on EQ-5D-5L data collected in the HER2CLIMB study following a protocol amendment, and published literature. Key utility values in the progression free state were 0.76 for the tucatinib combination, 0.71 for eribulin and 0.7 for both capecitabine and vinorelbine, and an additional utility increment for tucatinib (which was commercial-in-confidence and cannot be published). Key utility values in the progressed state were 0.698 for the tucatinib combination and 0.496 for eribulin, capecitabine and vinorelbine.

Medicine acquisition costs, administration costs, the costs of subsequent anti-cancer therapies upon progression and the costs associated with treating adverse events were all included. No wastage costs were described and the submitting company stated they did not expect wastage costs to apply in the tucatinib arm given that capecitabine and tucatinib are both orally administered and for trastuzumab they expect hospitals to utilize efficient preparation and dispensing to avoid wastage costs. The impact of changing the wastage costs assumption is not expected to considerably influence the ICER results. Additional resource use did not include medical oncology visits or imaging, even in the progression-free state but did include specialist nurse visits, GP visits and community nurse visits. The submitting company confirmed these resource use items as representative of clinical practice across the UK. A one-off cost was applied to the death state to account for end-of-life care.

A Patient Access Scheme (PAS) was proposed by the submitting company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a simple discount was offered on the list price. A PAS discount is also in place for eribulin and this was included in the results used for decision-making by using estimates of the comparator PAS price. In addition, an assumed discount was applied to the cost of trastuzumab and capecitabine in the results even though trastuzumab is not funded for post-progression treatment in NHSScotland.

The main economic results are shown in the table below (Table 2). These results have removed discounts on the list prices of biosimilar trastuzumab and generic capecitabine. The results presented do not take account of the PAS for tucatinib or for eribulin 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 eribulin due to commercial confidentiality and competition law issues.

Following discussion of the relevance of each comparator, NDC was of the view that a weighted comparator would be appropriate for consideration alongside the submitted base case. The

results for both the original base case comparison (versus eribulin) and the weighted comparator are both shown below.

Table 2: Base case and scenario analyses (list prices for all medicines)

No	Scenario	ICER vs eribulin (£/QALY)	ICER vs weighted comparator
Base case		84,724	93,169
1.	Time horizon: 5 years	Not reported	101,259
2.	Alternative survival distributions	85,485	93,935
3.	Tucatinib combination utilities: EQ-5D-5L	72,141	79,257
4.	Treatment duration: Restricted mean treatment exposure	52,004	60,251
5.	Treatment-independent utilities in PFS	Not reported	100,129
6.	Treatment-independent utilities in post-progression state	Not reported	127,990
7.	Treatment effect waning for PFS and OS	Not reported	95,060

EQ-5D-5L, EuroQoL 5 Dimensions 5-Levels; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; NMA, network meta-analysis; No, number; OS, overall survival; PFS, progression-free survival

The following limitations are noted regarding the economic evaluation:

- The submitting company did not initially provide index utility scores for patients in the HER2CLIMB trial, although these were provided in subsequent correspondence. The submitting company also provided additional scenarios on request whereby a) progression-free health state utilities for all treatments were assumed to be equivalent to that of eribulin (0.706) and b) post-progression health state utilities assumed to be equivalent to that of eribulin (0.496). This impacted the ICER results (Table 3, Scenarios 5 and 6). Considerable uncertainty remains regarding the utility scores from the tucatinib arm compared to the values from the literature used for the comparators and this uncertainty has a considerable impact on ICER results.
- The time horizon of 20 years may be too long given that it was noted more than 99.9% of patients in the model had died within 10 years. Although the submitting company provided additional scenario analyses for 10 and 15 years respectively, a time horizon of 5 years was thought to be relevant (Table 3, Scenario 1).
- Clinical experts consulted by SMC mentioned all three of the comparators explored in this economic evaluation, but the choice of most clinically appropriate comparator was unclear. On discussion at NDC, a blended comparison aligning with relative usage within NHSScotland was felt to be appropriate.
- The inclusion of discounts on the trastuzumab list price and generic capecitabine were not appropriate as only list prices or PAS prices should be included in line with SMC process.

The submitting company, on request, submitted revised ICERs removing these discounts.

- The submitting company provided further clarity on their method for extrapolating time to treatment discontinuation, but the effect of the restricted mean treatment exposure on the ICER was notable, highlighting the sensitivity of the results to duration of treatment (Table 3, Scenario 4).
- Subcutaneous trastuzumab was not considered in the model but may be relevant to clinical practice in Scotland compared with intravenous trastuzumab used in the economic evaluation.

The Committee also considered the benefits of tucatinib in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that the criterion for a substantial improvement in life expectancy in the patient population targeted in the submission was satisfied. In addition, as tucatinib 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, and after application of the appropriate SMC modifiers, the Committee accepted tucatinib for use in NHSScotland.

Additional information: guidelines and protocols

The 2020 European School of Oncology (ESO) - European Society of Medical Oncology (ESMO) International Consensus Guidelines for Advanced Breast Cancer (ABC 5) note that in the treatment of HER2-positive disease anti-HER2 therapy should be offered to all patients early and should be continued in those with progression after anti-HER2 therapy in combination with a cytotoxic or endocrine medicine. The optimal sequence of all available anti-HER2 therapies and the optimum duration of anti-HER2 therapy are currently unknown. For patients who have progressed after first-line trastuzumab-based therapy, trastuzumab emtansine provides superior efficacy relative to other HER2-based therapies in the second line (versus lapatinib-capecitabine) and beyond (versus treatment of physician's choice). In some patients with progression on trastuzumab-based therapy, the combination trastuzumab-lapatinib is a reasonable treatment option, however, there are no data on its use after progression on pertuzumab or trastuzumab emtansine (not recommended by SMC) Tucatinib-trastuzumab-capecitabine and trastuzumab deruxtecan are options in heavily pre-treated patients and those who have received pertuzumab and trastuzumab emtansine. After first-line of therapy, trastuzumab can be administered with several chemotherapies, including but not limited to, vinorelbine (if not given in first line), taxanes (if not given in first line), capecitabine, eribulin, liposomal anthracyclines, platinums, gemcitabine or metronomic cyclophosphamide-methotrexate. The decision should be individualised and take into account different toxicity profiles, previous exposure, patient preferences and country availability.[12]

Additional information: comparators

Capecitabine, vinorelbine, eribulin, anthracycline, low dose oral cyclophosphamide.

Additional information: list price of medicine under review

<table>
<tr><th>Medicine</th><th>Dose Regimen</th><th>Cost per 21-day cycle</th></tr>
<tr>
<td>tucatinib plus trastuzumab plus capecitabine</td>
<td>
<table>
<tr><th>Treatment</th><th>Dose</th><th>Treatment days</th></tr>
<tr><td>Tucatinib</td><td>300mg orally twice daily</td><td>Continuously</td></tr>
<tr><td>Capecitabine</td><td>1,000mg/m^2 orally twice daily</td><td>Days 1 to 14 every 21 days</td></tr>
<tr><td>Trastuzumab</td><td>IV: 8mg/kg initially (day 1), 6mg/kg thereafter

SC: 600mg</td><td>Every 21 days</td></tr>
</table>
</td>
<td>First cycle (IV trastuzumab) = £7,123

Subsequent cycles (IV trastuzumab) = £6,756

Using SC trastuzumab (first and subsequent cycles) = £6,878</td>
</tr>
</table>

Costs from BNF online and company submission on 01 September 2021. Costs calculated using the full cost of vials/ampoules assuming wastage. Costs calculated using a body surface area (BSA) of 1.8m^2 and a weight of 70kg. 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. This template does not incorporate any PAS discounts associated with comparator medicines or PAS associated with medicines used in a combination regimen.

*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 15 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.