Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2388

trastuzumab deruxtecan 100mg powder for concentrate for solution for infusion (Enhertu®)

Daiichi Sankyo UK Ltd

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

trastuzumab deruxtecan (Enhertu®) is accepted for use within NHSScotland on an interim basis subject to ongoing evaluation and future reassessment.

Indication under review: As monotherapy for the treatment of adult patients with unresectable or metastatic human epidermal growth factor receptor 2 (HER2)-positive breast cancer who have received two or more prior anti-HER2-based regimens.

In an open-label single-arm phase II study trastuzumab deruxtecan was associated with clinically relevant overall response rates in adults with unresectable or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens.

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.

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

Chairman
Scottish Medicines Consortium

Indication

As monotherapy for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens.[1]

Dosing Information

Trastuzumab deruxtecan 5.4 mg/kg given as an intravenous (IV) infusion once every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity. The initial dose should be administered as a 90-minute infusion and if well tolerated, subsequent doses may be given as 30-minute infusions. The summary of product characteristics (SPC) details dose modifications to manage adverse events.

Patients treated with trastuzumab deruxtecan should have HER2-positive tumour status as defined in the SPC. Trastuzumab deruxtecan should be prescribed by a physician and administered under the supervision of a healthcare professional experienced in the use of anticancer medicinal products. Trastuzumab deruxtecan should not be substituted with trastuzumab or trastuzumab emtansine.[1]

Product availability date

20 April 2021
Trastuzumab deruxtecan meets SMC end-of-life and orphan equivalent criteria.
Trastuzumab deruxtecan has conditional marketing authorisation from the Medicines and Healthcare Products Regulatory Agency (MHRA).

Summary of evidence on comparative efficacy

Trastuzumab deruxtecan is a HER2-targeted antibody-drug conjugate. Trastuzumab (an anti-HER2 IgG1 antibody) is attached to deruxtecan, a topoisomerase I inhibitor, by a cleavable linker. After the antibody portion binds to HER2 on the surface of certain tumour cells, the trastuzumab deruxtecan complex enters the cell and intracellular lysosomal enzymes release deruxtecan, which causes DNA damage and apoptotic cell death.[1]

The second part (part one comprised pharmacokinetics and dose-finding) of a two part phase II study (DESTINY-Breast 01) recruited adults (≥20 years in Japan and South Korea and ≥18 years in other countries) with HER2-positive unresectable or metastatic breast cancer who had disease progression on or after treatment with trastuzumab emtansine (cohort A) or had discontinued trastuzumab emtansine for reasons other than resistant or refractory disease (cohort B). Patients had at least one measurable lesion on Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 and an Eastern Co-operative Oncology Group (ECOG) performance score of 0 or 1. All patients received trastuzumab deruxtecan 5.4mg/kg IV infusion every three weeks until disease progression, unacceptable toxicity or withdrawal of consent. The primary outcome was overall response rate (ORR), defined as confirmed complete or partial response on RECIST version 1.1 assessed by an independent central review (ICR). This was assessed in all randomised patients. The

primary objective of the study was to assess ORR in the patients who had disease that was refractory or resistant to trastuzumab emtansine and received the licensed dose (5.4mg/kg) in part 1 or 2 of the study.[2,3] The primary analysis was performed after all patients had been followed for at least six months but results have not been published. Published results are available from updated analyses.[2-4]

One hundred and eighty-four patients received the licensed (5.4mg/kg) dose of trastuzumab deruxtecan, with a median follow-up of 11.1 months (range 0.7 to 19.9) and 20.5 months (range 0.7 to 31.4) at data cut-off points of August 2019 and June 2020, respectively in the updated analyses, with 43% and 20% of patients continuing on treatment. The primary outcome, ORR, was similar at both cut-off points. The European Medicines Agency (EMA) review noted a high rate of censoring in pre-specified analyses of duration of response (DOR) and considered a sensitivity analysis was more realistic, as detailed in Table 1.[2-4]

Health-related quality of life was not assessed in this study.

Table 1: Outcomes of DESTINY-Breast01 study with trastuzumab deruxtecan 5.4mg/kg.[2-4]

	August 2019 cut-off (N=184)	**June 2020 cut-off (N=184)**
Best overall response (ICR-assessed, RECIST v1.1)		
Objective response rate, % (n)	61% (112) 95% CI: 53% to 68%	61% (113) 95% CI: 54% to 69%
Complete response, % (n)	6.0% (11)	6.5% (12)
Partial response, % (n)	55% (101)	55% (101)
Stable disease, % (n)	36% (67)	36% (66)
Progressive disease, % (n)	1.6% (3)	1.6% (3)
Not evaluable, % (n)	1.1% (2)	1.1% (2)
DOR pre-specified analysis,[A] median	14.8 months	20.8 months
DOR sensitivity analysis,[B] median	13.8 months	14.6 months
Progression free survival (ICR-assessed, RECIST v1.1)		
Events	58	70
Median	16.4 months	19.4 months
Overall survival		
Deaths	25	65
Median	Not reached	24.6 months
Estimate at 12 months	86%	85%

ICR = independent central review; CI = confidence interval; DOR = duration of response.
A = DOR using independent central review (ICR)-confirmed data. Patients censored at the date of the last evaluable tumour evaluation on study treatment if progression-free; discontinued the study or start new anti-cancer therapy without death and disease progression (ICR-confirmed); or progress or die after missing ≥2 consecutive assessments.
B = DOR using ICR data with imputed events for patients without ICR-confirmed PFS event who had investigator-assessed progressive disease or treatment discontinuation for clinical progression.

Part 2 of an open-label phase I study (J101) recruited adults with HER2-postive advanced or unresectable breast cancer refractory to or with no available standard treatment who had previously received trastuzumab emtansine. At the 1 August 2019 data cut-off within the group that received the licensed dose of trastuzumab deruxtecan (5.4 mg/kg) median duration of follow-

up was 10.8 months (range: 0.8 to 36.4) and 14% of patients were continuing on study treatment. The ICR-confirmed ORR was 51% (26/51), median DOR was 10.8 months and median progression-free survival (PFS) was 13.7 months.[2,]

Eight unanchored matching adjusted indirect comparisons (MAIC) compared trastuzumab deruxtecan (individual patient level data from DESTINY-Breast 01)[2,3] with eribulin (four MAIC: Cortes 2011,[5] Cortes 2010,[6] Barni[7] and Gamucci[8]), capecitabine (three MAIC: EFG100151,[9-11] Fumoleau[12] and Blum[13]) and vinorelbine (one MAIC: Sim[14]). Analyses were conducted in adults with advanced or metastatic breast cancer who had received two or more prior therapies in the unresectable/metastatic setting for the outcomes: PFS, overall survival and response outcomes. The results suggested that trastuzumab deruxtecan was associated with improved outcomes relative to the comparators and PFS and ORR results were applied to the economic analyses.

Summary of evidence on comparative safety

In the DESTINY-Breast01 study at both the August 2019 and June 2020 data cut-offs almost all patients who received the licensed dose (5.4mg/kg) reported adverse events 99.5% (183/184), which were treated-related in 99.5% of patients. At the respective cut-offs 57% and 61% had reported adverse events of at least grade 3 severity, which were treatment-related in 48% and 53% of patients. Adverse events led to treatment discontinuation in 15% and 18% of patients. At the latest data cut off (June 2020) there were 10 patients (5.4%) who had a fatal adverse event and these were considered treatment-related in three patients (1.6%).[4]

At the August 2019 cut-off, gastrointestinal adverse events were common, including nausea (78%), vomiting (46%), constipation (36%) and diarrhoea (29%), as were haematological adverse events, including anaemia (30%) and decreases in neutrophil count (35%), white cell count (21%), lymphocyte count (14%) and platelet count (21%). Other common adverse events were fatigue (49%), alopecia (48%), headache (20%) and cough (19%).[3]

Adverse events of special interest included interstitial lung disease (ILD), which was reported by 14% and 15% of patients at the August 2019 and June 2020 cut-offs respectively. These were mainly mild to moderate, but were associated with a fatal outcome in four (2.2%) and five (2.7%) patients at the respective cut-offs. At the August 2019 cut-off, two of these deaths were considered primarily due to adverse events and two were primarily due to disease progression. The EMA review noted that the risk of treatment-related ILD is the most serious toxicity of trastuzumab deruxtecan.[2,4] Other adverse events of special interest include infusion reactions (2.2%), prolonged QT interval (4.9%) and decreased left ventricular ejection fraction (1.6%) at the August 2019 cut-off.[3]

Summary of clinical effectiveness issues

HER2-positive breast cancer is generally an aggressive disease that presents in younger patients, with locally advanced or metastatic cancers being incurable, despite improvements in treatment with anti-HER2 targeted therapies. Within the current standard of care pathways patients typically

receive a trastuzumab-containing regimen first-line (for example, trastuzumab-pertuzumab-taxane for first-line HER2-positive metastatic breast cancer or trastuzumab-pertuzumab-chemotherapy for early breast cancer at high risk of recurrence) then trastuzumab emtansine monotherapy second-line for HER2-positive, unresectable or metastatic breast cancer previously treated with trastuzumab and a taxane, separately or in combination (in patients who have either received prior therapy for locally advanced or metastatic disease, or developed disease recurrence during or within six months of completing adjuvant therapy). There is no clearly defined standard of care for patients with unresectable or metastatic HER2-positive breast cancer after two or more anti-HER2-based regimens and some of the approved regimens have moved to the setting of early breast cancer, such as trastuzumab emtansine and pertuzumab.[2]

Within NHS Scotland treatment options in this setting include capecitabine, vinorelbine or eribulin, which is given after capecitabine. Clinical experts consulted by SMC advised that capecitabine and vinorelbine are given to patients requiring third-line treatment of metastatic HER2-positive breast cancer (after a trastuzumab-containing regimen and trastuzumab emtansine monotherapy).

Clinical experts consulted by SMC considered that trastuzumab deruxtecan fills an unmet need in this therapeutic area, as it is a HER2-targeted treatment for use in third-line treatment after a trastuzumab-containing regimen and trastuzumab emtansine monotherapy. They believe that it is a therapeutic advancement due to its improved rates and duration of response compared with current chemotherapy treatments. The clinical experts noted that trastuzumab deruxtecan would be used in place of these.

Key strengths

- Trastuzumab deruxtecan is an antibody-drug conjugate, and the first to combine an anti-HER2 antibody (trastuzumab) with a topoisomerase inhibitor licensed in the UK. It is a HER2-targeted therapy licensed for use in HER2-positive unresectable or metastatic breast cancer after two lines of HER2-targeted therapy, including trastuzumab emtansine.[1] In this indication, it meets SMC end-of-life and orphan equivalent criteria.

- In the phase II DESTINY-Breast 01 study trastuzumab deruxtecan produced substantial responses (ORR about 60%) which were durable (median DOR 14.6 months [as per sensitivity analysis]) in adults with HER2-postive unresectable and/or metastatic breast cancer who had received treatment with at least 2 lines of HER2-targeted therapy (including trastuzumab and trastuzumab emtansine). At the latest data cut-off (June 2020) when 38% of patients had a PFS event and 35% of patients had died, estimates of median PFS and overall survival were 19.4 months and 24.6 months, respectively. The study in ongoing and these estimates may change as data become more mature.[2-4]

- Subgroup analysis suggest that trastuzumab deruxtecan is effective across important subgroups regardless of presence of negative prognostic factors such as old age, ECOG performance status of 1, visceral disease, hormone receptor-negative status. Also, ORR greater than 60% were seen in the subgroup of patients given trastuzumab emtansine just before entering the study, including those who did not respond to it .[2]

Key uncertainties

- The only evidence is from an open-label uncontrolled single arm study and there is a lack of long-term efficacy and safety data, in particular DOR, PFS and overall survival data are immature.[2-4] The lack of comparative data creates challenges in estimating the magnitude of any benefit in practice.
- There are no comparative data relative to the current treatment options. MAIC of trastuzumab deruxtecan versus capecitabine, vinorelbine and eribulin had limitations including heterogeneity in baseline characteristics (including HER2 status), study design, methods of assessing response and maturity of data. It was not possible to match for all identified treatment effect modifiers and prognostic indicators and there may be unknown effect modifiers. In some comparisons the effective sample size was reduced substantially by matching. Other statistical limitations were identified, including issues with data quality, the matching process and extrapolation of immature data.
- The DESTINY-Breast01 study population was heavily pre-treated, with 91% of patients having at least three regimens for locally advanced or metastatic breast cancer excluding hormone therapy and a median six prior lines (range 2 to 24).[2,3] In practice if trastuzumab deruxtecan were used for unresectable or metastatic breast cancer after trastuzumab and trastuzumab emtansine, it is possible that patients may have received only two prior lines of therapy. In the DESTINY-Breast01 study 17 patients (9% of the study population) had received only two prior lines of therapy and it is not possible to draw conclusions from this subgroup analysis, but it is reassuring to note that in this subgroup the ORR was 76% (95% CI: 50% to 93%).[3]
- In the DESTINY-Breast01 study 66% of patients had previously received pertuzumab, but only 28% received this as first or second line in the metastatic setting.[3] Within current practice it is likely that most patients eligible for trastuzumab deruxtecan would have received pertuzumab and it is reassuring that subgroup analysis found an ORR in patients (n=121) previously treated with pertuzumab of 64% (95% CI: 55% to 73%).[2,3]

Conditional marketing authorisation specific obligations

To confirm efficacy and safety the company has a specific obligation to submit interim results of an open-label phase III study (DESTINY-Breast02) comparing trastuzumab deruxtecan with investigator's choice of therapy for HER2-positve unresectable or metastatic breast cancer previously treated with standard HER2 therapies including trastuzumab emtansine. The company are also required to submit final study results from DESTINY-Breast01.[2] The specific obligations may address some of the key uncertainties in the clinical evidence presented.

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 trastuzumab deruxtecan, as an orphan equivalent and 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 with a poor prognosis and limited effective treatment options for patients with HER2-positive disease who have already received at least two lines of HER2-targeted therapy. There is an unmet need for therapies that control disease progression, extend life and have an acceptable tolerability.
- Trastuzumab deruxtecan produces unprecedented response rates and may offer survival improvements for patients with HER2-positive metastatic breast cancer that has progressed after at least two lines of therapy. No similar response rates or PFS results in this setting have been seen previously in solid tumour oncology.
- The data show that trastuzumab deruxtecan could lead to a prolonged period when the patient's disease is controlled and they are well and able to participate in family and social activities.
- Accessing trastuzumab deruxtecan, which patients regard as highly effective, may provide reassurance to patients that they are receiving the optimum treatment for their condition. This can have psychological benefits. Some patients may derive hope that any prolonged progression-free and overall survival may provide a bridge to a time when other new medicines become available.
- Trastuzumab deruxtecan is associated with increased risk of interstitial lung disease. The incidence of this has reduced with increasing patient and physician education and there is clinical experience in managing this adverse event. PACE participants noted that some patients may be happy to risk this for the opportunity of substantial clinical benefits with trastuzumab deruxtecan.

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 Now 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 trastuzumab deruxtecan for use in adult patients with unresectable or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens. The comparators included in the analysis were treatments approved for third-line use in advanced breast cancer irrespective of HER2 status (eribulin, capecitabine, and vinorelbine).

A *de novo* economic model was created in the form of a partitioned survival model with four distinct health states: progression-free (on treatment), progression-free (off treatment), progressed disease, and dead. A 1-week cycle length was used with a lifetime time horizon (40 years) and an NHSScotland and social work perspective was utilised.

The relative efficacy of trastuzumab deruxtecan versus comparator medicines was estimated from a combination of data sources given the single arm design of the DESTINY-Breast01 study[3]; a phase 3 open-label randomised study of eribulin monotherapy versus treatment of physician's choice[5] and a phase 3 randomised study comparing capecitabine monotherapy to lapatinib with capecitabine[11] were used in to inform progression free survival and overall survival for eribulin and capecitabine. Given limitations associated with the only study available to inform the relative efficacy of vinorelbine, the company assumed equivalent efficacy to capecitabine. A series of different probability distributions were explored to extrapolate beyond study follow-up with base case distributions selected using a combination of clinical expert opinion and goodness-of-fit statistics. However, the process used for overall survival versus progression free survival was inconsistent; overall survival was estimated by extrapolating survival data for each medicine directly whereas progression free survival was estimated via the application of treatment specific hazard ratios. Time to discontinuation was estimated via an analogous process for trastuzumab deruxtecan, however, no data was available to inform discontinuation for comparators and therefore treatment until progression was assumed.

Health-related quality-of-life (HRQoL) data was not collected as part of the DESTINY-Breast01 study therefore health state utility values used in a prior NICE submission for eribulin in metastatic breast cancer were used with adjustments for clinical data from the key direct evidence for trastuzumab deruxtecan (progressed disease: 0.558; progression free: 0.713 - 0.751). This submission used a published regression-based algorithm to map EORTC QLQ-C30 data to EQ-5D scores prior to applying the original UK EQ-5D tariff. These utility values were subsequently adjusted for declining HRQoL with age via the application utility multipliers estimated using general population data. Adverse event disutilities were also included.

Medicine acquisition, administration, and wastage costs were estimated for all medicines. The cost of disease management, palliative care and end of life costs were included and were sourced from

previously published health technology assessments. Resource use associated with adverse events were also included in the evaluation.

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 discount was offered on the list price. A comparator PAS discount is also in place for eribulin.

The main economic results are shown in Table 2; these imply that over a lifetime time horizon trastuzumab deruxtecan is associated with increased total costs relative to all comparators but also increased quality-adjusted life-years (QALYs).

The results presented do not take account of the PAS for eribulin or for trastuzumab deruxtecan 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.

Table 2: Main economic results (all list price)

Comparator	ICER (£/QALY)
Eribulin	£53,213
Capecitabine	£67,128
Vinorelbine	£63,306

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years

A selection of key scenario analyses are presented in Table 3 indicate that the cost-effectiveness of trastuzumab deruxtecan is sensitive to assumptions around vial sharing and the distributions used to extrapolate progression free survival and overall survival.

Table 3: Scenario analyses (list price)

Scenario	Description		ICER		
			Eribulin	Capecitabine	Vinorelbine
0	Base case		£53,213	£67,128	£63,306
1	Utility values from Le et al		£56,990	£71,016	£66,852
2	No vial sharing		£56,156	£71,176	£67,340
3	OS extrapolation: trastuzumab deruxtecan	Weibull	£75,000	£104,418	£98,467
4		Exponential	£50,808	£63,326	£59,760
5		Log-normal	£48,561	£59,810	£56,492
6		Log-logistic (base case)	£53,213	£67,128	£63,306
		Generalised gamma	£47,267	£57,820	£54,643
7		Gompertz	£96,052	£148,132	£140,150

8	PFS extrapolation: trastuzumab deruxtecan	Weibull	£57,629	£72,768	£68,860
9		Exponential	£56,063	£69,375	£66,081
10		Generalised gamma	£48,202	£60,413	£56,843
11		Log-logisitic	£53,074	£66,660	£62,957
12		Gompertz	£56,969	£70,701	£67,324

Abbreviations: ICER, incremental cost-effectiveness ratio;

The following limitations are noted regarding the economic evaluation:

- Given the single arm design of the study, there is no direct evidence comparing trastuzumab deruxtecan to comparators that can be used to inform relative efficacy across treatments. This creates significant uncertainty regarding the magnitude of any treatment benefit relative to comparators.
- Progression free survival and overall survival data from the DESTINY-Breast01 study are immature which increases the uncertainty associated with survival analyses required to conduct the economic evaluation.
- Furthermore, the approach to survival analysis for overall and progression free survival was inconsistent and contradicts advice given to the company by clinical experts further raising concerns about its reliability for use in the economic evaluation.

The Committee considered the benefits of trastuzumab deruxtecan in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that as trastuzumab deruxtecan 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, trastuzumab deruxtecan was accepted for use in NHSScotland subject to ongoing evaluation and future reassessment.

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. At third-line or

beyond, neritinib-capecitabine is not recommended as it had marginal benefit over lapatinib-capecitabine, which had previously been observed to be inferior to trastuzumab-capecitabine. Trastuzumab deruxtecan and the regimen of tucatinib-trastuzumab-capecitabine 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.[15]

The National Institute of Health and Care Excellence (NICE) clinical guideline number 81: Advanced breast cancer: diagnosis and treatment was updated in August 2017. This contains one recommendation in relation to HER2-targeted therapy, which was included at the time of initial publication in 2009. That is patients who are receiving treatment with trastuzumab for advanced breast cancer, should discontinue treatment with trastuzumab at the time of disease progression outside the central nervous system. Do not discontinue trastuzumab if disease progression is within the central nervous system alone.[16]

Additional information: comparators

In practice trastuzumab deruxtecan may be used in place of capecitabine, vinorelbine or eribulin.

Additional information: list price of medicine under review

Medicine	Dose Regimen	Cost per year (£)
Trastuzumab deruxtecan	5.4mg/kg intravenously every 21 days	£100,880

Costs from BNF online on 30 June 2021. Costs calculated using the full cost of vials/ampoules assuming wastage. Costs do not take patient access schemes into consideration. Costs based on body weight of 70kg.

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 17 September 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.