SMC Scottish Medicines Consortium
Advising on new medicines for Scotland
www.scottishmedicines.org.uk
NHS SCOTLAND
Delta House • 50 West Nile Street • Glasgow • G1 2NP • Tel 0141 225 6999 • Chairman: Dr Alan G MacDonald

bictegravir 50mg / emtricitabine 200mg / tenofovir alafenamide 25mg film-coated tablet (Biktarvy®) SMC2093

Gilead Sciences Ltd

10 August 2018

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 NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

bictegravir / emtricitabine / tenofovir alafenamide (Biktarvy®) is accepted for use within NHSScotland.

Indication under review: Treatment of adults infected with human immunodeficiency virus 1 (HIV-1) without present or past evidence of viral resistance to the integrase inhibitor class, emtricitabine or tenofovir.

Bictegravir / emtricitabine / tenofovir alafenamide was non-inferior for control of HIV-1 infection compared with anti-retroviral regimens comprising an integrase inhibitor plus backbone of dual nucleos(t)ide reverse transcriptase inhibitors (NRTIs) in treatment-naïve adults. Bictegravir / emtricitabine / tenofovir alafenamide was non-inferior to anti-retroviral regimens containing a dual NRTI backbone plus an integrase inhibitor or a protease inhibitor in maintaining virological suppression in virologically suppressed adults.

This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of bictegravir / emtricitabine / tenofovir alafenamide. This advice is contingent upon the continuing availability of the PAS in NHSScotland or a list price that is equivalent or lower.

Chairman
Scottish Medicines Consortium

Published 10 September 2018

Indication

Treatment of adults infected with human immunodeficiency virus 1 (HIV-1) without present or past evidence of viral resistance to the integrase inhibitor class, emtricitabine or tenofovir.[1]

Dosing Information

One tablet swallowed whole once daily.

Therapy should be initiated by a physician experienced in the management of HIV infection.[1]

Product availability date

July 2018

Summary of evidence on comparative efficacy

Biktarvy® is a fixed-dose formulation of a new integrase inhibitor, bictegravir, plus two nucleos(t)ide reverse transcriptase inhibitors (NRTIs), emtricitabine and tenofovir alafenamide fumarate (AF). It is licensed for treatment of HIV-1 infection in adults.[1]

Two similar double-blind studies (GS-US-380-1489 and GS-US-380-1490) recruited treatment-naïve adults with HIV-1 infection and HIV-1 ribonucleic acid (RNA) greater than 500 copies/mL. Randomisation was stratified by HIV RNA level (≤100,000 or >100,000 to ≤400,000 or >400,000 copies per mL), CD4+ cell count (<50 or 50 to 199 or ≥200 cells/microlitre) and region (US or non-US). Patients were equally randomised to 144 weeks' treatment with fixed-dose combinations of bictegravir 50mg, emtricitabine 200mg and tenofovir AF 25mg or to regimens containing the integrase inhibitor, dolutegravir 50mg plus a dual NRTI backbone, which was abacavir 600mg and lamivudine 300mg in study 1489, and emtricitabine 200mg and tenofovir AF 25mg in study 1490. In both studies the primary outcome was proportion of patients with HIV-1 RNA less than 50 copies/mL at week 48 (as defined by US Food and Drug Administration [FDA] snapshot algorithm) and the primary analysis was non-inferiority at a pre-specified margin of 12%. This was assessed in the full analysis set, which comprised all randomised patients who received at least one dose of study drug. In both studies bictegravir-containing regimens were non-inferior to dolutegravir-containing regimens, with results of the primary outcome detailed in table 1.[2-4]

Two phase III studies, one double-blind (study GS-US-380-1844) and one open-label (study GS-US-380-1878) recruited adults with HIV-1 infection who were virologically suppressed, defined as HIV-1 RNA less than 50 copies/mL, on anti-retroviral therapy (ART) consisting of dolutegravir plus abacavir and lamivudine in study 1844 and ritonavir- or cobicistat-boosted atazanavir or darunavir plus either emtricitabine and tenofovir disoproxil fumarate (DF) or abacavir and lamivudine in study 1878. In both studies patients were randomised equally to remain on their baseline ART or switch to bictegravir 50mg, emtricitabine 200mg and tenofovir AF 25mg fixed-dose preparation orally once daily. Randomisation was stratified by use of tenofovir DF at baseline (yes versus no) only in study 1878. The primary outcome was the proportion of patients with HIV-1 RNA at least 50 copies/mL at week 48 and the primary analysis was non-inferiority at a margin of 4%. This was assessed in the full analysis set, which comprised all randomised patients who received at least

one dose of study drug. In both studies bictegravir-containing regimens were non-inferior to comparator regimens, with results of the primary outcome detailed in table 1.[2]

Table 1: Primary and secondary outcome of studies 1489, 1490, 1844 and 1878.[2-4]

	Study 1489		**Study 1490**		**Study 1844**		**Study 1878**	
	BIC	**DOL**	**BIC**	**DOL**	**BIC**	**DOL**	**BIC**	**ART**
	N=314	**N=315**	**N=320**	**N=325**	**N=282**	**N=281**	**N=290**	**N=287**
HIV-1 RNA at week 48 (copies/mL) in full analysis set								
<50, n (%)	290 (92)	293 (93)	286 (89)	302 (93)	264 (94)	267 (95)	267 (92)	255 (89)
Diff (95CI)	**-0.6% (-4.8 to 3.6)***		**-3.5% (-7.9 to 1.0)***		-1.4% (-5.5 to 2.6)		3.2% (-1.6 to 8.2)	
≥50, n (%)	3 (1.0)	8 (2.5)	14 (4.4)	4 (1.2)	3 (1.1)	1 (0.4)	5 (1.7)	5 (1.7)
Diff (95CI)					**0.7% (-1.0 to 2.8)***		**0.0% (-2.5 to 2.5)***	
No data	21 (6.7)	14 (4.4)	20 (6.3)	19 (5.8)	15 (3.3)	13 (4.6)	18 (6.2)	27 (9.4)
CD4+ mean change from baseline to week 48 (cells/microlitre) in completer analysis								
	N=290	N=299	N=287	N=301	N=265	N=267	N=265	N=256
LSM	233	229	180	201	-31	4	25	0
Diff (95CI)	4 (-27 to 34)		-22 (-49 to 5)		-35 (-67 to -3)		25 (-2 to 52)	

BIC = fixed-dose combinations of bictegravir 50mg, emtricitabine 200mg and tenofovir alafenamide 25mg
DOL = regimen containing dolutegravir 50mg and dual nucleos(t)ide reverse transcriptase inhibitor (NRTI) backbone, which was abacavir 600mg and lamivudine 300mg in studies 1489 and 1844; and, in study 1490, was emtricitabine 200mg and tenofovir alafenamide 25mg.
ART = anti-retroviral therapy comprising ritonavir- or cobicistat-boosted atazanavir or darunavir plus emtricitabine-tenofovir disoproxil fumarate or abacavir-lamivudine.
Diff (95CI) = difference (95% confidence interval); LSM = least square mean; * primary outcome

There were no significant differences between treatment groups for the secondary outcome, mean change from baseline in CD4+ cell count, except in study 1844, which had a significant difference between the groups in baseline CD4+ cell count.[2]

Resistance analysis performed across the four phase III studies indicated that no patients who had virologic failure during the first year of treatment with bictegravir-emtricitabine-tenofovir AF or dolutegravir-based therapy developed treatment-emergent resistance to study drugs, with one patient who had ritonavir-boosted darunavir, abacavir plus lamivudine in study 1878 developing genotypic resistance to abacavir.[2]

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

Summary of evidence on comparative safety

The FDA review concluded that bictegravir has a generally comparable safety profile to other integrase inhibitors.[2]

Common adverse events in the treatment-naïve phase III studies (1489 and 1490) within the combined bictegravir group, dolutegravir-abacavir-lamivudine and dolutegravir - emtricitabine-tenofovir AF groups were diarrhoea (12%, 13% and 12%) headache (12%, 14% and 12%), nausea (9%, 23% and 9%), nasopharyngitis (7%, 9% and 10%), fatigue (6%, 9% and 8%) and upper respiratory tract infection (6%, 11% and 7%). Overall, treatment-related adverse events in the bictegravir group were similar to comparator groups, with the notable difference of higher rates of nausea in the dolutegravir-emtricitabine-tenofovir AF group (18% versus 3% to 5%). The FDA review noted that the rate of nausea in study 1489 with this medicine was higher than the reported rate in its registrational study (<1%). Overall the adverse events reported in virologically-suppressed treatment groups (studies 1844 and 1879) were generally similar to the treatment-naïve population, although adverse events were less frequently reported in general across all treatment groups in virologically-suppressed population.[2]

Serious adverse events were reported by similar proportions of patients across all treatment groups in the phase III studies, with rates in studies 1489 and 1490 of 9.2% in the combined bictegravir group, 7.9% with dolutegravir-abacavir-lamivudine and 7.1% with dolutegravir-emtricitabine-tenofovir AF. In study 1844 the rate was 5.3% in the bictegravir group and 7.8% with dolutegravir-lamivudine-abacavir and in study 1878 it was 6.5% in the bictegravir group and 7.7% in the comparator group. The most frequently reported class of serious adverse events was infections and infestations, reported by 3% to 4% of patients across all treatment groups. Discontinuations due to adverse events were low across the phase III studies, only 1% to 2% of patients in any treatment group.[2]

Summary of clinical effectiveness issues

Biktarvy® is a fixed-dose formulation of the fourth integrase inhibitor to be marketed in the UK, bictegravir, plus a backbone of the NRTIs, emtricitabine and tenofovir AF.[1] There is currently another fixed-dose formulation of an integrase inhibitor, elvitegravir (boosted by cobicistat) plus the NRTI backbone, emtricitabine and tenofovir AF (Genvoya®)[6] and another similar fixed-dose formulation containing the same medicines, except for tenofovir AF, which is replaced by tenofovir DF (Stribild®)[7]. Bictegravir-emtricitabine-tenofovir AF (Biktarvy®) is the first unboosted integrase inhibitor in combination with the emtricitabine-tenofovir AF backbone. A fixed-dose formulation of the integrase inhibitor, dolutegravir, plus a different NRTI backbone, abacavir and lamivudine (Triumeq®)[8] is also available. The other marketed integrase inhibitor, raltegravir (Isentress®)[9] is not formulated with NRTIs in a fixed-dose preparation. SMC has accepted these for use within NHSScotland with advice number 1142/ 16 for Genvoya®, number 887/13 for Stribild® and number 1009/ 14 for Triumeq®. SMC has accepted with restriction raltegravir, with advice number 613/10, which restricts it to patients intolerant or resistant to NNRTIs or protease inhibitors and number 461/08, which restricts it in ART-experienced patients to those with triple class resistant HIV.

The current British HIV Association (BHIVA) guideline for the treatment of HIV-1-positive adults with ART recommends that treatment-naïve people infected with HIV-1 should receive ART

containing dual NRTI backbone e.g. emtricitabine plus tenofovir DF or AF (preferred) or abacavir plus lamivudine (alternative) in combination with one of the following third agents: a ritonavir-boosted protease inhibitor, e.g. atazanavir or darunavir; a non-nucleoside reverse transcriptase inhibitor (NNRTI), e.g. rilpivirine or efavirenz; or an integrase inhibitor, dolutegravir, elvitegravir or raltegravir. Except for efavirenz (which is an alternative) all of these are preferred third agents as detailed below in additional information: guidelines and protocols.[10] The guideline makes no recommendation about switching ART in virologically suppressed patients.

Bictegravir-emtricitabine-tenofovir AF was non-inferior in treatment-naïve adults compared with ART containing the integrase inhibitor, dolutegravir, plus a dual NRTI backbone of emtricitabine-tenofovir AF in study 1490 and lamivudine-abacavir in study 1489. It was also non-inferior in virologically-supressed adults compared with ART containing an integrase inhibitor, dolutegravir, plus dual NRTI (abacavir-lamivudine) in study 1844 and a ritonavir- or cobicistat-boosted protease inhibitor (atazanavir or darunavir) plus NRTI backbone (emtricitabine-tenofovir DF or abacavir-lamivudine) in study 1878. All comparators are appropriate, however, the comparisons with regimens containing an integrase inhibitor may be the most relevant to clinical practice where a decision has been made to use this class of drug as the third agent.

The evidence base is limited by the open-label design of study 1878, which may affect reporting of subjective outcomes, such as adverse events, and patient disposition. The studies were too short to assess incidence of rare HIV-related clinical events, including acquired immune deficiency syndrome (AIDS)-defining conditions. The evidence base in patients co-infected with chronic hepatitis B or C virus is limited as very small numbers of patients, less than 5%, were included in the phase III studies, with studies 1489 and 1844 excluding completely patients co-infected with hepatitis B virus. The majority of patients recruited to the phase III studies were male and many were from the USA. However, subgroup analysis suggest that these criteria do not impact treatment effect.

Direct comparative data were available for one of the integrase inhibitor-containing fixed-dose regimens used in practice, as dolutegravir-abacavir-lamivudine (Triumeq®) was the comparator in studies 1489 and 1844. There were also direct comparative data, from study 1490, versus dolutegravir plus dual NRTI, emtricitabine-tenofovir AF (Descovy®). However, there were no direct comparative data relative to two fixed-dose formulations of the integrase inhibitor, elvitegravir (boosted by cobicistat) plus emtricitabine and tenofovir AF (Genvoya®) or tenofovir DF (Stribild®). Therefore an indirect comparison was performed using a Bayesian network meta-analysis (NMA).

The NMA compared bictegravir-emtricitabine-tenofovir AF (Biktarvy®) with a number of ART regimens using data from 21 studies in treatment-naïve adults with HIV-1 infection. Presentation of results focused on dolutegravir-lamivudine-abacavir (Triumeq®) and elvitegravir-cobicistat-emtricitabine-tenofovir AF (Genvoya®) and suggested no difference compared with bictegravir-emtricitabine-tenofovir AF (Biktarvy®) for the following week-48 outcomes: virological response (HIV-1 RNA <50 copies/mL), change from baseline in CD4 cell count, all-cause discontinuations and discontinuations due to adverse events. Limitations included the large and complex nature of the network and heterogeneity across the studies in design and patient populations. Also the NMA included only studies in treatment-naïve patients, which may limit application of results to virologically-suppressed patients. However, it does provide evidence to support the suggestion of equivalence.

Clinical experts consulted by SMC noted that bictegravir-emtricitabine-tenofovir AF (Biktarvy®) may replace some currently used ART regimens, especially fixed-dose formulations. They highlighted that it is the first fixed-dose formulation of an unboosted integrase inhibitor in

combination with the NRTI backbone emtricitabine-tenofovir AF and the absence of a boosting drug may confer advantages in terms of drug interactions. It was also noted that bictegravir-emtricitabine-tenofovir AF (Biktarvy®) can be given to patients with moderate renal impairment (i.e. creatinine clearance at least 30ml/minute), which may be an advantage relative to fixed-dose formulations that cannot be used in patients with renal impairment, e.g. those containing tenofovir DF.

Summary of comparative health economic evidence

The submitting company presented a cost-minimisation analysis (CMA) comparing Biktarvy® to Genvoya® and Triumeq® in the licensed indication. The choice of these two comparator treatments was on the basis of clinical expert opinion and market usage data suggesting these were the main comparator treatments, however, the company also provided a scenario analysis versus a blended comparator based on a weighted average across a wide range of treatment options. The time horizon for the analysis was one year.

Clinical data to support the CMA were taken from studies GS-US-380-1489 (treatment-naïve patients) and GS-US-380-1844 (treatment-experienced patients), both of which compared Biktarvy® to Triumeq®. For the comparison versus Genvoya®, there were no head-to-head studies and thus the NMA described above was used to provide evidence of similarity of outcomes between treatments.

Costs in the analysis related to medicines acquisition costs only, on the basis of treatments having similar administration and adverse event profiles.

A patient access scheme (PAS) was submitted by the company and was assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. PAS discounts are in place for Genvoya® and Triumeq® and these were included in the results used for decision-making by the SMC) by using estimates of the comparator PAS prices. The base case results and scenario analyses are presented in the tables below.

Table 2: Cost- minimisation results versus Genvoya® and Triumeq®

Comparator	Incremental cost versus Biktarvy® per annum using list prices for all medicines*
Genvoya®	£0
Triumeq®	£990

* A negative sign indicates Biktarvy® is cost-saving against the comparator.

For the scenario analysis using the blended comparator, the results are shown below:

Table 3: Cost- minimisation results versus blended comparator

Comparator	Incremental cost versus Biktarvy® per annum using list prices for all medicines*
Blended comparator	£3,654
Blended comparator but using generic pricing for FTC/TDF	£3,981

*A negative sign indicates Biktarvy® is cost-saving against the comparator.

The results presented do not take account of the PAS for Genvoya® and Triumeq® or the PAS for Biktarvy® but these were considered in the results used for decision-making at SMC. SMC is unable to present the results provided by the company which used an estimate of the PAS price for Genvoya® and Triumeq® due to commercial confidentiality and competition law issues.

Given the simplicity of the analysis, no sensitivity analysis was provided. While there were some limitations of the evidence base as noted in the clinical effectiveness section above, the economic case was considered demonstrated.

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

Summary of patient and carer involvement

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

- We received patient group submissions from Waverley Care and HIV Scotland, both are registered charities.

- In the last two years, Waverley Care has received 2% of its funding, and HIV Scotland 3.5% of its funding from the pharmaceutical industry, both including from the submitting company.

- HIV is a condition that dramatically changes people's lives due to high levels of stigma, discrimination and shame, which have implications for relationships and family life. It is this stigma and discrimination that can weaken people's resolve to test, start and stay on treatment, which impacts on their ability to keep themselves and their family or partner healthy.

- There are currently a range of effective HIV medications available to patients in Scotland, however some regimens consist of multiple tablets taken multiple times a day which can impact on a person's adherence. Some tablets are also quite large and difficult to swallow. Concerns about adverse effects can also raise anxieties about taking medications longer term.

- Simplification of treatment regimens to make them simple and easy to adhere to will help to ensure the best possible health outcomes for patients. As an effective small unobtrusive tablet taken once daily that is easy to swallow, Biktarvy® would be welcomed and may assist people to start and stay on treatment and achieve sustained viral suppression. Access to new treatments is important to ensure patients have a range of options to maintain viral suppression whilst reducing side effects to help them live longer and healthier lives.

Additional information: guidelines and protocols

In 2016 the BHIVA published an interim update of their guideline for the treatment of HIV-1-positive adults with ART. This recommends that treatment-naïve people infected with HIV-1 should receive ART with dual NRTIs plus one of the following: ritonavir-boosted protease inhibitor (atazanavir or darunavir), an integrase inhibitor (dolutegravir, elvitegravir or raltegravir) or NNRTI (rilpivirine or efavirenz) as detailed in the table 4 below.[10] The guideline makes no recommendations on switching treatment in virologically supressed patients.

Table 4: Summary of BHIVA recommendations for treatment-naïve patients with HIV-1[2]

	Preferred	Alternative
NRTI backbone	Emtricitabine and tenofovir disoproxil fumarate	Abacavir and lamivudine[B]
	Emtricitabine and tenofovir alafenamide	
Third agent (alphabetical order)	Atazanavir	Efavirenz
	Darunavir	
	Dolutegravir	
	Elvitegravir plus cobicistat[A]	
	Raltegravir	
	Rilpivirine[C]	

A = tenofovir-DF-emtricitabine-elvitegravir-cobicistat [Stribild®] fixed-dose combination should not be initiated in individuals with creatinine clearance (CrCl) <70 mL/min; tenofovir-AF-emtricitabine-elvitegravir-cobicistat [Genvoya®] fixed-dose combination should not be initiated in patients with estimated CrCl <30 mL/min.
B = Abacavir is contraindicated if an individual is HLA-B*57:01 positive. Use recommended only if baseline viral load less than 100,000 copies/mL except when initiated in combination with dolutegravir in which case abacavir-lamivudine can be used at any baseline viral load
C = Use recommended only if baseline viral load less than 100,000 copies/mL
NRTI = nucleos(t)ide reverse transcriptase inhibitor

Additional information: comparators

Currently used ART regimens, with those containing an integrase inhibitor relevant to practice where a decision has been made to use an integrase inhibitor as the third agent.

Cost of relevant comparators

Medicine	Dose Regimen	Cost per year (£)
Bictegravir, emtricitabine, tenofovir AF (Biktarvy®)	**One tablet once daily**	**10,671**
Elvitegravir, cobicistat, emtricitabine, tenofovir AF (Genvoya®)	One tablet once daily	10,671
Elvitegravir, cobicistat, emtricitabine, tenofovir DF (Stribild®)	One tablet once daily	10,671
Dolutegravir (Tivicay®) Emtricitabine, tenofovir AF 200mg/25mg (Descovy®)	One tablet once daily One tablet once daily	10,368
Dolutegravir (Tivicay®)	One tablet once daily	10,368

Emtricitabine, tenofovir DF 200mg/245mg (generic)	One tablet once daily	
Raltegravir (Isentress®) Emtricitabine, tenofovir AF (Descovy®)	400mg twice daily or 2x600mg once daily One tablet once daily	10,036
Raltegravir (Isentress®) Emtricitabine, tenofovir DF (generic)	400mg twice daily or 2x600mg once daily One tablet once daily	10,036
Dolutegravir, lamivudine, abacavir (Triumeq®)	One tablet once daily	9,684
Raltegravir (Isentress®) Lamivudine, abacavir (generic)	400mg twice daily or 2x600mg once daily One tablet once daily	9,171

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 3 May 2018. Costs do not take any patient access schemes into consideration.

Additional information: budget impact

The submitting company estimated there would be 5,239 patients would be eligible in year 1 rising to 6,327 in year 5 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.

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

References

1. Gilead Sciences Ltd. Summary of product characteristics for Biktarvy.
2. US Food and Drug Administration. Review of Biktarvy.
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4. Sax PE, Pozniak A, Montes ML, et al. Coformulated bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir with emtricitabine and tenofovir alafenamide, for initial treatment of HIV-1 infection (GS-US-380-1490): a randomised, double-blind, multicentre, phase 3, non-inferiority trial. Lancet 2017; 390: 2073–82.
5. *Commercial in Confidence**
6. Gilead Sciences Ltd. Summary of product characteristics for Genvoya®, last updated 26 April 2018.
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8. ViiV Healthcare Ltd. Summary of product characteristics for Triumeq®, last updated 20 March 2018.
9. Merck Sharpe and Dohme Ltd. Summary of product characteristics for Isentress®, last updated 12 April 2018.
10. British HIV Association. British HIV Association guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy 2015 (2016 interim update), August 2016.

This assessment is based on data submitted by the applicant company up to and including 15 July 2018.

**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 NHS Scotland 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 NHS Scotland 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.