MANAGEMENT IN CONFIDENCE

CLINICAL PRIORITIES ADVISORY GROUP
29 05 2019 and 30 05 2019

Agenda Item No	02.1
National Programme	Blood and Infection
Clinical Reference Group	HIV
URN	1702

Title
Bictegravir-emtricitabine-tenofovir alafenamide for the treatment of HIV-1 in adults

Actions Requested	1. Agree the policy proposition.
	2. Recommend its approval as an IYSD.

Proposition
For Routine commissioning. Bictegravir-emtricitabine-tenofovir alafenamide (B/F/TAF) contains bictegravir which is a new treatment for HIV-1. Bictegravir is combined with two nucleos(t)ide reverse transcriptase inhibitors (NRTIs), emtricitabine and tenofovir alafenamide,. The evidence looked at how safe and effective B/F/TAF is compared to other triple drug combinations. The evidence review showed that B/F/TAF is as effective as the two treatments it was compared against. The evidence review also looked at how safe and effective B/F/TAF is when switching from boosted protease inhibitor-based 3-drug regimens. The evidence showed the B/F/TAF is comparable to the treatments people were switched from in terms of maintaining HIV control and other important outcomes.

Clinical Panel recommendation
The Clinical Panel recommended that the policy progress as a routine commissioning policy.

The committee is asked to receive the following assurance:	
1.	The Head of Clinical Effectiveness confirms the proposal has completed the appropriate sequence of governance steps and includes an: Evidence Review; Clinical Panel Report.
2.	The Head of Acute Programmes / Head of Mental Health Programme confirms the proposal is supported by an: Impact Assessment; Stakeholder Engagement Report; Consultation Report; Equality Impact and Assessment

	Report; Clinical Policy Proposition. The relevant National Programme of Care Board has approved these reports.
3.	The Director of Finance (Specialised Commissioning) confirms that the impact assessment has reasonably estimated a) the incremental cost and b) the budget impact of the proposal.
4.	The Operational Delivery Director (Specialised Commissioning) confirms that the service and operational impacts have been completed.

The following documents are included (others available on request):	
1.	Clinical Policy Proposition
2.	Consultation Report
3.	Evidence Summary
4.	Clinical Panel Report
5.	Equality Impact and Assessment Report

No	*Metric*	*Summary from evidence review*
1.	Survival	
2.	Progression free survival	
3.	Mobility	
4.	Self-care	
5.	Usual activities	
6.	Pain	
7.	Anxiety / Depression	In Wohl et al. statistically significant differences in favour of B/F/TAF were found at 2 or more time points in the adjusted logistic regression model, as well as in the longitudinal models in the HIV symptom index domains for “sad/down/depressed” and “nervous/anxious” in treatment-experienced patients who had switched from dolutegravir, abacavir and lamivudine to B/F/TAF. See HIV Symptom Index outcome reported below.
8.	Replacement of more toxic treatment	
9.	Dependency on care giver / supporting independence	
10.	Safety	Drug-related adverse events

		Overall, the results suggest that B/F/TAF has a similar safety and tolerability profile to DTG/ABC/3TC, dolutegravir, emtricitabine and tenofovir alafenamide (DTG/F/TAF) and boosted protease inhibitor-based regimen (a therapy containing an additional drug which improves the ability of the medicine to kill the virus). Across all the studies included, fewer adverse events were reported in the bictegravir-emtricitabine-tenofovir alafenamide (B/F/TAF) group than in the comparator groups. In Gallant et al (2017), fewer drug-related adverse events were reported by the B/F/TAF group (26%) than in the dolutegravir, abacavir and lamivudine (DTG/ABC/3TC) group (40%). However, this was driven mainly by drug-related nausea which was 5% (n=17) in the B/F/TAF group and 17% (n=55) in the DTG/ABC/3TC group (p<0·0001). Across all studies included, people did not appear to discontinue their treatment with B/F/TAF due to adverse reactions which was similar to the discontinuation rates seen in the comparator groups.
11.	Delivery of intervention	

No	*Metric*	*Summary from evidence review*
1.	Proportion of patients with HIV-1 RNA less than 50 copies per ml of plasma	This outcome is a measurement of how effective the treatment has been in reducing the number of HIV-1 RNA copies per ml (viral load) in the patient's blood plasma. Suppression of plasma HIV-1 RNA viral load to less than 50 copies per ml is the main goal of ART treatment as it is associated with durable clinical and immunological benefits. When the HIV virus is slowed down, so is HIV disease. Overall, the evidence suggests that receiving bictegravir-emtricitabine-tenofovir alafenamide (B/F/TAF) is comparable to dolutegravir, abacavir and lamivudine (DTG/ABC/3TC), dolutegravir, emtricitabine and tenofovir alafenamide (DTG/F/TAF) or boosted protease inhibitor-based regimens in maintaining the level of detectable HIV-1 RNA in blood plasma (viral load) below 50 copies per ml at 48 weeks follow up or post treatment switching. In Gallant et al. (2017) there was no statistically significant difference between B/F/TAF and DTG/ABC/3TC (92.4% vs

		93% [95% CI: -4.8 to 3.6, p=0.78]) at 48 weeks follow up for this outcome. Both studies by Sax et al. (2017a and b) also showed no statistically significant difference in people receiving B/F/TAF when compared with DTG/F/TAF. In Molina et al. (2018) there was also no statistically significant difference between B/F/TAF and DTG/ABC/3TC (93.6% vs 95% [95% CI: -5.5 to 2.6; p=0.59]) at 48 weeks post treatment switching for this outcome. Similarly, Daar et al. (2018) showed no statistically significant difference between B/F/TAF and a boosted protease inhibitor-based regimen (92.1% vs 88.9% [95% CI: -1.6 to 8.2; p=0.20]) at 48 weeks post treatment switching for this outcome.
2.	Mean change in CD4 cell count from baseline	This outcome is a marker of likely disease progression which is independent of viral load. A decline in the CD4 (lymphocyte helper cells which help the immune system fight infection) cell count of an individual is caused by HIV-1 infection with an increase in cell count indicating that the HIV-1 viral load has been reduced. The lower the CD4 cell count, the greater the damage to the immune system and the greater the risk of illness. Overall, the evidence suggests that receiving bictegravir-emtricitabine-tenofovir alafenamide (B/F/TAF) is comparable to dolutegravir, abacavir and lamivudine (DTG/ABC/3TC), dolutegravir, emtricitabine and tenofovir alafenamide (DTG/F/TAF) or boosted protease inhibitor-based regimens at increasing the mean CD4 cell count from the start of treatment (baseline) to 48 weeks. In Gallant et al. (2017) there was no statistically significant difference between B/F/TAF and DTG/ABC/3TC at increasing the mean CD4 cell count from the start of treatment (baseline) to 48 weeks follow up (233 per µl [SD ± 185.2] vs 229 per µl [SD ± 188.8] respectively; p=0.81). Both studies by Sax et al. (2017a and b) showed no statistically significant difference between B/F/TAF and DTG/F/TAF at increasing the mean CD4 cell count from the start of treatment (baseline) to 48 weeks follow up. Molina et al. (2018) showed no statistically significant difference between B/F/TAF and DTG/ABC/3TC in increasing the mean CD4 cell count (difference: -21 cells per µl [95% CI: -51 to 9; p=0.18]) at 48 weeks post treatment switching. Similarly, Daar et al. (2018) showed no statistically significant difference between B/F/TAF and a boosted protease inhibitor-based regimen in increasing mean CD4 cell count (+25 per µl

		[SD ± 151.2] vs +0 per µl [SD ± 159.4], respectively; p=0.068) at 48 weeks post treatment switching:
3	HIV symptom index	The outcome is a HIV disease specific validated tool which uses patient elicitation to capture changes in 20 symptoms which are indicative of improvements in their condition. For the treatment naïve population, statistically significant differences in favour of B/F/TAF compared to dolutegravir, abacavir and lamivudine were found at 2 or more time points ($p<0.05$) in the adjusted logistic regression model in the following domains of the HIV symptom index: • fatigue/loss of energy; • dizziness/light headedness; • nausea/vomiting; and • difficulty sleeping. In the longitudinal models, there were statistically significant differences in the fatigue/loss of energy and nausea/vomiting domains with fewer reports in B/F/TAF group. For treatment-experienced patients switched from dolutegravir, abacavir and lamivudine to B/F/TAF, statistically significant differences in favour of B/F/TAF were found at 2 or more time points in the adjusted logistic regression model, as well as in the longitudinal models in the following domains: • nausea/vomiting; • sad/down/depressed; • nervous/anxious; and • difficulty sleeping (as well as the poor sleep quality domain in the Pittsburgh Sleep Quality Index).

Considerations from review by Rare Disease Advisory Group
Not applicable.

Pharmaceutical considerations
BFTAF is a combination of three anti-retroviral drugs (bictegravir sodium, emtricitabine, tenofovir alafenamide fumarate) licensed for the treatment of HIV in adults (ie 18 and above). The policy recommends use in a specified cohort of patients with particular presentations that prevents the use of alternative lower cost HIV treatments. The product is excluded to tariff.

Considerations from review by National Programme of Care
1) The proposal received the full support of the Blood and Infection PoC Board on the 28th February 2019.