MANAGEMENT IN CONFIDENCE

CLINICAL PRIORITIES ADVISORY GROUP
XX XX XX 2019

Agenda Item No	
National Programme	Blood and Infection
Clinical Reference Group	HIV
URN	1822

Title
Doravirine for treating human immunodeficiency virus type 1 (HIV-1) in adults

Actions Requested	1. Agree the policy proposition
	2. Recommend the relative priority

Proposition
Routine commissioning **Associated clinical commissioning documents** None

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

The Benefits of the Proposition		
No	*Outcome measures*	*Summary from evidence review*
1.	Survival	Not reported
2.	Progression free survival	Not reported
3.	Mobility	Not reported
4.	Self-care	Not reported
5.	Usual activities	Not reported
6.	Pain	Not reported
7.	Anxiety / Depression	Not reported
8.	Replacement of more toxic treatment	Not reported
9.	Dependency on care giver / supporting independence	Not reported
10.	Safety	Adverse events are unintentional and undesirable signs and symptoms reported during a study. If an event is thought to be related to the drugs being used in a study, it is known as a drug-related adverse event. In the two studies with treatment naive participants (DRIVE-FORWARD and DRIVE-AHEAD), treatment related adverse events were reported in 31% of the participants in the doravirine group in each study, and 32% and 63% of participants in the other antiretroviral therapy group. Around 1% of participants in each group in each study had a serious treatment related adverse event. Around 1% and 2% of participants in the doravirine group and 2% and 6% of participants in the other antiretroviral therapy groups discontinued treatment because of treatment related adverse events. One of the studies

		(see table 4 of the DRIVE-AHEAD study for confidence interval) reported statistically significantly fewer participants with treatment related adverse events and discontinuations from treatment related adverse events (p values not reported). The statistical significance of the differences in the other study (DRIVE-FORWARD) was not reported. Neuropsychiatric adverse events were reported as an event of clinical interest in the DRIVE-FORWARD study and as the primary safety outcome in the DRIVE-AHEAD study. In the DRIVE-FORWARD study, 6% of participants in the doravirine group and 5% in the other antiretroviral therapy group had a treatment related neuropsychiatric adverse event (statistical significance not reported). In the DRIVE-AHEAD study there were statistically significantly fewer participants reporting dizziness (8.8% vs. 37.1%, p≤0.001), sleep disorders/disturbances (12.1% vs. 25.2%, p≤0.001), and altered sensorium (4.4% vs. 8.2%, p=0.033) in the doravirine group. In the doravirine group in the same study, fewer participants reported depression and suicide/self-injury (4.1% vs. 6.6%), or psychosis and psychotic disorders (0.3% vs. 1.1%), but the statistical significance of these results was not reported. In the third study (DRIVE-SHIFT), participants were either switched to doravirine or remained on their existing antiretroviral therapy regimen. Treatment related adverse events were reported in 20% of participants in the doravirine group at 48 weeks and 2% of the participants in the other antiretroviral therapy group at 24 weeks. Less than 1% of participants in each group had a serious treatment related adverse event. Around 2% of participants in the doravirine group and none of the participants in the comparator group discontinued treatment because of treatment related adverse events. The statistical significance of the difference between the groups was not reported. Please note, people remaining on their existing regimen may be less likely to experience an adverse event compared with those switching treatments because they have already demonstrated some tolerance to it. It is not possible to determine from the evidence whether there was a difference in the number of drug-related adverse events with doravirine compared to other antiretroviral treatments. The

		evidence suggests that the use of doravirine leads to fewer treatment related adverse events than the treatments it was compared against but the evidence was not conclusive. The results should be interpreted with caution as the studies were powered on the primary outcome, a viral load less than 50 copies per ml. In the DRIVE-AHEAD study the NRTI backbone used in the treatment and comparator differs, making it difficult to attribute differences to doravirine alone. In the DRIVE-SHIFT study it is unclear what NRTI backbone was used in the comparator arm so again making it more difficult to be certain that differences in outcomes are due to doravirine alone. It is not clear how generalizable the results are to the UK as although some of the participants were from the UK, it is not clear how many participants from other countries in the studies were similar to the UK population.
11.	Delivery of intervention	Not reported

Other health outcome measures determined by the evidence review		
No	Outcome measure	Summary from evidence review
1.	Viral load	Viral load is a measure of how much HIV virus is in the blood. Higher levels of HIV in the blood increase the risk of a person with HIV becoming ill from other infections and passing the virus on to other people. The aim of antiretroviral therapy is to reduce viral load to less than 50 copies/ml. The 3 studies reported that the number of participants who had a viral load of less than 50 copies/ml at week 48 was statistically significantly non-inferior in the group that took doravirine compared with the group who received other antiretroviral therapy (DRIVE-FORWARD 84% vs. 80%, treatment difference 3.9%, 95% CI -1.6 to 9.4; DRIVE-AHEAD 84% vs. 81%, treatment difference 3.5%, 95% CI -2.0 to 9.0; DRIVE-SHIFT 91% at week 48 with doravirine vs. 95% at week 24 with existing antiretroviral therapy, treatment difference -3.8%, 95% CI -7.9 to 0.3). The results remained non-inferior for subgroups based on baseline characteristics, with the exception of age in the DRIVE-AHEAD study.

		The evidence suggests that doravirine is as effective as other antiretroviral treatments in maintaining a viral load of less than 50 copies/ml. See the final paragraph of row 10 ‘Safety’ in the table above for the limitations with this evidence.
2.	CD4 cell count	CD4 cells are white blood cells that fight infections in the body. The HIV-1 virus kills CD4 cells, increasing the risk of the person with HIV developing serious illnesses. The 3 studies reported that there was no statistically significant difference in change in CD4 cell count with doravirine compared to other antiretroviral therapy (DRIVE-FORWARD increase of 193 cells/µl vs. increase of 186 cells/µl, mean difference 7.1 cells/µl, 95% CI -20.8 to 35; DRIVE-AHEAD increase of 198 cells/µl vs. increase of 188 cells/µl, mean difference 10.1 cells/µl, 95% CI -16.1 to 36.3; DRIVE-SHIFT increase of 14 cells/µl with doravirine at week 48 vs. increase of 18 cells/µl with existing antiretroviral therapy at week 24, mean difference not reported). The evidence suggests that doravirine is as effective as other antiretroviral treatments in promoting CD4 cells. See the final paragraph of row 10 ‘Safety’ in the table above for the limitations with this evidence.
3.	Blood lipids	Blood lipids are fats in the blood, such as fatty acids and cholesterol. Generally, the presence of elevated or abnormal levels of lipids or lipoproteins in the blood (hyperlipidaemia) increases the risk of developing heart disease, gall bladder disease and pancreatitis. In the 3 studies there was a statistically significantly greater decrease in LDL cholesterol ($p<0.0001$ in all studies) and non-HDL cholesterol ($p<0.0001$ in all studies) from baseline with doravirine compared to other antiretroviral therapy. There was also a reduction in cholesterol and triglycerides from baseline with doravirine compared to other antiretroviral therapy, but the statistical significance of this was not reported. The results for change in total cholesterol/HDL cholesterol ratio from baseline were mixed, with 1 study (DRIVE-AHEAD) reporting a statistically non-significant difference between doravirine and other antiretroviral therapy and

		another study (DRIVE-SHIFT) reporting a smaller reduction with doravirine compared to other antiretroviral therapy, but without reporting the statistical significance. HDL cholesterol was lower with doravirine in all 3 of the studies, however, it was only reported to be statistically significant (p value not reported) in 1 of the studies (DRIVE-SHIFT). The evidence suggests a statistically significant reduction in blood lipid levels with doravirine compared to other antiretroviral treatments. See the final paragraph of row 10 ‘Safety’ in the table above for the limitations with this evidence.
4.	Viral resistance	Viral resistance refers to when a virus is no longer affected by a drug that used to be effective against it. It means that a virus will continue to multiply despite the presence of a drug that would usually kill it. There were 2 (1%) reported cases of resistance to doravirine in one of the studies (DRIVE-FORWARD), with no reported cases of resistance to other antiretroviral therapy. However, in another study (DRIVE-AHEAD) fewer people developed resistance to doravirine (7 [2%] people with genotypic resistance and 6 [2%] people with phenotypic resistance) compared to other NNRTIs (9 [2%] people with genotypic resistance and 11 [3%] people with phenotypic resistance). There were no reported cases of resistance to doravirine or other NNRTIs in the third study (DRIVE-SHIFT). The statistical significance of the differences in viral resistance between the groups was not reported. The results suggest that doravirine is as effective as other antiretroviral treatments in avoiding viral resistance to treatment. See the final paragraph of row 10 ‘Safety’ in the table above for the limitations with this evidence.

Considerations from review by Rare Disease Advisory Group
Not applicable / [TO BE COMPLETED BY AC WHERE APPLICABLE]

Pharmaceutical considerations
[TO BE COMPLETED BY NHS ENGLAND (Malcolm Qualie). Katie Jones compiling.

Considerations from review by National Programme of Care
Select appropriate option: 1) The proposal received the full support of the <insert PoC name> PoC Board on the <insert date> 2) The proposal received the support of the <insert PoC name> PoC Board on the <insert date>, subject to the following comments <insert comments> 3) The proposal received the support of the <insert PoC name> PoC Board on the <insert date> but CPAG is asked to note that the proposal did not have the full support of the Policy Working Group, who have raised the following concerns: <insert reasons> 4) Other – free text (only for minority of cases not fitting into the above)