CADTH

CADTH COMMON DRUG REVIEW

CADTH Canadian Drug Expert Committee Recommendation

(Final)

Doravirine (Pifeltro — Merck Canada Inc.)
Indication: In combination with other antiretroviral medicinal products, for the treatment of adults infected with HIV-1 without past or present evidence of viral resistance to doravirine (DOR).

RECOMMENDATION
The CADTH Canadian Drug Expert Committee (CDEC) recommends that DOR be reimbursed for the treatment of adults infected with HIV-1 without past or present evidence of viral resistance to DOR only if the following condition is met:

Condition for Reimbursement

Pricing Condition

1. Reduction in price.

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Recommendation

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Reasons for the Recommendation

1. In two double-blind randomized controlled trials conducted in treatment-naive patients with HIV-1 (DRIVE-FORWARD, N = 769 and DRIVE-AHEAD, N = 728), with a primary outcome of the proportion of patients with HIV-1 ribonucleic acid (RNA) < 50 copies/mL at week 48, DOR was noninferior to ritonavir-boosted darunavir (DRV/r) when both were given in combination with emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) or abacavir/lamivudine (ABC/3TC), and DOR/3TC/TDF was noninferior to efavirenz (EFV)/FTC/TDF.

2. DOR is not considered to be cost-effective at the manufacturer's submitted price. In the submitted economic model for treatment-naive patients, a price reduction of more than 25% is required for DOR + TDF/FTC to be the optimal treatment regimen relative to the least costly single tablet regimen (STR, EFV/TDF/FTC) if a decision-maker is willing to pay $50,000 per quality-adjusted life-year (QALY). When compared with multiple-tablet regimens, a price reduction of more than 40% is required for DOR + TDF/FTC to be the optimal treatment regimen if a decision-maker is willing to pay $50,000 per QALY. CADTH was unable to address several key limitations, resulting in uncertainty regarding the likely incremental cost-utility ratio (ICUR) in the treatment-naive population. As such, a greater price reduction would improve the likelihood that DOR is cost-effective. The cost-effectiveness of DOR is unknown in the population that is switching from previous antiretroviral therapy.

Discussion Points

- The committee discussed that there is minimal unmet need for additional ARV drugs for the treatment of HIV-1, and that the US Department of Health and Human Services recommends that initial regimens for most people with HIV are integrase strand transfer inhibitor (INSTI)-containing regimens. The committee considered that DOR could potentially be an option for some patients as part of an initial regimen or for patients switching from an INSTI-containing or other regimen due to intolerance or convenience; however, prescribing of the single-ingredient DOR as part of an ARV regimen is likely to be infrequent.

- The committee discussed that DOR-containing regimens were demonstrated to be noninferior with respect to achieving virologic success, and suggested a more favourable safety profile with respect to neuropsychiatric adverse events (AEs) and lipid profile versus comparators in DRIVE-FORWARD and DRIVE-AHEAD. However, it was noted that the comparator regimens in both trials contained older ARV drugs that are not often used in current clinical practice, often due to known unfavourable AE profiles. For example, the committee noted that EFV is well known to be associated with neuropsychiatric AEs. The comparative benefit of DOR versus more commonly used ARV drugs for the initial treatment of HIV-1 is unknown The manufacturer's indirect treatment comparison did not fully address this lack of evidence due to methodologic limitations, including the failure to include many relevant comparators.

- The committee discussed that the DRIVE-SHIFT trial suggested that virologically suppressed patients on a stable ARV regimen who switch to the DOR-containing regimen DOR/3TC/TDF are able to maintain virologic suppression at 48 weeks.

However, the committee noted that DRIVE-SHIFT had a number of methodologic limitations. Hence, there is some uncertainty surrounding the comparative effectiveness of DOR/3TC/TDF in treatment-experienced patients. In addition, none of the available trials provide evidence of the clinical benefit of DOR in patients who have failed prior antiretroviral therapy.

Background

DOR has a Health Canada indication for the treatment of adults infected with HIV-1 without past or present evidence of viral resistance to DOR, in combination with other antiretroviral medicinal products. DOR is a non-nucleoside reverse transcriptase inhibitor of HIV-1. It is available as 100 mg tablets and the Health Canada–approved dosage is one 100 mg tablet taken orally once daily with or without food.

Summary of Evidence Considered by CDEC

The committee considered the following information prepared by the CADTH Common Drug Review: a systematic review of randomized controlled trials of DOR, a critique of the manufacturer-submitted indirect treatment comparison, and a critique of the manufacturer's pharmacoeconomic evaluation. The committee also considered input from a clinical expert with experience in treating patients with HIV, and patient group–submitted information about outcomes and issues important to patients.

Summary of Patient Input

One patient group, the Canadian Treatment Action Council, provided input for this submission. Patient perspectives were obtained from a consultation workshop in Toronto and survey data collected for the patient submission on dolutegravir (DTG). The following is a summary of key input from the perspective of the patient group:

- Patients are generally able to manage their symptoms and disease progression; however, they are more susceptible to inflammation and noninfectious comorbidities. Patients indicated that stigma, discrimination, and resulting stress are a major obstacle to their well-being.
- The physical and mental state of patients can often be exacerbated by various social determinants of health, including access to treatment, experience of health care professionals in treating patients with HIV, and the availability of resources.
- Patients noted that that their treatments were generally effective at suppressing viral load, and resulted in an improved quality of life and ability to engage in daily activities. Instances of treatment-associated side effects and failure to achieve viral suppression despite trying multiple treatments were noted; thus, the patient input emphasized the importance of having the maximum possible treatment options available.
- The patient group was not able to consult with any patients on DOR, and no information was provided on expectations for DOR alone or as a combination therapy. However, patients noted that new medications with fewer side effects and different chemical composition would be beneficial; patients considered that the latter would likely lower the risk of developing drug resistance and drug-drug interactions.

Clinical Trials

The systematic review included three phase III active-controlled, noninferiority trials: two double-blind (DB) trials (DRIVE-FORWARD, N = 769, and DRIVE-AHEAD, N = 728) conducted in treatment-naive patients; and one open-label (OL) trial (DRIVE-SHIFT, N = 673) conducted in virologically suppressed patients on a stable ARV regimen. The DB and OL trials had a total follow-up duration of 96 weeks and 48 weeks, respectively.

Treatments administered in the DB trials were DOR (100 mg) or DRV/r (800 mg/100 mg), each given in combination with FTC/TDF 200 mg/300 mg or ABC/3TC 600 mg/300 mg (in DRIVE-FORWARD), and DOR/3TC/TDF or EFV/FTC/TDF (in DRIVE-AHEAD). In DRIVE-SHIFT, patients either immediately switched to DOR/3TC/TDF to be received for 48 weeks (immediate switch group [ISG]) or continued their baseline regimen for 24 weeks (consisting of a ritonavir- or cobicistat-boosted protease inhibitor or cobicistat-boosted INSTI, or non-nucleoside reverse transcriptase inhibitor, each administered with two nucleoside reverse transcriptase inhibitors)

before switching to DOR/3TC/TDF (delayed switch group [DSG]). Overall discontinuations between treatment groups ranged from 18% to 29% in the DB trials by week 96, and 8% to 10% in the OL trial by week 48.

Limitations in the DB trials include the use of comparator regimens that are not commonly prescribed in Canadian clinical practice due to their associated side effects, which may overstate the comparative safety of DOR. In addition, the higher discontinuation rate in the comparator groups compared with the DOR groups may overestimate the comparative efficacy of DOR, given that those who discontinued the study were considered not to have achieved the primary outcome. DRIVE-SHIFT had a number of limitations, including the primary efficacy end point not being consistent with the latest FDA recommendations, not following the FDA-recommended snapshot algorithm for addressing missing values (specifically for the primary outcome), and an unequal follow-up duration between the treatment groups for the primary analyses.

Outcomes

Outcomes were defined a priori in the CADTH Common Drug Review systematic review protocol. Of these, the committee discussed the following:

- Virologic success: Proportion of patients with HIV-1 RNA fewer than 50 copies/mL as determined by the US FDA-defined snapshot algorithm (primary outcome for all studies)
- Virologic failure: Proportion of patients with HIV-1 RNA greater than or equal to 50 copies/mL as determined by the US FDA-defined snapshot algorithm
- CD4 cell count
- Adherence to medication
- Resistance
- Notable harms: lipid profile and neuropsychiatric AEs

Efficacy

Treatment-Naive

Among treatment-naive patients, the primary outcome (proportion of patients with HIV-1 RNA less than 50 copies/mL at week 48) was achieved by 83.8% and 79.9% of patients receiving DOR and DRV/r in DRIVE-FORWARD, respectively; and by 84.3% and 80.8% patients receiving DOR/3TC/TDF and EFV/FTC/TDF in DRIVE-AHEAD, respectively. The between-treatment differences in the two trials were 3.9% (95% confidence interval [CI], –1.6 to 9.4) and 3.5% (95% CI, –2.0 to 9.0), respectively. In both cases, the pre-specified noninferiority margin of 10% was met, since the lower bound of the 95% CI for treatment differences were above −10 percentage points. Noninferiority was confirmed in the per-protocol population and sensitivity analyses using the observed failure (missing = excluded) approach in both trials. The proportions of patients with virologic success at week 96 were 73.1% and 66.0% for patients receiving DOR and DRV/r in DRIVE-FORWARD, respectively; and 77.5% and 73.6% for patients receiving DOR/3TC/TDF and EFV/ FTC/TDF in DRIVE-AHEAD, respectively. The proportion of patients with HIV-1 RNA greater than or equal to 50 copies/mL (virologic failure) at week 48 were similar between the treatment groups in both trials; 11.2% versus 13.1% for DOR and DRV/r, respectively, in DRIVE-FORWARD, and 10.7% versus 10.2% for DOR/3TC/TDF and EFV/FTC/TDF, respectively, in DRIVE-AHEAD. The proportion of patients with HIV-1 RNA greater than or equal to 50 copies/mL at 96 weeks was 17.2% versus 20.2% for DOR and DRV/r, respectively, in DRIVE-FORWARD, and 15.1% versus 12.1% for DOR/3TC/TDF and EFV/FTC/TDF in DRIVE-AHEAD.

The between-treatment differences in mean changes in CD4 cell count from baseline in DRIVE-FORWARD and DRIVE-AHEAD were 7.1 (95% CI, –20.8 to 35.0) and 10.1 (95% CI, –16.1 to 36.3) at week 48, respectively, and 17.4 (95% CI, –14.5 to 49.3) and 14.7 (95% CI, –18.7 to 48.2) at week 96, respectively.

Resistance to any of the study medications occurred very infrequently — less than 15 cases in any treatment group in both trials. Among patients who completed each trial, adherence to treatment was generally high, with most patients (more than 85%) reporting an adherence of 90% or more.

Treatment-Switch/Experienced

In DRIVE-SHIFT, the proportion of patients with HIV-1 RNA less than 50 copies/mL was 90.8% at week 48 in the ISG group compared with 94.6% in the DSG group at week 24; treatment difference of –3.8% (95% CI, -7.9 to 0.3). Given the lower bound of the 95% CI was not less than -8%, switching to DOR/3TC/TDF was considered noninferior to continued treatment with baseline regimen. However, DRIVE-SHIFT had a number of methodologic issues leading to questionable validity with respect to establishing comparative efficacy between switching to DOR/3TC/TDF versus staying on baseline regimens. The comparison of virologic suppression between groups based on different durations of follow-up is unusual; between-treatment comparisons based on the same duration of follow-up would have more internally validity. The between-treatment difference for the proportion of patients with HIV-1 RNA less than 50 copies/mL at the same time point in each group (24 weeks) was –0.9% (95% CI, –4.7 to 3.0). Further, based on guidance from the FDA, the appropriate end point for treatment-switch trials is the proportion of patients with HIV-1 RNA greater than or equal to 50 copies/mL with an associated noninferiority margin of 4%. The proportions of patients with HIV-1 RNA greater than or equal to 50 copies/mL were similar between the ISG and DSG groups at weeks 48 and 24 (1.6% and 1.8%, respectively), and between the ISG and DSG groups at week 24 for each group (1.8% in both groups); between-treatment differences were –0.2 (95% CI, –2.5 to 2.1) and –0.0 (95% CI, –2.3 to 2.3), respectively; however, statistical testing was not controlled for multiplicity.

The treatment differences in mean CD4 cell count changes from baseline at the primary (ISG 0-48 versus DSG 0 to 24 weeks) and secondary time points (ISG 0 to 24 versus DSG 0 to 24 weeks) were –4.0 (95% CI, –31.6 to 23.5) and –12.8 (95% CI, –41.1 to 15.4), respectively.

One incidence of resistance was reported by week 48. Adherence with the study medication regimen was 90% or greater for most participants in the ISG group and for the DSG group before and after switching treatment.

Harms (Safety)

Treatment-Naive

- Overall AEs were largely similar between treatment groups in DRIVE-FORWARD (84.6% and 82.8% of patients in the DOR and DRV/r groups, respectively) and in DRIVE-AHEAD (88.2% and 93.1% of patients in the DOR/3TC/TDF and EFV/FTC/TDF groups, respectively) at week 96. Serious AEs were also reported in a similar proportion between treatment groups: 7.0% versus 8.6% in DRIVE-FORWARD and 5.8% and 8.2% in DRIVE-AHEAD.
- The proportion of patients who withdrew from the trials due to AEs ranged 1.6% to 3.4% in DRIVE-FORWARD and 3.0% to 7.4% in DRIVE-AHEAD.
- In total, there were 11 deaths in the two studies. None of the deaths were deemed related to treatment.
- An assessment of lipid profile showed an improvement with DOR treatment versus comparators, with statistically significant between-treatment differences in mean changes from baseline in fasting low density lipoprotein of -14.61 (95% CI, -18.15 to -11.06) and -10.01 (95% CI, -13.53 to -6.49) and in mean changes from baseline in fasting non-high density lipoprotein (HDL) of -19.34 (95% CI, -23.33 to -15.35) and -17.02 (95% CI, -20.89 to -13.16) in DRIVE-FORWARD and DRIVE-AHEAD, respectively, at week 48. These treatment differences were carried forward at week 96; however, these analyses were not controlled for multiplicity. Results for other lipid outcomes were not adjusted for multiplicity.
- A number of neuropsychiatric AEs were assessed in both trials; however, statistical comparisons with multiplicity adjustment were only done in DRIVE-AHEAD. In this study, statistical superiority of DOR over EFV was shown for the proportion of patients experiencing three categories of neuropsychiatric AEs at week 48: dizziness, sleep disorders and disturbances, and altered sensorium, with between-treatment differences of -28.3% (95% CI, -34.0 to -22.5), -13.5% (95% CI, -19.1 to -7.9), and -3.8% (95% CI, -7.6 to -0.3), respectively.

Treatment-Switch/Experienced

- Overall, 80.3% of the patients in the ISG group experienced AEs at week 48. Patients in the ISG group experienced more AEs compared with the baseline regimen at week 24 for the DSG group (68.9% versus 52.5%, respectively), 60.3% of patients in the DSG group experienced AEs post-treatment switch. The number of patients experiencing serious AEs and withdrawals due to AEs did not exceed 5% in any groups at either time point.
- There were two deaths, both in the ISG group, one of which was deemed related to treatment, although no confirmatory diagnosis was made.
- DOR showed an improvement in fasting low density lipoprotein and non-HDL versus the comparator group at week 24, with between-treatment differences of –15.29 (95% CI, –18.99 to –11.59) and –23.90 (95% CI, –28.14 to –19.65), respectively. These results and other lipid outcomes were not adjusted for multiplicity. Neuropsychiatric AEs were not analyzed statistically.

Indirect Treatment Comparisons

The manufacturer-submitted network meta-analysis (NMA) suggests that, with respect to virologic success (HIV-1 RNA fewer than 50 copies/mL) [redacted] The NMA did not provide adequate information on the statistical analyses plan to assess the validity of the results and NMA assumptions. The missing information, coupled with the small network size, the lack of assessing NMA assumptions, and the differences in trial design and the definition used for protocol derived virologic failure to determine virologic response, translates to a high degree of uncertainty in the presented efficacy and safety results. Other limitations include the limited scope of the manufacturer-submitted NMA, where only interventions that are relevant to their economic model in treatment-naive patients were analyzed, without assessing relevant comparators such as [redacted]

Cost and Cost-Effectiveness

DOR is available as a 100 mg oral tablet taken once daily with or without food in combination with other ARV medicinal products. At the manufacturer-submitted price of $16.65 per tablet, the annual cost of DOR is approximately $6,077 per patient. Common backbone treatments range from $2,185 (ABC/3TC) to $9,527 (tenofovir alafenamide/FTC) per year based on public prices.

The manufacturer submitted a cost-utility analysis that assessed the impact of DOR in addition to TDF/FTC compared with STRs (DTG/ABC/3TC, EFV/TDF/FTC, and DRV/r + TDF/FTC) and multiple-tablet regimens (MTRs; DOR + TDF/FTC, DTG + TDF/FTC, EFV + TDF/FTC, and DRV/r + TDF/FTC) in treatment-naive patients. In the model, patients could receive up to two additional lines of active therapy before moving on to a “salvage therapy” (including non-suppression and partial suppression), which they would remain on until death. The analysis was undertaken over a lifetime time horizon from the Canadian public health care payer perspective. Data from a pooled ad hoc analysis of Protocol 007 (for DOR, the 100 mg group only), Protocol 018, and Protocol 21, as well as a manufacturer-supplied NMA were used to inform patient characteristics, clinical efficacy, and safety inputs. Key health outcomes and risks in the model were CD4 cell counts, lipid profiles, risk of cardiovascular disease, and risk of diabetes.

In the manufacturer’s base case, in a treatment-naive population, compared with STRs, strategies starting with DOR + TDF/FTC were associated with the lowest total costs. DTG/ABC/3TC was associated with greater total costs and more QALYs. The ICUR for DTG/ABC/3TC was $441,884 per QALY when compared with DOR + TDF/FTC. When compared with MTRs, strategies starting with EFV, DOR, or DTG were the most efficient treatment options. Initial treatment with EFV was the optimal strategy up to a willingness to pay (WTP) of $205,967 per QALY gained. If a decision-maker’s WTP is between $205,967 and $308,278 per QALY, DOR was the optimal strategy. If a decision-maker’s WTP is more than $308,278 per QALY, DTG was the optimal strategy. The results were driven by the cost of and time on initial treatment regimens.

CADTH identified the following key limitations with the manufacturer's submitted economic analysis:

- The economic evaluation by the manufacturer was limited to patients who were treatment-naive. As such, the clinical effectiveness and cost-effectiveness of DOR in patients who had failed previous treatment is unknown.
- Relevant comparators were excluded in the manufacturer's economic evaluation. The backbone treatment for DOR (e.g., TDF/FTC) is unlikely to be used in clinical practice. ABC/3TC or a tenofovir alafenamide-based regimen is more likely to be used.
- The manufacturer's clinical effectiveness estimates for the economic model were based on the NMA that had notable limitations, reducing CADTH's ability to validate the results, resulting in significant uncertainty in the results.
- The manufacturer modelled disease progression using CD4 counts, which was considered to be inappropriate by the CADTH clinical expert. Viral load was considered a better prognostic marker by the expert, which is also supported by the literature.
- CADTH also identified limitations related to AEs, mortality, comparator costs, and annual medical care costs for HIV-1. Additionally, CADTH noted that the prices of the individual components of DTG/ABC/3TC (e.g., DTG and ABC/3TC) are substantially less costly than the STR.

When correcting for the price for EFV/TDF/FTC STR, DOR + TDF/FTC is no longer the least costly option in the STR analysis, and is associated with an ICUR of $168,387 per QALY compared with EFV/TDF/FTC in a treatment-naive population. CADTH also undertook scenarios assessing the impact of utility values and HIV-care costs, modelling multiple lines of therapy and an alternative pricing scenario for DTG/ABC/3TC. Removing subsequent, non-salvage lines of therapy had the largest impact on which regimens were considered most cost-effective. A price reduction of between 25% and 40% (depending on whether comparing with STRs or MTRs) is required to achieve an ICUR below $50,000 per QALY based on the economic analysis in a treatment-naive population.

CDEC Members

Dr. James Silvius (Chair), Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Peter Jamieson, Mr. Allen Lefebvre, Ms. Heather Neville, Dr. Rakesh Patel, Dr. Emily Reynen, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

April 10, 2019 Meeting

Regrets

Two CDEC members did not attend.

Conflicts of Interest

None.