BRITISH COLUMBIA
CENTRE *for* EXCELLENCE
in HIV/AIDS

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Dear Healthcare Provider:

RE: **BC-CfE Drug Formulary Addition: Doravirine (Pifeltro®) and Doravirine-Lamivudine-Tenofovir DF (Delstrigo®)**

Doravirine, a non-nucleoside reverse transcriptase inhibitor (NNRTI), is available through the BC-CfE Drug Treatment Program, as an ***alternative*** option for the treatment of HIV-1 infection in adults, in combination with other antiretroviral (ARV) agents.

Doravirine has been evaluated in the following settings:

- In antiretroviral therapy (ART)-naïve adults
    - As a component of 3-drug ART, where there is no evidence of resistance to doravirine or the other regimen components.
    - Doravirine in combination with 2 nucleoside reverse transcriptase inhibitors, has demonstrated non-inferior virologic efficacy to both efavirenz and darunavir/ritonavir-based 3-drug regimens.
    - The efficacy and safety of doravirine compared to integrase inhibitors has not been evaluated.

- In stable, virologically suppressed adults
    - As a switch strategy, in virologically suppressed adults on a stable ART regimen, with no history of treatment failure, and no known mutations associated with resistance to doravirine or the other regimen components.
    - Rates of viral suppression were comparable in participants randomized to switch to doravirine/lamivudine/tenofovir DF versus those continuing a baseline regimen of a boosted protease inhibitor, an NNRTI or boosted elvitegravir, with 2 nucleoside reverse transcriptase inhibitors.

Doravirine has a favourable impact on lipids compared to darunavir/ritonavir or efavirenz, and a lower frequency of neuropsychiatric effects (e.g. dizziness, sleep disturbance, altered sensorium) compared to efavirenz.

In vitro and other limited data suggest that doravirine may retain activity against HIV-1 strains harbouring certain **individual** NNRTI mutations; however, additional data are needed to confirm this preliminary data and further inform resistance interpretation algorithms. ***Caution should be undertaken when considering doravirine use in the setting of any NNRTI mutations***. Consultation with an HIV expert is recommended.

Prescribing and administration:

Doravirine is available on BC-CfE Drug Formulary in the following products:

- Doravirine 100 mg tablet (Pifeltro®): The recommended dose is one tablet orally once daily, in combination with other ARV medications.
- Doravirine/lamivudine/tenofovir DF 100-300-300 mg tablet (Delstrigo®) single tablet regimen: The recommended dose is one tablet orally once daily.

Other considerations when prescribing Doravirine:

- Doravirine and Delstrigo® can be taken with or without food, and can be co-administered with gastric acid suppressing agents such as proton pump inhibitors or H2 blockers.
- Doravirine may interact with other medications, and is susceptible to drug interactions with hepatic enzyme inducers or inhibitors. Use with strong cytochrome P450 3A enzyme inducers (e.g. phenytoin, carbamazepine, rifampin) is contraindicated. When doravirine is coadministered with rifabutin, the doravirine dose should be increased to 100 mg twice daily. Seek guidance from an HIV pharmacist or clinician for management.
- Adverse effects reported with doravirine include nausea (6-7%), diarrhea (4-5%), fatigue (6%), headache (6%), dizziness (3-5%), and abnormal dreams (1-3%).
- Doravirine is not recommended for use in pregnancy due to insufficient safety data.
- Due to the tenofovir DF and lamivudine components, Delstrigo® is not recommended in patients with estimated creatinine clearance <50 mL/min.
- Doravirine should not be used with other NNRTIs.

Requests for doravirine or Delstrigo® require submission of a BC-CfE HIV Drug Treatment Program Prescription Request form (found at http://www.bccfe.ca/drug-treatment-program/how-obtain-hiv-medication). **As these are alternative products to those listed on the 'BC-CfE Guideline for ART Regimens for Initial Therapy and for Switching ART in Virologically Stable Suppressed Adults', prescribers are asked to provide justification and relevant supporting documentation with the Prescription Request.**

Sincerely,

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BC Centre for Excellence in HIV/AIDS

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Executive Director and Physician-in-Chief
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Summary of clinical trial evidence for doravirine:

The efficacy and safety of doravirine have been evaluated in two Phase 3, randomized, double-blind non-inferiority trials in **treatment-naïve adults** with HIV-1 infection:

- In **DRIVE-FORWARD** (n=766), doravirine was evaluated against darunavir/ritonavir, each given with either emtricitabine/tenofovir DF or abacavir/lamivudine. At week 48, doravirine was non-inferior to darunavir/ritonavir, in achieving the primary outcome of HIV-1 plasma viral load (pVL) <50 copies/mL (83.8% vs. 79.9%) with a between-treatment difference of 3.9% (95% CI, -1.6 to 9.4) (Molina JM, 2018). At 96 weeks, the difference was 7.1% (95% CI, 0.5 to 13.7). Most adverse effects were mild to moderate in nature. A between-treatment difference in adverse effects of at least 5% was seen for diarrhea (17.0% vs 23.8%) and upper respiratory tract infection (13.3% vs. 7.8%) (Molina JM, 2020).
- In **DRIVE-AHEAD** (n=728), doravirine/lamivudine/tenofovir DF was non-inferior to efavirenz/emtricitabine/tenofovir DF in achieving pVL <50 copies/mL at 48 weeks (84.3% and 80.8%) with a treatment difference of 3.5% (95% CI, -2.0 to 9.0) (Orkin C, 2019). At 96 weeks, the between-treatment difference was 3.8% (95% CI, -2.4 to 10.0) Differences between doravirine and efavirenz arms at 96 weeks in adverse effects were noted in dizziness (10.1% vs 38.2%), abnormal dreams (4.9% vs 12.1%) and rash-related events (5.5% vs 12.4%). A greater proportion of efavirenz vs. doravirine participants withdrew from the study due to adverse events (7.4% vs 3.0%) (Orkin C, 2020).
- In both studies, fasting LDL and non-HDL levels were decreased in the doravirine arm, and increased in the comparator arms at week 48.

Doravirine has also been evaluated in **treatment-experienced patients** in a randomized, open-label switch trial **DRIVE-SHIFT** (n=670) in patients virologically suppressed for at least 6 months on two nucleoside reverse transcriptase inhibitors plus a boosted protease inhibitor (70%), an NNRTI (24%), or boosted elvitegravir (5.5%), with no history of treatment failure, and no resistance to doravirine, lamivudine or tenofovir DF. Participants were randomized 2:1 to immediately switch to doravirine/lamivudine/tenofovir DF or to continue the baseline regimen until week 24. At week 24, 93.7% on doravirine/lamivdine/tenofovir DF vs. 94.6% on baseline regimen had pVL <50 copies/mL [difference -0.9% (95% CI, -4.7 to 3.0)]. For the primary endpoint, 90.8% of the immediate switch group achieved pVL <50 copies/mL (at 48 weeks) vs. 94.6% in the delayed switch group (at 24 weeks) [treatment difference -3.8% (95% CI, -7.9 to 0.3)] (Johnson M, 2019).

References

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