CDEC FINAL RECOMMENDATION

DOLUTEGRAVIR
(Tivicay — ViiV Healthcare ULC)
Indication: HIV Infection

Recommendation:
The Canadian Drug Expert Committee (CDEC) recommends that dolutegravir be listed for the treatment of HIV in both treatment-naive and treatment-experienced adults and children 12 years of age and older weighing at least 40 kg, in combination with other antiretrovirals.

Reasons for the Recommendation:
1. Two randomized controlled trials (RCTs) conducted in treatment-naive patients demonstrated that dolutegravir was non-inferior to raltegravir (SPRING-2; N = 822) and, in combination with abacavir/lamivudine, superior to efavirenz/tenofovir/emtricitabine (SINGLE; N = 833). One RCT (SAILING; N = 724) demonstrated that dolutegravir was superior to raltegravir in treatment-experienced patients.
2. At the submitted price and recommended dose ($18.50; 50 mg once daily), dolutegravir is less costly than raltegravir ($27.00; 400 mg twice daily).

Background:
Dolutegravir is an HIV integrase strand transfer inhibitor (INSTI) indicated for use in combination with other antiretroviral drugs for the treatment of HIV infection in adults and children 12 years of age and older who weight at least 40 kg. Dolutegravir is available as 50 mg oral tablets and the usual dose is one tablet daily. For adult patients with demonstrated viral resistance to other INSTI drugs, the recommended dose is 50 mg twice daily. Dolutegravir is also recommended to be given as 50 mg twice daily in INSTI-naive patients who are being treated concomitantly with potent cytochrome P450 inducers.

Summary of CDEC Considerations
CDEC considered the following information prepared by the CADTH Common Drug Review (CDR): a systematic review of RCTs of dolutegravir, a critique of the manufacturer's pharmacoeconomic evaluation, and a summary of patient group-submitted information about outcomes and issues important to individuals living with HIV.

Patient Input Information

The following is a summary of key information provided by one patient group that responded to the CDR call for patient input:

- Many people living with HIV experience negative mental health outcomes, either as side effects from treatment, or from facing stigma, discrimination, and related stress. Fatigue is common, both before and after treatment is initiated, making it difficult to maintain diet and exercise routines, and may impact an individual's ability to work.
- The majority of people with HIV can live long lives by achieving an undetectable viral load (viral suppression) and manage their HIV as a chronic condition. However, adherence to HIV treatment is essential and non-adherence can lead to drug class resistance, requiring the adoption of a new regimen selected from the remaining treatment options. Treatment regimens may change often for people with HIV; hence, there needs to be a variety of HIV treatments available and accessible.

Clinical Trials

Three RCTs and one non-comparative open-label study were included in the CDR systematic review, including two in treatment-naive patients and two in treatment-experienced patients.

- Treatment-naive patients: SPRING-2 and SINGLE were phase 3, double-blind, non-inferiority RCTs conducted in antiretroviral drug naive patients. Participants in SPRING-2 were randomized to either dolutegravir 50 mg once daily or raltegravir 400 mg twice daily, each in combination with either abacavir/lamivudine or tenofovir/emtricitabine once daily. Participants in SINGLE were randomized to either dolutegravir 50 mg once daily in combination with abacavir/lamivudine once daily or to efavirenz/tenofovir/emtricitabine once daily.
- Treatment-experienced patients: SAILING was a phase 3 double-blind, double dummy, active-controlled, multi-centre, parallel group, non-inferiority RCT conducted in patients resistant to ≥ 2 antiretroviral drug classes but INSTI naive. Patients were randomized to either dolutegravir 50 mg once daily or raltegravir 400 mg twice daily, both in combination with optimized background therapy (OBT) selected by the investigator. VIKING-3 was a non-comparative, open-label study in HIV patients with prior extensive exposure to antiretroviral drugs and who harboured virus with phenotypic and/or genotypic evidence of INSTI resistance. To be eligible for VIKING-3, patients had to have plasma HIV ribonucleic acid (RNA) ≥ 500 copies/mL and demonstrated resistance to raltegravir and/or elvitegravir, and to drugs in two or more other classes of antiretroviral drugs.

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, CDEC discussed the following:

- Virologic success — the proportion of patients with plasma HIV RNA (viral load) < 50 copies/mL through week 48 using the Food and Drug Administration (FDA)-defined snapshot analysis. In this algorithm, patients whose last available HIV RNA value in the week 48 analysis window (i.e., from week 42 through week 54) was < 50 copies/mL were considered as having had a response; patients whose HIV RNA level was ≥ 50 copies/mL in the analysis window, or who did not have available data in the analysis window, were considered as not having had a response.
- Virologic failure — the proportion of patients with plasma HIV RNA ≥ 50 copies/mL.

- EQ-5D — a generic, non-disease-specific; preference-based utility instrument that includes a descriptive system used to rate five dimensions of health; mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.
- HIV-associated conditions/disease progression (morbidity) — recorded and assessed according to the 1993 CDC Revised Classification System for HIV Infections in Adults.
- Changes from baseline in CD4+ counts.
- INSTI resistance — the proportion of patients with detectable virus that has genotypic or phenotypic evidence of INSTI resistance by week 48.
- Serious adverse events, total adverse events, and withdrawals due to adverse events.

The primary efficacy end point was the proportion of patients with HIV RNA < 50 copies/mL at week 48 for both the SPRING-2, SINGLE, and SAILING studies, and at week 24 for the VIKING-3 study.

Efficacy

Studies in antiretroviral therapy-naive patients

- The proportion of patients with < 50 copies/mL plasma HIV RNA was reported as follows:
  - SPRING-2: In the intention to treat (ITT) analysis, 88% in the dolutegravir group and 85% in the raltegravir group with adjusted difference of 2.5 (95% CI: –2.2 to 7.1). In the per-protocol (PP) analysis, 90% in the dolutegravir group and 88% in the raltegravir group with an adjusted difference of 1.6 (95% CI: –2.7 to 5.9). Dolutegravir demonstrated non-inferiority to raltegravir, but not superiority at week 48.
  - SINGLE: In the ITT analysis, 88% in the dolutegravir + abacavir/lamivudine group and 81% in the efavirenz/tenofovir/emtricitabine group with an adjusted difference of 7.4 (95% CI: 2.5 to 12.3). In the PP analysis, 90% in the dolutegravir + abacavir/lamivudine group and 81% in the efavirenz/tenofovir/emtricitabine group with an adjusted difference of 8.7 (95% CI: 3.9 to 13.4). Dolutegravir demonstrated non-inferiority and superiority to efavirenz/tenofovir/emtricitabine at week 48.
- The proportion of patients with plasma HIV RNA ≥ 50 copies/mL was reported as follows:
  - SPRING-2: 5% in the dolutegravir group compared with 8% in the raltegravir group at week 48. At week 96, the reported rate (5%) of patients with HIV RNA ≥ 50 copies/mL was maintained for the dolutegravir group, while the proportion in the raltegravir group increased to 10%.
  - SINGLE: the proportion of patients with HIV RNA ≥50 copies/mL at week 48 was 5% and 6%, respectively, for the dolutegravir + abacavir/lamivudine and the efavirenz/tenofovir/emtricitabine groups. 7% of patients in both groups had HIV RNA ≥ 50 copies/mL at week 96.
- There was no statistically significant difference in EQ-5D between the dolutegravir and raltegravir groups at week 48 (P = 0.452) and week 96 (P = 0.301) in SPRING-2 or between the dolutegravir + abacavir/lamivudine and the efavirenz/tenofovir/emtricitabine groups at week 48 (P = 0.891) and week 96 (P = 0.516).
- The proportion of patients who experienced HIV-related morbidity was reported as follows:
  - SPRING-2: 2% in the dolutegravir versus 2% with raltegravir at week 48 and 3% in dolutegravir versus 2% with raltegravir at week 96.
  - SINGLE: 3% with dolutegravir + abacavir/lamivudine versus 4% with efavirenz/tenofovir/emtricitabine at week 48 and 5% with dolutegravir + abacavir/lamivudine versus 6% with efavirenz/tenofovir/emtricitabine at week 96.

Studies in antiretroviral therapy-experienced patients

- The proportion of patients with < 50 copies/mL plasma HIV RNA was reported as follows:
  - SAILING: In the ITT analysis, 71% in the dolutegravir group and 64% in the raltegravir group with adjusted difference of 7.4 (95% CI: 0.7 to 14.2). In the PP analysis, 73% in the dolutegravir group and 66% in the raltegravir group with an adjusted difference of 7.5% (95% CI: 0.6% to 14.3%). Dolutegravir demonstrated non-inferiority and superiority to raltegravir at week 48.
  - VIKING-3: 69% of patients at week 24 and 63% at week 48.
- There was no statistically significant difference in EQ-5D between the dolutegravir and raltegravir groups at week 48 in SAILING.
- In SAILING, the percentage of patients with plasma HIV RNA ≥ 50 copies/mL was lower with dolutegravir compared with raltegravir (20% versus 28% at week 48).

Harms (Safety and Tolerability)

- The proportion of patients with at least one adverse event was reported as follows:
  - SPRING-2: 82% with dolutegravir and 83% with raltegravir at week 48 and 85% in both groups at week 96.
  - SINGLE: 89% with dolutegravir + abacavir/lamivudine and 92% with efavirenz/tenofovir/emtricitabine at week 48 and 91% with dolutegravir and 94% with efavirenz/tenofovir/emtricitabine at week 96.
  - SAILING: 78% with dolutegravir and 79% with raltegravir at week 48.
  - VIKING-3: 91% with dolutegravir at week 48.
- The proportion of patients who reported at least one serious adverse event was reported as follows:
  - SPRING-2: 7% with dolutegravir and 8% with raltegravir at week 48 and 10% with dolutegravir and 12% with raltegravir at week 96.
  - SINGLE: 9% with dolutegravir + abacavir/lamivudine and 8% with efavirenz/tenofovir/emtricitabine at week 48 and 11% with dolutegravir and 12% with efavirenz/tenofovir/emtricitabine at week 96.
  - SAILING: 9% with dolutegravir and 12% with raltegravir at week 48.
  - VIKING-3: 21% with dolutegravir at week 48.
- The proportion of patients who withdrew as a result of adverse events was reported as follows:
  - SPRING-2: 2% with dolutegravir and 2% with raltegravir at week 48 and week 96.
  - SINGLE: 2% with dolutegravir + abacavir/lamivudine and 10% with efavirenz/tenofovir/emtricitabine at week 48 and 3% with dolutegravir and 12% with efavirenz/tenofovir/emtricitabine at week 96.
  - SAILING: 2% with dolutegravir and 4% with raltegravir at week 48.
  - VIKING-3: 4% with dolutegravir at week 48.

Cost and Cost-Effectiveness

The manufacturer submitted a cost-utility analysis in both treatment-naive and treatment-experienced (integrase inhibitor naive) patients, over a lifetime time horizon from the Canadian public-payer perspective. A micro-simulation approach was used in the economic model that allowed individual histories of accumulating events to influence the probability of disease progression, including factors such as CD4+ cell count, viral load, opportunistic infection prophylaxis status, age, gender and Framingham risk score. Simulated patients transitioned

through mutually exclusive health states, defined in terms of HIV with or without opportunistic infections, combined with cardiovascular disease health state. As patients passed through the model, they experienced the natural progression of HIV infection. The clinical outcomes included: HIV RNA < 50 copies/mL at week 48, viral suppression rate, monthly CD4+ cell count, and monthly rate of viral rebound (late failure rate).

In the treatment-naive analysis, dolutegravir was compared with the following first-line regimens: raltegravir + 2 nucleoside reverse transcriptase inhibitors (NRTIs), efavirenz/tenofovir/emtricitabine (Atripla), darunavir booster with ritonavir + 2 NRTIs, atazanavir boosted with ritonavir + 2 NRTIs, cobicistat/elvitegravir/emtricitabine/tenofovir (Stribild), emtricitabine/rilpivirine/tenofovir (Complera), and lopinavir boosted with ritonavir (LPV/r) + 2 NRTIs. Comparative clinical efficacy and safety were derived from clinical trials (dolutegravir versus Atripla [SINGLE]; dolutegravir versus raltegravir [SPRING-2]; and dolutegravir versus darunavir booster with ritonavir [FLAMINGO and STARTMRK]) and a network meta-analysis for other comparators.

In the treatment-experienced (but integrase inhibitor naive) analysis, dolutegravir was compared with raltegravir, and with OBT. Efficacy data were obtained from SAILING. A regimen of darunavir booster with ritonavir + tenofovir was assumed to be OBT based on the SAILING baseline population.

The manufacturer reported, for treatment-naive patients, dolutegravir was the dominant strategy (i.e., less costly and more effective) when compared with raltegravir + 2 NRTIs, Atripla, darunavir booster with ritonavir + 2 NRTIs and other indirect comparators (Complera, Stribild, atazanavir boosted with ritonavir + 2 NRTIs, and LPV/r + 2 NRTIs). In patients who are treatment-experienced (integrase naive), the manufacturer reported dolutegravir being the dominant strategy when compared with raltegravir, each in combination with OBT.

CDR noted the following limitations with the manufacturer's model; however, dolutegravir remained cost saving compared with most of the comparators:

- While surrogate outcomes are used in the economic model and linked to clinical outcomes, these surrogates are well-accepted markers of future clinical events, and are used by prescribers to influence treatment decisions.
- The cost of antiretroviral therapy is the key driver of costs (comprising ~87% of total costs). Antiretroviral therapy costs are lower for dolutegravir, driven by either lower drug acquisition costs of dolutegravir (in some but not all comparators), as well as a lower likelihood of treatment failure/resistance (associated with use of second through sixth-line therapies, which are more costly).
- The recommended daily dose of dolutegravir in patients who harbour the virus resistant to other integrase inhibitors is 50 mg twice daily ($37.00 per day). No economic information was provided for this patient population.

The economic attractiveness of dolutegravir is driven by the submitted price, at the recommended daily dose of 50 mg daily, dolutegravir ($18.50 per day) is less costly than raltegravir ($27.00 per day; 400 mg twice daily).

Other Discussion Points:

CDEC noted the following:

- Although the Health Canada indication for dolutegravir includes patients between 12 to 18 years of age, none of the RCTs included adolescents in this age group. Upon request, the manufacturer submitted a phase 1/2 open-label, non-comparative study (IMPAACT P1093) investigating the safety of dolutegravir + OBT in five age-defined cohorts, including 23 adolescents (≥ 12 to < 18 years of age) who had completed a 24-week study.
- Dolutegravir is not currently available as a component of any fixed-dose combination products; therefore, a regimen involving dolutegravir may have increased daily pill burden compared with some alternative treatment regimens. Studies of dolutegravir combined in a single tablet with backbone regimens are currently in development.
- FLAMINGO, a 96-week randomized, open-label phase 3 non-inferiority study compared dolutegravir 50 mg once daily with darunavir 800 mg plus ritonavir 100 mg (darunavir booster with ritonavir), a protease inhibitor regimen, once daily in treatment-naive patients. This trial was not included in the review because the study results were not available at the time of submission. At 48 weeks, dolutegravir was non-inferior and statistically superior to the darunavir booster with ritonavir for HIV RNA < 50 copies/mL, with no differences in EQ-5D and no treatment-emergent resistant mutations. The overall safety profile of dolutegravir was similar to darunavir booster with ritonavir over 48 weeks.

CDEC Members:

Dr. Robert Peterson (Chair), Dr. Lindsay Nicolle (Vice-Chair), Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Ms. Cate Dobhran, Mr. Frank Gavin, Dr. John Hawboldt, Dr. Peter Jamieson, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. James Silvius, and Dr. Adil Virani.

July 15, 2014 Meeting

Regrets:

None

Conflicts of Interest:

None

About this Document:

CDEC provides formulary listing recommendations or advice to CDR participating drug plans. CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CDEC deliberated on a review and made a recommendation or issued a record of advice. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CDEC deliberations.

The manufacturer has reviewed this document and has not requested the removal of confidential information in conformity with the *CDR Confidentiality Guidelines*.
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