



## CDEC FINAL RECOMMENDATION

### DARUNAVIR/COBICISTAT

(Prezcobix — Janssen Inc.)

**Indication: HIV-1, Treatment-Naive and Treatment-Experienced**

#### **Recommendation:**

The Canadian Drug Expert Committee (CDEC) recommends that darunavir/cobicistat (DRV/COBI) be listed for the treatment of HIV infection in treatment-naive and treatment-experienced patients without darunavir (DRV) resistance-associated mutations (RAMS), if the following condition is met:

#### **Condition:**

- List in a manner similar to darunavir (DRV)

#### **Reasons for the Recommendation:**

1. A 48-week, open-label, single-group study (GS-US-216-0130 [study 130]; N = 314) demonstrated that treatment with DRV/COBI in combination with nucleoside reverse transcriptase inhibitors (NRTIs) resulted in a significant proportion of patients achieving virologic success (i.e., HIV-1 ribonucleic acid (RNA) < 50 copies/mL) at 24 weeks (82.4%; 95% CI, 77.8% to 86.5%) and 48 weeks (80.8%; 95% CI, 76.0% to 85.0%).
2. At the submitted price (\$23.17 per tablet), the daily cost of treatment with DRV/COBI is similar to darunavir boosted with ritonavir (DRV/r) (\$23.18) and less than atazanavir boosted with ritonavir (ATV/r) (\$23.90).

#### **Of Note:**

- Study 130 did not include pediatric patients with HIV-1 infection, and DRV/COBI is not currently indicated for use in this population.

#### **Background:**

DRV/COBI is a fixed-dose combination product with a Health Canada indication for the treatment of HIV-1 infection in treatment-naive and treatment-experienced patients with no DRV RAMs, when administered in combination with other antiretroviral drugs. DRV/COBI is available as a fixed-dose combination tablet containing 800 mg DRV and 150 mg COBI, and the recommended dose is one tablet taken once daily with food.

### Summary of CDEC Considerations:

CDEC considered the following information prepared by the CADTH Common Drug Review (CDR): a systematic review of randomized controlled trials (RCTs) and pivotal studies of DRV/COBI, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group-submitted information about outcomes and issues that are 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:

- HIV affects patients in a variety of ways, which may include negative mental health outcomes, fatigue, difficulty maintaining diet and exercise routines, and work.
- Patients and caregivers noted the impact of social determinants of health, particularly living conditions, on the management of HIV with regard to medication adherence. The simplified dosing of DRV/COBI may increase adherence and convenience.

### Clinical Trials

The CDR systematic review included one phase 3, 48-week, open-label, single-group study. Study 130 (N = 314) evaluated the safety and efficacy of DRV/COBI as separate dosage forms administered in combination with two fully active NRTIs in treatment-naive (n = 295) and treatment-experienced (n = 18) HIV-1 infected patients with no DRV RAMs. The majority of patients (97%) were on a backbone regimen of emtricitabine/tenofovir.

### Outcomes

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

- Virologic success — percentage of patients with a viral load < 50 copies/mL using the FDA-defined snapshot analysis at 24 weeks (primary outcome) and 48 weeks (secondary end point) and using the FDA-defined time to loss of virologic response (TLOVR) algorithm (secondary end point).
- Reduction of log<sub>10</sub> viral load from baseline to week 48.
- Change in CD4+ cell count from baseline to week 48.
- Total adverse events, serious adverse events, withdrawals due to adverse events, and renal adverse events.

### Efficacy

- The proportion of treatment-naive patients achieving HIV-1 RNA viral load suppression below 50 copies/mL using the snapshot analysis with DRV/COBI was similar at week 24 (83.7%) and week 48 (82.7%). Similar results were demonstrated using the TLOVR analysis (week 24: 83.7%; week 48: 83.1%). The treatment-experienced cohort consisted of 18 patients, limiting the data on the efficacy of once-daily DRV/COBI for this patient population.
- [REDACTED]
- The mean (SD) increase from baseline in CD4+ cell count was 145 (131.6) cells/μL at week 24 and 194 (152.1) cells/μL at week 48 in treatment-naive patients. In treatment-

experienced patients, the mean (SD) increase was 99 (161.9) cells/ $\mu$ L at week 24 and 121 (157.0) cells/ $\mu$ L at week 48.

### **Harms (Safety and Tolerability)**

- A total of 4.8% and 8.3% of patients experienced a serious adverse event through week 24 and week 48, respectively.
- A total of 91.4% of patients experienced an adverse event of any severity through week 48. The most commonly reported adverse events included diarrhea (27.8%), headache (12.1%), nausea (23.0%), rash (15.7%), and upper respiratory tract infection (14.1%).
- A total of 16 (5.1%) treatment-naïve patients discontinued study treatment due to an adverse event through week 48.

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### **Cost and Cost-Effectiveness**

The manufacturer submitted a cost-minimization analysis comparing DRV/COBI with darunavir alone (800 mg) boosted with ritonavir (100 mg) (DRV/r), considering daily drug costs only. The assumption of similar efficacy for DRV/COBI and DRV/r was based on an adjusted comparison of study 130 with trials of DRV/r using non-standard methods that was submitted by the manufacturer. The manufacturer also considered the costs of other antiretroviral treatment (ART) regimens. These were based on the “Preferred,” “Alternate,” and “Other — Regimens that may be chosen but are less satisfactory than preferred and alternate regimens” as outlined in the US Department of Health and Human Services (HHS) guidelines for the use of antiretroviral drugs in HIV-1–infected adults and adolescents (February 2013).

CDR identified the following key limitation with the manufacturer’s economic submission: clinical data for DRV/COBI focus on bioequivalence studies, complicating the assessment of comparative clinical effectiveness compared with other treatments. As a result, the clinical equivalence of DRV/COBI with other treatments has not been established, which is the basis for a cost-minimization analysis.

At the submitted price of \$23.17 per 800 mg/150 mg tablet, the daily cost of DRV/COBI when used in combination with the backbone emtricitabine/tenofovir (\$50) is similar to that of both the HHS recommended initial ART protease inhibitor (PI)–based regimens (DRV/r and ATV/r, when used in combination with emtricitabine/tenofovir). Alternatively, when compared with single tablet integrase strand transfer inhibitor or non-nucleoside reverse-transcriptase inhibitors regimens, DRV/COBI plus emtricitabine/tenofovir is more expensive than rilpivirine/tenofovir/emtricitabine (\$9 more costly), efavirenz/tenofovir/emtricitabine (\$8 more costly), and elvitegravir/cobicistat/tenofovir/emtricitabine (\$6 more costly).

When backbone emtricitabine/tenofovir cannot be used, DRV/COBI may be used in combination with abacavir/lamivudine. The cost of this regimen (\$47) is equivalent to the other ART PI-based regimens with the same backbone drugs.

### Other Discussion Points:

CDEC noted the following:

- Study 130 is limited by the single-group design, which precluded an evaluation of the comparative effectiveness and safety of DRV/COBI versus other anti-HIV regimens.
- The treatment-experienced cohort of study 130 was small (n = 18, 5.7%), limiting the generalizability of the study findings to this patient population.
- There were no pediatric patients included in study 130; however, a phase 2/3 trial is currently under way to study the pharmacokinetics, safety, and efficacy of DRV/COBI and ATV/COBI in treatment-experienced HIV-1 patients between 3 and 18 years of age (NCT02016924).
- The results of study 130 are generally consistent with those seen in the trials of DRV/r in treatment-naïve and treatment-experienced patients.

### CDEC Members:

Dr. Lindsay Nicolle (Chair), Dr. James Silvius (Vice-Chair), Dr. Silvia Alessi-Severini, Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Mr. Frank Gavin, Dr. Peter Jamieson, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, and Dr. Adil Virani

### February 18, 2015 Meeting

#### Regrets:

Two CDEC members were unable to attend the meeting.

#### 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 requested the removal of confidential information. CADTH has redacted the requested confidential information in accordance with the *CDR Confidentiality Guidelines*.

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## Common Drug Review