# CDEC FINAL RECOMMENDATION

## DOLUTEGRAVIR/ABACAVIR/LAMIVUDINE
## (Triumeq — ViiV Healthcare ULC)
## Indication: HIV-1 infection

**Recommendation:**
The Canadian Drug Expert Committee (CDEC) recommends that dolutegravir (DTG)/abacavir (ABC)/lamivudine (3TC) be listed for the treatment of human immunodeficiency virus (HIV-1) infection in adults, if the following condition is met:

**Condition:**
- List in a manner similar to other HIV-1 treatment regimens.

**Reasons for the Recommendation:**
1. One randomized controlled trial (RCT) (SINGLE; N = 833) demonstrated that DTG 50 mg once daily in combination with ABC/3TC once daily (DTG+ABC/3TC) was statistically superior to efavirenz/tenofovir/emtricitabine (EFV/TDF/FTC) for virologic success.
2. A single combined formulated tablet of DTG 50 mg, ABC 600 mg, and 3TC 300 mg (DTG/ABC/3TC) has been shown to be bioequivalent to the individual components of DTG (50 mg) and ABC/3TC (600 mg/300 mg).
3. At the submitted price, DTG/ABC/3TC ($41.01 per day) is less costly than the individual components of DTG ($18.50 per day) and ABC/3TC ($23.62 per day) and less costly than other United States Department of Health and Human Services (DHHS)–recommended first-line single-tablet regimens (STRs), including EFV/TDF/FTC, emtricitabine/rilpivirine /tenofovir (FTC/RPV/TDF), and cobicistat/elvitegravir/emtricitabine/tenofovir (COBI/EVG/FTC/TDF) (cost savings ranging from $1 to $5 daily).

**Background:**
Triumeq is an STR that contains DTG (50 mg), ABC (600 mg), and 3TC (300 mg) and is indicated for the treatment of HIV-1 infection in adults. The recommended dose is one tablet once daily, taken with or without food.

**Summary of CDEC Considerations:**
CDEC considered the following information prepared by the CADTH Common Drug Review (CDR): a review of manufacturer-provided information on the therapeutic rationale, place in

therapy, bioequivalence, efficacy, and harms for combined use of DTG, ABC, and 3TC; a critique of the manufacturer's pharmacoeconomic evaluation; and information submitted by patient groups about outcomes and issues important to individuals living with HIV.

***Patient Input Information***

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

- Patients indicated that, while serious and potentially fatal, HIV is now usually a chronic disease, and progression can be effectively controlled with access and adherence to highly active antiretroviral treatment.
- Mental health problems — which can be side effects of HIV treatment or the results of stigma, discrimination, and related stress — are common in those living with this condition. Many people with HIV live in poverty, often in poor housing, and have a diminished quality of life. Incomes frequently drop because fatigue makes patients unable to work, or to work as much.
- Patients indicated they were satisfied with their current treatment regimens; however, they acknowledge the importance of having alternative treatments.
- Patients think a single tablet that needs to be taken only once daily and that does not have to be taken along with a meal will increase adherence rates, especially among patients who are poor and/or homeless.

***Clinical Trials***

The CDR review included one phase 3, double-blind, non-inferiority RCT (SINGLE) and one phase 1 bioequivalence study (ING114580). SINGLE was conducted in 833 antiretroviral drug-naive patients who were randomized (1:1) to either DTG 50 mg once daily in combination with ABC/3TC once daily, or to EFV/TDF/FTC once daily.

Study ING114580 was a single-centre, randomized, two-part, open-label, crossover study conducted in healthy adult patients to evaluate the bioequivalence of a single combined formulated tablet of DTG 50 mg, ABC 600 mg, and 3TC 300 mg compared with co-administration of the separate tablet formulations of DTG 50 mg and ABC/3TC in the fasted state, and to evaluate the effect of food on the bioavailability of the combined formulation. The treatment phase was divided into two periods (part A and part B). Part A consisted of two single-dose treatment sequences with a ≥ 7 day washout between doses. In part A, 62 participants received both treatments. Twelve subjects who completed part A participated in part B and received a single dose of DTG/ABC/3TC administered with a high-fat meal.

***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 ribonucleic acid (RNA) (viral load) < 50 copies/mL through week 48 using the 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 to have 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 to have not had a response.
- Virologic failure — the proportion of patients with plasma HIV RNA ≥ 50 copies/mL.

- EuroQol 5-Dimensions questionnaire (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.
- Bioequivalence — as defined by Health Canada's recommended criteria.
- 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.

***Efficacy (SINGLE)***

- The proportion of patients with < 50 copies/mL plasma HIV RNA was 88% in the DTG+ABC/3TC group and 81% in the EFV/TDF/FTC group with an adjusted difference of 7.4 (95% confidence interval [CI], 2.5 to 12.3) in the intention-to-treat analysis. In the per-protocol analysis, the proportions were 90% in the DTG+ABC/3TC group and 81% in the EFV/TDF/FTC group with an adjusted difference of 8.7 (95% CI, 3.9 to 13.4). DTG+ABC/3TC demonstrated non-inferiority and superiority to EFV/TDF/FTC at week 48.
- The proportion of patients with HIV RNA ≥ 50 copies/mL at week 48 was 5% and 6%, respectively, for the DTG+ABC/3TC and the EFV/TDF/FTC groups. In both groups, 7% of patients had HIV RNA ≥ 50 copies/mL at week 96.
- There was no statistically significant difference in EQ-5D between the DTG+ABC/3TC and the EFV/TDF/FTC groups at week 48 ($P$ = 0.891) and week 96 ($P$ = 0.516).
- The proportion of patients who experienced HIV-related morbidity was 3% with DTG+ABC/3TC versus 4% with EFV/TDF/FTC at week 48, and 5% with DTG+ABC/3TC versus 6% with EFV/TDF/FTC at week 96.

***Harms (SINGLE)***

- The proportion of patients with at least one adverse event was:
  - Week 48: 89% with DTG+ABC/3TC and 92% with EFV/TDF/FTC
  - Week 96: 91% with DTG+ABC/3TC and 94% with EFV/TDF/FTC.
- The proportion of patients who reported at least one serious adverse event was:
  - Week 48: 9% with DTG+ABC/3TC and 8% with EFV/TDF/FTC
  - Week 96: 11% with DTG+ABC/3TC and 12% with EFV/TDF/FTC.
- The proportion of patients discontinuing due to adverse events at 48 and 96 weeks was lower for patients treated with DTG+ABC/3TC (2% and 3%, respectively) compared with EFV/TDF/FTC (10% and 12%, respectively).

***Bioequivalence (ING114580)***

- DTG/ABC/3TC (50 mg/600 mg/300 mg) demonstrated bioequivalence to DTG (50 mg) and ABC/3TC (600 mg/300 mg). The 90% CIs for the geometric least squares mean ratios for the area under the curve and the maximum observed concentration ($C_{max}$) were within Health Canada's recommended range of 0.8 to 1.25.
- Health Canada granted the approved indication primarily based on the established bioequivalence of DTG/ABC/3TC to the existing approved DTG+ABC/3TC products.

***Cost and Cost-Effectiveness***

The manufacturer submitted a comparison of drug costs for DTG/ABC/3TC and costs for the individual components of DTG and ABC/3TC. At the submitted price of $41.01 per tablet, DTG/ABC/3TC is cost-saving ($1 daily) compared with the sum of the costs of the individual components DTG ($18.50) and ABC/3TC ($23.62), and is less costly than other fixed-dosed combination products that may be displaced, including EFV/TDF/FTC ($43.25), FTC/RPV/TDF ($42.53), and COBI/EVG/FTC/TDF ($45.52) — cost savings range from $1 to $5 daily.

**Other Discussion Points:**

CDEC noted the following:

- DTG/ABC/3TC is not associated with significant cytochrome P450 3A enzyme interactions.
- The components of DTG/ABC/3TC are currently recommended as first-line treatments for HIV infection in the most recent edition of the United States DHHS guidelines.

**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.

**March 18, 2015 Meeting**

**Regrets:**

One CDEC member was 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 not requested the removal of confidential information.

The CDEC recommendation or record of advice neither takes the place of a medical professional providing care to a particular patient nor is it intended to replace professional advice.

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