CADTH

CADTH COMMON DRUG REVIEW

CADTH Canadian Drug Expert Committee Recommendation

(Final)

TENOFOVIR ALAFENAMIDE (VEMLIDY — GILEAD SCIENCES CANADA, INC.)
Indication: Chronic Hepatitis B

RECOMMENDATION
The CADTH Canadian Drug Expert Committee (CDEC) recommends that tenofovir alafenamide (TAF) be reimbursed for the treatment of chronic hepatitis B in adults with compensated liver disease, if the following condition is met:

Condition
- The drug plan cost of TAF should not exceed that of the lowest-cost preparation of tenofovir disoproxil fumarate (TDF).

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- The drug plan cost of TAF should not exceed that of the lowest-cost preparation of tenofovir disoproxil fumarate (TDF).

Reasons for the Recommendation

1. In two manufacturer-sponsored, multi-centre, double-blind randomized controlled trials (RCTs) comparing TAF with TDF in patients with chronic hepatitis B (hepatitis B e antigen [HBeAg]-negative patients in Study 108, N = 426, and HBeAg-positive patients in Study 110, N = 875), the proportion of patients who achieved undetectable hepatitis B virus (HBV) DNA with TAF was noninferior to TDF in Study 108 (94.0% versus 92.9% at week 48) and in Study 110 (63.9% versus 66.8% at week 48). This was based on a noninferiority margin set at –10% for the lower boundary of the 95% confidence interval (CI) of the difference between TAF and TDF. The proportion of patients who achieved undetectable HBV DNA at 96 weeks, who experienced hepatitis B surface antigen (HBsAg) loss, or who experienced HBeAg loss or seroconversion (Study 110 only), was similar between TAF and TDF treatment arms.
2. The annual cost of TAF ($7,137 per patient) is $5,353 more than that of the lowest-cost preparation of TDF available ($1,784 per patient). The manufacturer submitted a cost analysis assuming equivalent efficacy and safety between TAF and TDF. Thus, it was impossible to assess the cost-effectiveness of TAF versus TDF considering the two drugs' potential advantages or disadvantages in terms of adverse event profile over the long term.

Discussion Points

- CDEC noted that the TAF formulation allows patients to receive a lower dosage than the TDF formulation yet achieve therapeutic levels of tenofovir, thereby reducing systemic exposure to tenofovir. This implies that TAF has the potential to reduce the toxicity associated with TDF, particularly the bone and renal effects. Although both studies identified a smaller per cent reduction in bone mineral density, both in the spine and hip, after 48 weeks in the TAF group versus the TDF group, the clinical significance of these differences is uncertain.
- CDEC noted that the proportion of patients with grade 3 events of elevated fasting low-density lipoprotein cholesterol (LDL-C) was numerically higher in patients receiving TAF compared with TDF in Study 108 and in Study 110. The importance of lipid effects in the context of life-long therapy is an important safety consideration; however, it is unclear whether these numerical differences represent a harm related to TAF therapy, whether TDF has lipid-lowering properties that TAF does not possess, or both. Furthermore, it is unclear whether these numerical differences translate into an increased risk of cardiovascular events.

Background

TAF has a Health Canada–approved indication for the treatment of chronic hepatitis B in adults with compensated liver disease. TAF is a prodrug of tenofovir, a DNA polymerase inhibitor. It is available as a 25 mg tablet, and the Health Canada–recommended dose is 25 mg daily, to be taken with or without food.

Summary of CDEC Considerations

The committee considered the following information prepared by the CADTH Common Drug Review (CDR): a systematic review of double-blind RCTs of TAF and a critique of the manufacturer's pharmacoeconomic evaluation. The committee also considered input from a clinical expert with experience treating patients with chronic hepatitis B, and information submitted by patient groups about outcomes and issues important to patients.

Patient Input Information

Two patient groups, the Canadian Liver Foundation (CLF) and the Hepatitis C Education & Prevention Society (HepCBC), provided input for this submission. For the CLF submission, patient perspectives were obtained from patients, caregivers, and health care professionals through an online questionnaire. For the HepCBC submission, two authors contributed to the submission (one author was a researcher and a patient advocate, and the other author was living with hepatitis C). The following is a summary of key input from the perspective of the patient groups:

- Patients with chronic hepatitis B expressed concern about the disease causing damage to their liver that goes relatively undetected until complications such as cirrhosis and hepatocellular carcinoma arise. The disease carries a social stigma that may limit their employment prospects, as well as relationships, plans for immigration, and eligibility for loans and life insurance.
- Patients identified a significant psychological burden associated with the potential for passing the virus on to family members. As the disease progresses and complications arise, this can have a significant burden on caregivers.
- Patients identified avoidance of liver cancer and bone disease and preservation of liver and kidneys as important unmet needs of current therapy. One health professional responding to the survey described the current therapies available for chronic hepatitis B as suboptimal; however, patients did not elaborate on these limitations from their perspective.

Clinical Trials

The CDR systematic review included two double-blind RCTs of patients with chronic hepatitis B.

Study 108 included 426 patients with a diagnosis of chronic hepatitis B who were HBeAg-negative, and Study 110 included 875 patients with a diagnosis of chronic hepatitis B who were HBeAg-positive, for at least six months in both studies. Patients in both studies could be either treatment-naive or treatment-experienced. Patients were randomized 2:1 to either TAF 25 mg daily or TDF 300 mg daily. At the time of this review, the studies were both ongoing, as the double-blind treatment phase had been extended, first, from 48 weeks to 96 weeks, and then from 96 weeks to 144 weeks under two protocol amendments. Approximately half of the original randomized population had completed 96 weeks of treatment by the time of the second protocol amendment. Therefore, only half of the population will have 144-week data, and this analysis was not yet available to CDR at the time of this submission.

The main limitations of both trials were that they were not designed to assess key clinical outcomes such as morbidity and mortality, and the assessment of the key safety outcome of bone disorders relied on bone mineral density, a surrogate marker. No adjustments for multiple statistical comparisons were made for the 96-week data or for assessments of liver health (liver enzymes, fibrosis), increasing the risk of type I error.

Outcomes

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

- HBV DNA: the proportion of patients with undetectable virus (HBV DNA < 29 IU/mL) at week 48
- Fibrosis: assessed by FibroTest (composite of five serum biochemical parameters — alpha-2-macroglobulin, apolipoprotein A1, haptoglobin, L-glutamyltranspeptidase, and bilirubin)
- Bone health: assessed using hip and spine bone mineral density measured by dual-energy X-ray absorptiometry

- Renal function: assessed using serum creatinine, estimated glomerular filtration rate (eGFR) (three different formulas: Cockcroft-Gault, Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] creatinine, and cystatin-C equations), protein, retinol-binding protein, and beta-2 microglobulin
- Alanine aminotransferase (ALT) normalization: defined as ALT greater than the upper limit of normal (ULN) (by central laboratory normal range or American Association for the Study of Liver Diseases [AASLD] normal range) at baseline, but within normal range at a post-baseline visit
- Lipid measures: events graded as grade 0, grade 1 (mild), grade 2 (moderate), grade 3 (severe), or grade 4 (life-threatening) using criteria specified in the protocol
- Adverse events, serious adverse events, and withdrawals due to adverse events.

The primary outcome in both trials was the proportion of patients with HBV DNA of < 29 IU/mL at 48 weeks, testing the noninferiority of TAF to TDF, with the margin for noninferiority set at –10% for the lower boundary of the 95% CI of the difference between TAF and TDF. Health-related quality of life was not assessed in either of the studies. In their input to CDR, patient groups were concerned about the serious long-term sequelae associated with chronic hepatitis B, most notably hepatocellular carcinoma and cirrhosis, and the included studies were not designed to assess these outcomes.

Efficacy

In both studies, TAF was noninferior to TDF for the primary outcome, the proportion of patients with undetectable HBV DNA at 48 weeks. At week 48, 94.0% of TAF patients and 92.9% of TDF patients had undetectable HBV DNA in Study 108, and 63.9% of TAF patients and 66.8% of TDF patients had undetectable HBV DNA in Study 110. There was no statistically significant difference between TAF and TDF groups after 48 weeks in either Study 108 (difference in proportions between groups of 1.8%; 95% CI, −3.6% to 7.2%]) or Study 110 (–3.6%; 95% CI, –9.8% to 2.6%). Criteria for noninferiority were met in both studies, as the lower boundary of the 95% CI of the difference in proportions between groups was greater than –10%. Similar results were observed at 96 weeks, with no statistically significant difference between groups in each study. There were very few clinical events (deaths, hepatic-related morbidity), and no clear differences in the proportion of patients experiencing these events between groups.

Serologic responses were not statistically significantly different between TAF and TDF groups. Other clinical outcomes, such as ALT normalization and fibrosis, were not adjusted for multiple comparisons. Therefore, although there was some evidence of an improvement for patients receiving TAF versus TDF, these findings should be considered hypothesis-generating.

Harms (Safety and Tolerability)

In Studies 108 and 110, there were similar overall adverse events and similar serious adverse events with TAF and with TDF after 96 weeks.

The effects of TAF on bone and renal health were assessed as secondary safety outcomes in both studies. Statistically significant improvements in bone mineral density (hip or spine) were reported for TAF versus TDF at 48 weeks, and there was a smaller increase in serum creatinine for TAF versus TDF in Study 110, but not in Study 108. However, the impact of these findings over the long term remains uncertain.

There were numerically more patients in the TAF treatment group than in the TDF group who experienced grade 3 events of elevated LDL-C in both studies (Study 108: [redacted] versus [redacted], and Study 110: [redacted] versus [redacted]). The impact of this finding on long-term cardiovascular risk remains uncertain.

Cost and Cost-Effectiveness

The manufacturer submitted a price of $19.55 per 25 mg tablet of TAF. At the recommended dosage of 25 mg per day, the daily cost is $19.55 per patient.

The manufacturer submitted a cost analysis comparing the cost of 25 mg of TAF daily to that of 300 mg of TDF daily, using Ontario Drug Benefit (ODB) Formulary list prices. The perspective was that of a public drug payer, and the time horizon was one day of

therapy. Only drug acquisition costs were included, as all other costs and resource use were assumed to be equal. The manufacturer assumed similar efficacy between TAF and TDF in both HBeAg-positive and HBeAg-negative patients on the basis of the two RCTs. The manufacturer also stated that, although TAF was designed to reduce potential toxicity associated with TDF, particularly bone and renal effects, the harms associated with TAF would conservatively be considered equivalent to TDF for the purposes of the cost analysis. The manufacturer reported that, at an ODB list price of $19.55 per 300 mg tablet for TDF, the submitted daily cost of TAF is equivalent.

CDR identified the following key limitations in the manufacturer's analysis:

- Newly available generic formulations of TDF were not considered.
- The assumption of clinical similarity is uncertain because of potential differences in adverse event profiles.
- The method of analysis is inappropriate given potential differences in clinical outcomes.
- Entecavir was not included as a comparator.

Reanalyses conducted by CDR included the cost of generic TDF and extended the analysis time horizon to one year. As generic TDF is listed on the ODB Formulary at $4.89 per 300 mg tablet, the annual cost of TAF ($7,137 per patient) is $5,353 more than that of TDF ($1,784 per patient). Differences in adverse events were excluded from the manufacturer's analysis, and, thus, it was impossible to assess the cost-effectiveness of TAF compared with TDF.

CDEC Members

Dr. James Silvius (Chair), Dr. Silvia Alessi-Severini, Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Peter Jamieson, Dr. Anatoly Langer, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

February 21, 2018 Meeting

Regrets

One CDEC member did not attend.

Conflicts of Interest

None