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CADTH COMMON DRUG REVIEW

Pharmacoeconomic Review Report

TENOFOVIR ALAFENAMIDE (VEMLIDY)

(Gilead Sciences Canada, Inc.)

Indication: Treatment of chronic hepatitis B in adults with compensated liver disease

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Abbreviations

CHB	chronic hepatitis B
CDR	CADTH Common Drug Review
HBeAg	hepatitis B e-antigen
HBV	hepatitis B virus
ODB	Ontario Drug Benefit
RCT	randomized controlled trial
TAF	tenofovir alafenamide
TDF	tenofovir disoproxil fumarate

Drug	Tenofovir alafenamide (Vemlidy)
Indication	Treatment of chronic hepatitis B in adults with compensated liver disease
Listing request	As per indication
Dosage form(s)	25 mg tablet
NOC date	May 17, 2017
Manufacturer	Gilead Sciences Canada, Inc.

Executive Summary

Background

Tenofovir alafenamide (TAF, Vemlidy) is a prodrug of tenofovir, which is indicated for the treatment of chronic hepatitis B (HBV) in adults with compensated liver disease.[1] The manufacturer submitted a price of $19.55 per 25 mg tablet, which, at the recommended dose of 25 mg daily, costs $19.55 per patient per day.

Another prodrug of tenofovir, tenofovir disoproxil fumarate (TDF), has been marketed in Canada since 2004 and received a Notice of Compliance from Health Canada for the treatment of HBV in 2008.[2] TDF was reviewed by CADTH Common Drug Review (CDR) for this indication in 2008 and received a recommendation for reimbursement for the treatment of chronic hepatitis B (CHB) infection in adult patients with cirrhosis with an HBV DNA concentration above 2,000 IU/mL.[3]

TAF was previously reviewed by CDR as a component of three combination products for the treatment of HIV: Descovy, Genvoya, and Odefsey.[4-6] If TAF-containing regimens were more expensive than similar TDF-containing regimens, CDR recommended that TAF-containing regimens be reimbursed if the cost did not exceed that of similar regimens including TDF.[4,5]

Summary of the Economic Analysis Submitted by the Manufacturer

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) list prices (as of September 1, 2017). 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 to TDF in both hepatitis B e-antigen (HBeAg)-positive and -negative patients on the basis of two randomized controlled trials.[7,8] The manufacturer also stated that, although TAF was designed to reduce potential toxicity associated with TDF, particularly bone and renal effects, the safety of TAF would conservatively be considered equivalent to TDF for the purposes of the economic analysis.[9]

The manufacturer reported an ODB list price of $19.55 per 300 mg tablet for TDF; the submitted daily cost of 25 mg TAF is equivalent.[9] Other provincial list prices ranged from $18.48 to $19.55 per day for TDF. The manufacturer also noted that the ODB list price of entecavir, another commonly used oral HBV antiretroviral, was $16.50 daily, but that entecavir had a much smaller market share than TDF. No sensitivity analyses were conducted. The manufacturer did not consider the price of the newly available TDF generics in its submitted analysis.[9]

Key Limitations

Newly available generic: Generic forms of TDF 300 mg received Health Canada approvals for chronic HBV indications beginning in July 2017 and were added to the ODB formulary in September 2017 as general benefits, interchangeable with branded TDF. The manufacturer did not consider the generic TDF in its cost comparison. Currently, ODB reimburses TDF only to the list price of the least expensive generic, regardless of the brand dispensed. This reduces the daily cost to ODB of the manufacturer's chosen comparator from $19.55 to $4.89.

Clinical similarity uncertain due to adverse event profile: The manufacturer indicated TAF was specifically designed to reduce potential toxicity associated with TDF, particularly bone and renal effects. Bone-related harms were numerically smaller in the TAF group in both studies, and both studies showed statistically significantly smaller reductions in bone mineral density. However, as only surrogate markers were captured, the clinical significance of these results is unknown. Few renal harms were noted over the length of the included studies, although TAF was associated with numerically smaller decreases in glomerular filtration rates and with smaller increases in serum creatinine. Patients in the TAF group were, however, more likely to have higher low-density lipoprotein cholesterol (LDL-C) levels than those using TDF, which may or may not outweigh potential benefits in other outcomes. The clinical significance of these findings in terms of relative health outcomes and patient quality of life is unknown.

Inappropriate method of analysis: The manufacturer's economic conclusions state that TAF has efficacy and improved safety comparable to those of TDF; however, no attempt has been made to quantify these differences to allow for an assessment of cost-effectiveness. Where clinical differences are believed to exist, a cost-utility analysis is appropriate to assess cost-effectiveness.

Missing comparator of interest: The manufacturer's analysis considered branded TDF to be the only comparator of interest. Entecavir was mentioned in the submitted report but not included, as it was deemed irrelevant by the manufacturer because of its smaller market share. The clinical expert consulted by CDR agreed that, of the oral antiretrovirals indicated for the treatment of HBV in Canada (adefovir, entecavir, lamivudine, telbivudine, and TDF), TDF and entecavir were the most relevant comparators for the indicated population. However, the expert did not agree that entecavir was a less appropriate comparator than TDF, with the exception of patients infected with lamivudine-resistant HBV strains. However, given physician prescribing patterns and the availability of comparative data, TAF may be more likely to be prescribed to patients who would otherwise receive TDF as it enters the market, rather than to those who would otherwise receive entecavir.

Insufficient time horizon: The manufacturer's choice of a one-day time horizon is insufficient to reflect cost differences between comparators at a scale relevant to public payer decision-makers.

Results / Conclusions

With the availability of generic TDF, public drug plans now reimburse TDF only to the cost of the generic; patients wanting branded TDF must pay the difference themselves or through private insurance. TAF may confer advantages or disadvantages in terms of adverse event profile compared with TDF; however, the manufacturer did not attempt to quantify the probability or magnitude, and thus an assessment of the cost-effectiveness of TAF compared with TDF or its other comparators is not possible. From a public payer perspective, the annual cost of TAF ($7,137 per patient) is $5,353 more than that of TDF ($1,784 per patient).

Cost Comparison Table

Clinical experts have deemed the comparator treatments presented in Table 1 to be appropriate. Comparators may be recommended (appropriate) practice rather than actual practice. Comparators are not restricted to drugs but may include devices or procedures. Costs are manufacturer's list prices, unless otherwise specified. Existing Product Listing Agreements are not reflected in the table and, as a result, the table may not represent the actual costs to public drug plans.

Table 1: Cost Comparison Table for Chronic Hepatitis B

Drug / Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Average Daily Drug Cost ($)	Average Annual Drug Cost ($)
Tenofovir alafenamide (Vemlidy)	**25 mg**	**Tab**	**19.5537**[a]	**25 mg daily**	**19.56**	7,137
Tenofovir disoproxil (Viread and generics)	300 mg	Tab	4.8884	300 mg daily	4.89	1,784
Adefovir dipivoxil (generic)	10 mg	Tab	20.4400	10 mg daily	20.44	7,461
Entecavir (generics)	0.5 mg	Tab	16.5000	0.5 mg daily Lamivudine-resistant: 1 mg daily	16.50 33.00	6,022 12,045
Lamivudine (generic)	100 mg	Tab	3.5316	100 mg daily	3.53	1,289
Telbivudine (Sebivo)	600 mg	Tab	18.6907[b]	600 mg daily	18.69	6,822
Interferons						
Interferon alpha-2b (Intron A)	18 million IU 30 million IU 60 million IU	Pen kit	218.7600[c] 364.6000[c] 729.1900[c]	HBeAg+ 5 MIU daily or 10 MIU three times weekly SC/IM for 16 to 24 weeks[d] HBeAg- 5-10 MIU three times weekly SC/IM for 1 to 2 years; discontinue after 12 weeks if no response[d]	52.09 to 60.78 25.97 to 52.94	5,834 to 10,209 per course 9,479 to 18,959 per year
Pegylated interferon alpha-2a (Pegasys)	180 mcg/0.5 mL 180 mcg/mL	Pre-filled syringe Vial	407.3900	180 mcg once weekly 24 to 48 weeks[d]	58.20	9,777 to 19,554 per course

HBeAg = hepatitis B e-antigen; IM = intramuscular; SC = subcutaneous.

Note: All prices are from the Ontario Drug Benefit Formulary (accessed November 2017), unless otherwise indicated, and do not include dispensing fees.

[a] Manufacturer's submitted price.

[b] QuintilesIMS Delta PA wholesale price (retrieved November 2017).[10]

[c] Saskatchewan Formulary (November 2017).

[d] Management of chronic hepatitis B: Canadian Association for the Study of the Liver consensus guidelines.[11]

Appendix 1: Price Reduction Analysis

As the manufacturer's submission deferred consideration of the newly available generic tenofovir disoproxil fumarate (TDF) as a comparator until price negotiations, CADTH Common Drug Review quantified how much the price of tenofovir alafenamide (TAF) would need to be reduced to be considered cost-neutral to TDF in a cost analysis. As of September 28, 2017, the Ontario Drug Benefit Formulary reimburses TDF, regardless of brand, at a list price of $4.8884. Thus, the manufacturer is, in effect, requesting a price premium for TAF compared with TDF. To be considered cost-neutral, the submitted price of TAF would need to be reduced by 75% (Table 2).

Table 2: CDR Price Reduction Analysis for TAF Compared With Generic TDF

Price Reduction (%)	Daily Cost of TAF at Reduced Price (%)	Daily Cost of TDF[a] ($)	Daily Incremental Cost of TAF Versus TDF ($)	Annual Incremental Cost of TAF Versus TDF ($)
Submitted Price	19.55	4.89	14.67	5,353
10	17.60		12.71	4,639
20	15.64		10.75	3,925
30	13.69		8.80	3,212
40	11.73		6.84	2,498
50	9.78		4.89	1,784
60	7.82		2.93	1,071
70	5.87		0.98	357
75	4.89		0.00	0
80	3.91		–0.98	–357
90	1.96		–2.93	–1,071

CDR = CADTH Common Drug Review; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate.

[a] Ontario Drug Benefit Formulary list price of generic TDF (November 2017).

Appendix 2: Reviewer Worksheets

Table 3: Summary of Manufacturer's Submission

Drug product	**Tenofovir alafenamide (Vemlidy)**
Treatment	TAF 25 mg daily
Comparator(s)	TDF 300 mg daily
Study question	What is the cost of TAF compared with TDF in patients with HBV infection?
Type of economic evaluation	Cost analysis
Target population	Patients with HBV
Perspective	Health care system, i.e., a public drug payer
Outcome(s) considered	Drug cost
Key data sources	
Cost	Manufacturer's submitted price Provincial drug plan list prices for comparator
Clinical efficacy	Two RCTs comparing TAF with TDF in HBeAg-positive[8] and HBeAg-negative[7] HBV patients
Harms	Two RCTs comparing TAF with TDF in HBeAg-positive[8] and HBeAg-negative[7] HBV patients
Time horizon	Single day
Results for base case	At the submitted price of $19.55, the manufacturer reported TAF as priced at parity with branded TDF in Ontario, but more expensive than entecavir.

HBV = hepatitis B virus; HBeAg = hepatitis B e-antigen; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate.

Manufacturer's Results

The manufacturer submitted a cost analysis comparing the cost of 25 mg of tenofovir alafenamide (TAF) daily with that of 300 mg of tenofovir disoproxil fumarate (TDF) daily, using Ontario Drug Benefit (ODB) list prices (as of September 1, 2017). 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 that efficacy was noninferior to TDF in both hepatitis B e-antigen (HBeAg)-positive and -negative patients on the basis of two randomized controlled trials.[7,8] The manufacturer also stated that, although TAF was designed to reduce potential toxicity associated with TDF, particularly bone and renal effects, the safety of TAF would "conservatively" be considered equivalent to TDF for the purposes of the economic analysis.

The manufacturer reported an ODB list price of $19.55 per 300 mg TDF tablet, equivalent to the submitted daily cost of 25 mg TAF. Other provincial list prices ranged from $18.49 to $19.55 per day for TDF (Table 4). The manufacturer did not present incremental costs; these have been added by CADTH Common Drug Review (CDR) for convenience.

Table 4: Manufacturer's Cost Comparison of TAF to TDF Across Provincial Jurisdictions

Jurisdiction	Daily Cost of TAF at Submitted Price ($)	Daily Cost TDF at Listed Price ($)	Incremental Daily Cost of TAF
Manitoba, Newfoundland and Labrador, Nova Scotia, Ontario, Prince Edward Island	19.5537	19.5537	0
British Columbia, New Brunswick		19.4467	0.0870
Saskatchewan		18.7680	0.7857
Alberta		18.4880	1.0657

TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate.

Adapted from Manufacturer's economic submission, Table 4.[9] Incremental cost calculated by CDR. Original pricing source uncited.

The manufacturer also noted that the ODB list price of entecavir, another commonly used oral antiretroviral for the treatment of hepatitis B virus, was $16.50 daily (see Table 5), but did not consider it an important comparator, stating that "[TDF] is overwhelmingly preferred by clinicians with 68% of the HBV market share." The manufacturer indicated that approximately 10% of patients use each of adefovir, entecavir, and lamivudine (data from July 2017).[12] However, it was unclear whether these data were restricted to patients reimbursed by public plans.[12] Of note, generic TDF was not available on the public drug plans as of July 2017.

Table 5: Manufacturer's Cost Comparison of TAF With Entecavir in Ontario

Jurisdiction	Daily Cost TAF at Submitted Price ($)	Daily Cost Entecavir at Listed Price ($)	Incremental Daily Cost of TAF ($)
Ontario	19.5537	16.5000	3.0537

TAF = tenofovir alafenamide fumarate.

Adapted from Manufacturer's economic submission, page 10.[9] Incremental cost calculated by CDR. Original pricing source uncited (presumed ODB Formulary directly).

No sensitivity analyses were conducted.

CADTH Common Drug Review Results

CDR reanalyses include extending the time horizon to one year and including generic TDF as a comparator, as reimbursement of the generic was reported by Ontario, New Brunswick, British Columbia, and Saskatchewan beginning in the third quarter (July to September) of 2017, and all 10 provinces have formulary prices listed for generic TDF as of November 2017.

Table 6: CDR's Cost Comparison of TAF With Generic TDF Across Provincial Jurisdictions

Jurisdiction	Daily Cost of TAF at Submitted Price ($)	Daily Cost of TDF at Listed Price ($)	Annual Cost of TAF ($)	Annual Cost of TDF ($)	Incremental Annual Cost of TAF Versus TDF
Newfoundland and Labrador	19.5537	5.3284	7,137	1,945	5,192
British Columbia		5.2795		1,927	5,210
Prince Edward Island		5.1817		1,891	5,246
Alberta, Manitoba, New Brunswick, Nova Scotia, Ontario, Quebec, Saskatchewan		4.8884		1,784	5,353

TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate.

Adapted from Manufacturer's economic submission, Table 4.[9] Incremental cost calculated by CDR. Price source IQVIA Delta PA (November 2017).[10]

Using Ontario pricing, at the submitted price, the annual cost of TAF ($7,137 per patient per year) is $5,353 more than that of TDF ($1,784 per patient per year). A price-reduction scenario in Table 2 explores the relative cost of TAF, assuming various discounts on the submitted price.

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