CEDAC FINAL RECOMMENDATION and REASONS for RECOMMENDATION

TENOFOVIR DISOPROXIL FUMARATE (Viread® – Gilead Sciences Canada, Inc.) New Indication: Chronic Hepatitis B Infection

Description:

Tenofovir is a nucleotide reverse transcriptase HBV polymerase inhibitor approved for use by Health Canada for the treatment of adult patients with chronic hepatitis B infection. The Canadian Expert Drug Advisory Committee previously reviewed tenofovir for HIV-1 infection (see Notices of CEDAC Final Recommendation on Reconsideration August 25, 2004 and March 15, 2006).

Dosage Forms:

Supplied as tablets containing 300 mg tenofovir disoproxil fumarate. The recommended dose is 300 mg taken once daily.

Recommendation:

The Canadian Expert Drug Advisory Committee recommends that tenofovir be listed for the treatment of chronic hepatitis B infection in patients with cirrhosis documented on radiologic or histologic grounds and a HBV DNA concentration above 2000 IU/mL.

Reasons for the Recommendation:

1. In two randomized controlled trials (RCTs), treatment with tenofovir resulted in statistically significant improvements in hepatitis B viral suppression in hepatitis B e antigen negative (HBeAg-) and hepatitis B e antigen positive (HBeAg+) patients, compared to adefovir. As well, histologic response rates were similar between tenofovir and adefovir groups.
2. Resistance to tenofovir in nucleos(t)ide-naïve and experienced patients was not observed during the randomized phases of the tenofovir trials and only two cases were reported during the open-label extension phases up to 96 weeks.
3. The annual cost of tenofovir at a dose of 300 mg daily is $6,109, compared to $1,865 for lamivudine. The manufacturer submitted an economic evaluation based on a mixed treatment comparison meta analysis. They estimated an incremental cost per quality adjusted life year (QALY) of $48,700 in patients who were nucleos(t)ide naïve with cirrhosis over a 10 year time horizon for a regimen of tenofovir followed by lamivudine compared to lamivudine followed by best supportive care. In patients without cirrhosis, the incremental cost per QALY provided by the manufacturer increased to $96,300 for this same treatment regimen.

Summary of Committee Considerations:
The committee considered a systematic review that included two randomized double blind active-controlled trials of 48 weeks duration, GS-0102 (n=382) and GS-0103 (n=272). Both trials evaluated the non-inferiority and superiority of tenofovir 300 mg once daily compared with adefovir 10 mg once daily in patients with HBV mono-infection. Patients with decompensated liver disease were excluded. GS-0102 was conducted in HBeAg- patients who were either nucleos(t)ide naïve or nucleoside experienced; GS-0103 was conducted in HBeAg+ patients who were nucleos(t)ide naïve. Only six patients across two RCTs had documented resistance to lamivudine at baseline. Therefore, there was insufficient evidence of clinical effectiveness or cost-effectiveness of tenofovir in patients with lamivudine resistance. Patients with and without cirrhosis were included in both trials.

The primary outcome in the trials was the proportion of patients who achieved both HBV DNA < 400 copies/mL and a histologic response (at least a 2-point decrease in Knodell necroinflammatory score without worsening in the Knodell fibrosis score). Other efficacy outcomes in the studies were viral rebound, s antigen loss, s antigen seroconversion, e antigen loss, e antigen seroconversion and resistance to tenofovir (defined as conserved site HBV polymerase mutations plus viral rebound). Quality of life was not measured in either of the included trials.

In both studies, a greater proportion of patients in the tenofovir group achieved the primary outcome. The magnitude of the effect was greater in the study involving HBeAg+ patients compared to the study involving HBeAg- patients (absolute risk reduction: 54% and 24%, respectively). Viral suppression rates were statistically significantly higher in patients taking tenofovir compared to adefovir. The 'complete response' outcome was influenced primarily by viral load suppression since the histologic response rates were similar between tenofovir and adefovir groups. Viral rebound was low and similar between tenofovir and adefovir in HBeAg+ patients, but statistically significantly lower for tenofovir in HBeAg- patients.

Three HBeAg- patients receiving tenofovir were diagnosed with hepatocellular carcinoma. There were no other reports of hepatic-related morbidity or liver transplantation. No deaths were reported during the double-blind portion of the study. Serious adverse events were infrequent and not statistically significant between tenofovir and adefovir in either trial. None were related to renal function or hepatic steatosis; one patient receiving tenofovir had a fracture. Withdrawals, and withdrawals due to adverse events were low and not statistically different. Nausea and arthralgia were reported statistically more frequently with tenofovir than adefovir in HBeAg+ and HBeAg- patients, respectively.

The manufacturer submitted a cost-utility analysis comparing tenofovir to adefovir and entecavir (alone or in combination with lamivudine), lamivudine, and best supportive care in three patient groups [nucleos(t)ide naive patients without cirrhosis, nucleos(t)ide naive patients with cirrhosis, and lamivudine resistant patients] over a lifetime (33 year) time horizon. Clinical inputs were based on a mixed treatment comparison meta analysis performed by the manufacturer, based on 23 RCTs identified through a systematic review. CDR reviewers noted that the results were sensitive to changes in the analysis time frame and that the model was based on a number of assumptions regarding the long term efficacy of tenofovir and the efficacy in patients with lamivudine resistance. CDR was unable to conduct re-analyses for these variables as a result of the modeling approach used by the manufacturer. When considering a 10-year time horizon, the manufacturer reported incremental cost per QALY estimates of $48,700 in nucleos(t)ide naïve patients with cirrhosis, $96,300 in nucleos(t)ide naive patients without cirrhosis, $120,200 in patients resistant to lamivudine.

The daily cost of tenofovir ($16.74) is greater than that of lamivudine ($5.11), and less than telbivudine ($17.00), entecavir ($23.17 or $46.34 for lamivudine resistance), and adefovir ($23.17).

Of Note:

1. Both published and unpublished data were reviewed and taken into consideration in making this recommendation.
2. The presence of cirrhosis is a strong prognostic factor for decompensated liver disease, hepatocellular carcinoma and death due to liver-related causes.
3. No long-term randomized data currently exist for any hepatitis B antiviral therapy that confirms which intermediate virological and/or histological markers best predict clinically relevant outcomes. Therefore, there remains uncertainty regarding both the existence and the magnitude of long-term benefits of therapy.

Background:

CEDAC provides formulary listing recommendations to publicly funded drug plans. Recommendations are based on an evidence-based review of the medication's effectiveness and safety and an assessment of its cost-effectiveness in comparison to other available treatment options. For example, if a new medication is more expensive than other treatments, the Committee considers whether any advantages of the new medication justify the higher price. If the recommendation is not to list a drug, the Committee has concerns regarding the balance between benefit and harm for the medication, and/or concerns about whether the medication provides good value for public drug plans.

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