

## CEDAC FINAL RECOMMENDATION on RECONSIDERATION and REASONS for RECOMMENDATION

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### ADEFOVIR DIPIVOXIL (Hepsera<sup>®</sup> – Gilead Sciences Canada, Inc.)

#### **Description:**

Adefovir dipivoxil is an orally administered prodrug of adefovir, an inhibitor of hepatitis B virus (HBV) DNA polymerase. It is approved for the treatment of chronic hepatitis B in adults with compensated and decompensated liver disease with evidence of active viral replication, and either evidence of histologically active disease or elevation in serum aminotransferases (ALT or AST).

#### **Dosage Forms:**

10 mg tablets. The recommended dose is 10 mg once daily.

#### **Recommendation:**

The Canadian Expert Drug Advisory Committee (CEDAC) recommends that adefovir dipivoxil not be listed.

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

1. There is no evidence from randomized controlled trials (RCTs) that adefovir results in any difference in the incidence of death, or serious morbidity including hepatocellular carcinoma or the need for liver transplantation.
2. The annual cost of adefovir dipivoxil therapy is approximately \$8,000 compared to \$1,600 for lamivudine. The pharmacoeconomic evaluation submitted by the manufacturer reported an incremental cost per quality adjusted life year (QALY) of approximately \$18,000 for adefovir compared to no treatment in patients who failed lamivudine therapy, but this was based on different discount rates applied to the benefits versus the costs of therapy. A more conservative approach using the same discount rates for benefits and costs (5% per year) yields a cost per QALY of at least \$75,000. Given the uncertainty around the incremental cost-effectiveness of adefovir dipivoxil, the Committee did not feel that its high cost was justified.

#### **Summary of Committee Considerations:**

The Committee considered a systematic review of RCTs of adefovir in adult patients with chronic hepatitis B infection. Six randomized controlled trials (RCTs), with a maximum duration of 52 weeks, comparing adefovir dipivoxil with placebo in a total of 1449 patients met the inclusion criteria for the systematic review.

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Three RCTs compared adefovir monotherapy with placebo, though only two of these trials reported statistical analyses of the results. In these two RCTs, adefovir resulted in statistically significant improvements in histologic scores for necroinflammation and fibrosis, HBV viral suppression and normalization of alanine aminotransferase levels. One RCT reported on loss or seroconversion of hepatitis B virus e antigen and there was a statistically significant improvement for this outcome in the adefovir group.

In one RCT in treatment-naïve patients, all of whom received lamivudine during the study, adefovir was compared to placebo. The addition of adefovir to lamivudine did not result in improvement in HBV viral suppression, hepatic transaminase levels and loss or seroconversion of hepatitis B antigen but was associated with a reduction in the development of lamivudine-resistant HBV.

Two of the RCTs enrolled patients with evidence of lamivudine resistance. In one study, patients were randomized to continue lamivudine alone, add adefovir to lamivudine or switch from lamivudine to adefovir; in the other, patients were randomized to continue lamivudine alone or add adefovir to lamivudine. In both studies, the use of adefovir resulted in statistically significant improvements in HBV viral suppression and normalization of alanine aminotransferase levels, in comparison to continued lamivudine therapy. There was no statistically significant difference reported in loss or seroconversion of hepatitis B virus e antigen in these trials and neither trial used histologic scores for necroinflammation and fibrosis as an outcome. It is uncertain if improvements in HBV viral suppression and/or normalization of alanine aminotransferase levels are valid surrogate endpoints for long-term improvements in clinical outcomes.

There were no statistically significant differences in the incidence of adverse effects or withdrawals due to adverse effects between adefovir and comparator arms in any of the RCTs.

**Of Note:**

1. Both published and unpublished data were reviewed and taken into consideration in making this recommendation.

**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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