Canadian Agency for Drugs and Technologies in Health

Agence canadienne des médicaments et des technologies de la santé

CEDAC FINAL RECOMMENDATION and REASONS for RECOMMENDATION

ADEFOVIR DIPIVOXIL
(Hepsera® – 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).

The review of adefovir dipivoxil by the Common Drug Review was in response to a Request for Advice from the Advisory Committee on Pharmaceuticals which questioned if the CEDAC recommendation of November 29, 2006 should be changed given the introduction of new antivirals for the treatment of chronic hepatitis B.

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 be listed, when used in combination with lamivudine, in patients who have developed failure to lamivudine, as defined by an increase in HBV DNA of ≥ 1 $\log_{10}$ IU/mL above the nadir, measured on two separate occasions within an interval of at least one month, after the first three months of lamivudine therapy, and when failure to lamivudine is not due to poor adherence to therapy

Reasons for the Recommendation:
1. Two randomized controlled trials (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, in addition to lamivudine, resulted in statistically significant improvements in HBV viral suppression and normalization of alanine aminotransferase levels, in comparison to continued lamivudine therapy.

2. Resistance to the combination of adefovir and lamivudine has not been reported in lamivudine-resistant patients in trials with follow-up of up to five years, while resistance has been reported when therapy is switched from lamivudine to adefovir monotherapy in these patients.

3. The annual cost of adefovir dipivoxil therapy is approximately $8,000 compared to $1,600 for lamivudine. The economic 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 discounts rates for benefits and costs (5% per year) yields a cost per QALY of approximately $75,000. Although this cost per QALY is relatively high, the Committee felt that it was important to offer a treatment option to patients with active hepatitis B who had been compliant with but had failed first line therapy with lamivudine.

4. There is insufficient evidence to support the use of adefovir dipivoxil over other treatment alternatives in nucleos(t)ide-naive patients.

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, in a total of 1449 patients met the inclusion criteria for the systematic review. The Committee also considered information on the development of viral resistance from long-term uncontrolled trials.

Three RCTs compared adefovir monotherapy with placebo in nucleos(t)ide-naïve patients, 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, lamivudine monotherapy was compared to combination therapy with adefovir plus lamivudine. 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.

Although 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, adefovir use has been associated with renal dysfunction.

Of Note:

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

2. The Committee recognizes that the management of chronic hepatitis B infection is rapidly evolving and recommends that drug plans seek further advice from the Committee based on emerging treatment options and strategies for the treatment of chronic hepatitis B infection.

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.