

B.C. Ministry of Health Services Drug Coverage Decisions

About PharmaCare	B.C. PharmaCare helps British Columbians with the cost of eligible prescription drugs and specific medical supplies.
PharmaCare Coverage	The Ministry of Health Services (Ministry) makes PharmaCare coverage decisions by considering existing PharmaCare policies, programs and resources, and the evidence-based recommendations of an independent advisory body called the Drug Benefit Council (DBC). The DBC's advice to the Ministry is based upon a review of many considerations, including available clinical and pharmacoeconomic evidence, clinical practice and ethical considerations, and the recommendations of the national Common Drug Review, when applicable.
Inside	Page 1 includes the Ministry's decision and reasons in wording that is easier for readers without a medical background to understand. Pages 2 and 3 summarize the DBC recommendation, the Ministry's decision and the reasons for the Ministry's decision.

Adefovir (Hepsera®) for chronic hepatitis B infection

Understanding the DBC Recommendation and PharmaCare Coverage Decision

Background

- **Hepatitis B** is an infection of the liver, caused by a virus. It is spread by contact with blood and body fluids of infected people (e.g. during sex, sharing needles or passing from mother to child during birth).
- New infections do not usually require treatment because most adults clear the infection on their own. However, some people develop a chronic hepatitis B infection after 6 months. **Chronic infections** can lead to liver damage or scarring (cirrhosis) and liver cancer.
- **Antiviral drugs** are used to treat some patients with chronic hepatitis B. The goal of treatment is to stop the virus from growing and to stop the progress of liver damage. **Resistance** occurs when the antiviral is no longer effective.
- **Adefovir** has the trade name **Hepsera®**. It is an antiviral drug and belongs to the drug class called **nucleosides and nucleotides**.
 - It is used to treat chronic hepatitis B in adults with liver damage.
 - Adefovir prevents the virus from growing and infecting new liver cells.
- **Lamivudine** is also an antiviral used to treat hepatitis B, and is a limited coverage benefit.

Why was this drug reviewed?

- Drug company request.

What did the review find?

- In patients with chronic hepatitis B where lamivudine is no longer effective, studies show that adefovir alone, or combined with lamivudine, is more effective than lamivudine alone.
- Adefovir and lamivudine have similar rates of side effects, although adefovir may have side effects affecting the kidneys while lamivudine does not.
- In patients with chronic hepatitis B where lamivudine is no longer effective, the evidence does not clearly show whether adefovir combined with lamivudine is better than adefovir alone.
- Adefovir is more costly than lamivudine, which is a limited coverage benefit.
- External clinical experts were consulted to determine prescribing criteria for this drug.

What decision was made?

- Adefovir will have **limited coverage** for patients with chronic hepatitis B who have taken lamivudine for at least 3 months without it being effective based on lab test results.

Key Term (s)

- **Limited coverage** drugs are not normally considered the first choice in treatment, or other drugs may offer better value. To receive coverage, the patient's physician must submit a Special Authority request to PharmaCare. If the request is approved, the drug is covered up to the usual PharmaCare coverage limits. Actual reimbursement depends on the rules of a patient's PharmaCare plan including any annual deductible requirement.

This document is intended for information only. It does not take the place of advice from a physician or other qualified health care provider.

Please visit us online to find out more about the Pharmaceutical Services Division and the PharmaCare program at www.health.gov.bc.ca/pharmacare. To find out more about how drugs are considered for PharmaCare coverage, visit www.health.gov.bc.ca/pharmacare/formulary.



Adefovir (Hepsera®) for chronic hepatitis B infection

Drug Class

- Nucleosides and nucleotides

Available Dosage Forms

- 10 mg tablets

Sponsor/Requestor

- Gilead Science

Submission (Request) to PharmaCare

- Drug review of adefovir (Hepsera®) for the following Health Canada-approved indication:
 - Treatment of chronic hepatitis B (HBV) infections in adults with compensated and decompensated liver disease with evidence of active viral replication, and either evidence of histological active disease or elevation in serum aminotransferases (ALT or AST).

Drug Benefit Council (DBC) Recommendations

- Adefovir (Hepsera®) be listed as a limited coverage drug for monotherapy with the following Special Authority criteria:
 - For treatment of chronic hepatitis B infection in patients who have developed failure to lamivudine, as defined by an increase in HBV DNA of $\geq 1 \log_{10}$ copies/mL above the nadir, measured on two separate occasions within an interval of at least 1 month, after the first 6 months of lamivudine therapy; and
 - When failure to lamivudine is not due to poor adherence to therapy.

Reasons for the Ministry of Health Services Decision

- Two randomized controlled trials (RCTs) were identified in patients with lamivudine-resistant HBV. In one study, patients were randomized to continue lamivudine alone, add adefovir to lamivudine, or switch from lamivudine to adefovir; in the other study, patients were randomized to continue lamivudine alone or add adefovir to lamivudine.
 - There were statistically significant improvements in normalization of alanine aminotransferase levels and HBV viral suppression when adefovir alone (or combined with lamivudine) was compared to continued lamivudine monotherapy. It is not clear if adefovir alone (or combined with lamivudine) is more efficacious than

lamivudine alone at hepatitis B surface antigen (HBsAG) loss/seroconversion since the reported number of event rates were too low.

- 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; however, adefovir use has been associated with renal dysfunction.
- Adefovir is more costly than lamivudine. Based on the economic evaluation submitted by the manufacturer, an incremental cost per quality adjusted life year (QALY) is approximately \$18,000 for adefovir monotherapy compared to no treatment in patients who failed lamivudine therapy. A more conservative approach with appropriate discounting yielded a cost per QALY of approximately \$75,000.
- The Canadian Expert Drug Advisory Committee (CEDAC) recommended use of adefovir in combination with lamivudine in patients who develop failure to lamivudine. The recommendation for combination therapy rather than a switch to adefovir monotherapy was based on data from one observational trial, with follow-up of up to 5 years. Based on this trial, resistance to the combination of adefovir and lamivudine has not been reported in lamivudine-resistant patients, while resistance has been reported when therapy was switched from lamivudine to adefovir monotherapy.
- The DBC recommended the use of adefovir as monotherapy in patients who develop lamivudine resistance based on the only RCT in the CEDAC review that directly compared lamivudine monotherapy, adefovir monotherapy, or the combination of adefovir and lamivudine in patients with lamivudine-resistant HBV.
 - This trial failed to detect any additional antiviral benefit from the combination of adefovir and lamivudine compared to adefovir monotherapy.
 - There was no clear evidence to suggest that resistance rates are lower with combination therapy.

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Adefovir (Hepsera[®]) for chronic hepatitis B infection

Reasons for the Ministry of Health Services Decision

(continued)

- Additional information available at the time of the DBC recommendation came from an open-label RCT^a that was not included in the CEDAC review.
 - Based on this trial, there were no statistically significant differences in normalization of ALT or HBV viral suppression between adefovir monotherapy versus the combination of adefovir and lamivudine in patients with lamivudine-resistant HBV.
 - Based on the same trial, there was a concern regarding the rate of hepatocellular carcinoma in HBeAg negative patients treated with combination therapy. Although this was not statistically significant, 3/12 (25%) patients in the combination therapy group who were HBeAg negative and had cirrhosis at baseline developed hepatocellular carcinoma, as compared to 0/4 (0%) patients who received adefovir monotherapy.
- Given the lack of proven additional benefit, possible reduced safety, and increased cost of adefovir and lamivudine combination therapy, the committee supported adefovir monotherapy for patients with lamivudine-resistant HBV.
- An external multidisciplinary working group (the Working Group) was also consulted to assist in the development of coverage criteria for adefovir. The Working Group included input from hepatologists, laboratory directors, general practitioners and hospital pharmacy – infectious disease.

Decision and Status

- **Limited coverage** for up to 12 months initially, as per the coverage criteria set forth in the DBC recommendation (page 2 of this document) with the exception of shortening the required length of prerequisite trial of lamivudine from 6 months to 3 months.
- Renewal coverage for up to 12 months, with the following coverage criteria:
 1. HBV DNA undetectable within the last 3 months, or
 2. HBV DNA positive within the last 3 months where viral load is stable or decreasing.
- Effective March 27, 2008

^aRapti I, Dimou E, Mitsoula P, et al. Adding-on versus switching-to adefovir therapy in lamivudine-resistant HBeAg-negative chronic hepatitis B. *Hepatology*. 2007; 45(2):307-13.

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