

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. Page 2 summarizes the DBC recommendation, the Ministry's decision and the reasons for the Ministry's decision.

Entecavir (Baraclude™) for chronic hepatitis B in patients with liver damage

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 need 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.
- **Entecavir** has the trade name **Baraclude™**. 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.
 - Entecavir 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?

- Studies show that entecavir decreases the growth of

the virus in patients with chronic hepatitis B and improves blood test and liver biopsy results. It is likely cost-effective for treating patients with cirrhosis and not cost-effective for treating patients without cirrhosis.

- In patients who have never received drug treatment for hepatitis B, resistance will only develop in less than 1% of the patients each year if they take entecavir over a 3-year period.
- In patients who do not respond to lamivudine, entecavir may not be effective in 29% of patients who are given entecavir over a 3-year period.
- Entecavir and lamivudine have similar side effect rates.
- There is not enough evidence to show that entecavir is cost-effective for patients with hepatitis B who are not responding to lamivudine.
- External clinical experts were consulted to determine prescribing criteria for this drug.

What decision was made?

- Entecavir will have **limited coverage** for patients with chronic hepatitis B who have liver damage.

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.



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Entecavir (Baraclude™) for chronic hepatitis B in patients who develop cirrhosis

Drug Class

- Nucleosides and nucleotides

Available Dosage Forms

- 0.5 mg tablets

Sponsor/Requestor

- Bristol Meyers Squibb

Submission (Request) to PharmaCare

- Drug review of entecavir for the following Health Canada approved indication:
 - Treatment of chronic hepatitis B virus (HBV) infections in adults (and adolescents 16 years of age and older) with evidence of viral replication and either evidence of persistent elevations in serum aminotransferases (ALT or AST) or histologically active disease.

Drug Benefit Council (DBC) Recommendations

- Entecavir (Baraclude®) be listed as limited coverage for up to 6 months with the following Special Authority criteria:
 - 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.
- Entecavir (Baraclude®) not be listed for the treatment of chronic hepatitis B infection in patients without cirrhosis or in lamivudine-resistant HBV.

Reasons for the Ministry of Health Services Decision

- Four randomized controlled trials (RCTs) were identified that compared entecavir with lamivudine in nucleos(t)ide-naïve patients.
- Entecavir treatment resulted in statistically significant improvements in hepatitis B viral suppression in all trials, normalization of alanine aminotransferase in three of four trials, and improvement in histologic response in two trials that measured this outcome.
- Resistance to entecavir in nucleos(t)ide-naïve patients has been reported to be less than 1% for each of the first 3 years of therapy.
- There were no statistically significant differences in rates of adverse drug reactions and serious adverse drug reactions

between entecavir and lamivudine.

- Based on the pharmacoeconomic analysis reviewed, entecavir is likely cost-effective for cirrhotic patients, but it is unlikely that it would be cost-effective for patients without cirrhosis.
- Two RCTs were identified that compared entecavir to lamivudine in patients with persistent viremia despite lamivudine therapy or had developed documented resistance to lamivudine. In a 52-week trial, entecavir resulted in a statistically significant improvement in the proportion of patients with histologic response as assessed by the Knodell Histology Activity Index score on liver biopsy at 1 year compared to baseline, undetectable HBV DNA, normalization of alanine aminotransferase and virologic rebound.
- An observational study of entecavir in patients with documented lamivudine resistance reported 29% resistance to entecavir after 3 years of therapy.
- There is insufficient evidence that entecavir is cost-effective for lamivudine-resistant patients at 1 mg per day dose, and the available pharmacoeconomic analysis assumed a dose of 0.5 mg per day.
- A clinical stakeholders working group was consulted to help further define the elements for Special Authority coverage.

Decision and Status

- **Limited coverage** for up to 12 months initially, with the following criteria:
 1. Diagnosis of chronic hepatitis B, plus:
 - a. Histologic or radiologic evidence of cirrhosis, or
 - b. Evidence of portal hypertension, plus
 2. Lab results consistent with:
 - a. HBV DNA ≥ 1 M copies, or
 - b. HBV DNA $> 10,000 < 1$ M copies and ALT $\geq 3 \times$ ULN (upper limit of normal).
- Renewal coverage for up to 12 months, with the following 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

Key Term(s)

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