CEDAC FINAL RECOMMENDATION on RECONSIDERATION and REASONS for RECOMMENDATION

ENTECAVIR
(Baraclude™ – Bristol-Myers Squibb Canada)

Description:
Entecavir is a guanosine nucleoside analogue that is approved for treatment of chronic hepatitis B virus (HBV) infection in adults with evidence of active viral replication and either evidence of persistent elevations in serum aminotransferases or histologically active disease.

Dosage Forms:
0.5 mg tablets. The usual recommended dose is 0.5 mg once daily. For patients with a history of hepatitis B viremia while receiving lamivudine or with known lamivudine resistance mutations, the recommended dose of entecavir is 1 mg once daily.

Recommendation:
The Canadian Expert Drug Advisory Committee (CEDAC) recommends that entecavir 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. Four randomized controlled trials (RCTs) compared entecavir with lamivudine in nucleos(t)ide-naïve patients. Entecavir 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 the two trials that measured this outcome.

2. Resistance to entecavir in nucleos(t)ide-naïve patients is rare and has been reported to be <1% for each of the first three years of therapy. In contrast, resistance to lamivudine has been reported in approximately 70% of patients after four years of therapy.

3. The annual cost of entecavir at a dose of 0.5 mg daily in nucleos(t)ide-naïve patients is $8,000, compared to $1,600 for lamivudine. The manufacturer submitted an economic evaluation based on the results of clinical trials in this patient population. It estimated an incremental cost per quality adjusted life year (QALY) of less than $10,000. However, the evaluation assumed that patients would be treated with entecavir for one year but would continue to benefit from treatment for the 10 year time horizon of the evaluation. Published economic evaluations of antivirals in chronic hepatitis B infection have reported that, in comparison to lamivudine, these agents are unlikely to be cost-effective in patients without cirrhosis but suggest their use may be cost-effective in patients with

cirrhosis. Therefore, the Committee felt that entecavir should be reserved for patients who are at the highest risk of complications from chronic hepatitis B infection.

4. The Committee felt that there was insufficient evidence of the cost-effectiveness of entecavir in patients with lamivudine resistance, given that the recommended dose of entecavir in these patients is 1 mg daily at a cost of $16,000 per year. Additionally, an observational study has reported that 29% of lamivudine-resistant patients developed resistance to entecavir after three years of therapy.

Summary of Committee Considerations:

The Committee considered a systematic review of RCTs in adult patients with chronic hepatitis B infection. Nine RCTs ranging in duration from four to 52 weeks in a total of 2,909 patients met the inclusion criteria for the systematic review. Four RCTs compared entecavir to lamivudine in nucleos(t)ide-naïve patients, two RCTs compared entecavir to placebo in nucleos(t)ide-naïve patients, two RCTs compared entecavir to continued lamivudine therapy in patients who had failed or developed resistance to lamivudine therapy and there was one placebo controlled RCT in patients who had failed or developed resistance to lamivudine therapy. The Committee also considered information on the development of viral resistance from long-term uncontrolled trials.

In the four trials comparing entecavir with lamivudine in nucleos(t)ide-naïve patients, entecavir resulted in statistically significant improvements in the proportion of patients achieving undetectable HBV DNA in all trials, normalization of alanine aminotransferase in three of four trials and improvement in histologic response as assessed by the Knodell Histology Activity Index score on liver biopsy at one year compared to baseline in the two trials that measured this outcome. There were no statistically significant differences in the rate of seroconversion of hepatitis B virus e antigen in the two trials that measured this outcome.

Two RCTs compared entecavir with continued lamivudine therapy in patients who had persistent viremia despite lamivudine therapy or had developed documented resistance to lamivudine. In a 52 week trial of 286 patients who were hepatitis B virus e antigen positive, entecavir resulted in statistically significant improvements in the proportion of patients with histologic response as assessed by the Knodell Histology Activity Index score on liver biopsy at one year compared to baseline, undetectable hepatitis B viral DNA, normalization of alanine aminotransferase and virologic rebound, defined as a confirmed increase in HBV DNA by ≥1 log copy/mL from the nadir value. However, an observational study of entecavir in patients with documented resistance to lamivudine has reported that 29% of patients develop resistance to entecavir after three years of therapy.

The rates and profile of adverse events and serious adverse events observed with entecavir are comparable to lamivudine.

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.