The Cost-Effectiveness of Alternative Therapeutic Strategies for the Management of Chronic Hepatitis B in Poland

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ABSTRACT

Objective: The aim of the study was to estimate the cost-effectiveness of alternative therapeutic strategies for the management of chronic hepatitis B (CHB) in Poland.

Methods: The model for the Polish health-care context was based on clinical data from the literature and local data on health-care resource utilization and unit costs. Costs and effects of a population of CHB patients were modeled using four scenarios, which attempt to reflect real-life practice in which patients may receive any of the treatment options available and in which a proportion of patients may still receive no treatment because therapy is not suitable. Strategies A and B assumed the availability of both treatment options: the first choice of treatment is A, lamivudine, and in B, interferon alpha (IFN-α). In strategy C, the only approved treatment is IFN-α, and in strategy D, the patients receive no antiviral treatment. The outcome measures were HBeAg seroconversion and nonprogression to cirrhosis—the surrogate marker with predictive value for improved survival. Only direct medical costs were analyzed. The payer’s perspective and time horizon of 1 year were adopted. One-way sensitivity analysis and extreme scenario analysis were performed.

Results: The best results in terms of seroconversion and nonprogression to cirrhosis were achieved for strategy A, costs were lowest for strategy D, and strategies B and C were dominated by strategy A. The incremental cost-effectiveness ratio (ICER) comparing strategy A with strategy D was 57,855 Polish new zloty (PLN) per extra seroconversion and 79,550 PLN per cirrhosis case avoided.

Conclusions: Cirrhosis reduces estimated life expectancy by 37.76 years and by 20 years among 30- and 50-year-olds, respectively. The ICER for strategies A and D was 2105 PLN and 3978 PLN per life-years gained for the population at ages 30 and 50, respectively, and was below the suggested threshold for cost-effectiveness, based on treatment costs for 1 year of hemodialysis in Poland (62,400 PLN). Changing the value of key drivers for sensitivity analysis did not have a significant effect on the ICER.

Keywords: lamivudine, interferon alpha, chronic hepatitis B, cost-effectiveness analysis.

Introduction

Hepatitis B is an infectious disease caused by hepatitis B virus (HBV). It has been estimated that HBV infection affects 2 billion people worldwide. HBV infection has many clinical forms: from subclinical carrier state to acute or chronic hepatitis, which may lead to cirrhosis of the liver, hepatocellular carcinoma, hepatic failure, and death [1]. It is also associated with extrahepatic diseases, such as membranous glomerulonephritis, periarteritis nodosa, and other vascular connective tissue diseases. The WHO estimates that chronic hepatitis B is responsible for approximately 1 million deaths each year [2].

The number of chronic carriers is approximately 350 million [2]. Chronic hepatitis B is the most common cause of hepatic cirrhosis and leads to approximately 60% of all hepatocellular carcinomas [2,3]. It has been estimated that cirrhosis of the liver and liver cancer accounts for the premature death of 25% to 40% of chronic carriers [3]. Therefore, chronic hepatitis B represents a significant health and economic burden. From the public health policy perspective, the most important issue is prevention of hepatitis B. However, the efficacy of the hepatitis B vaccine developed in early 1980s is less than 100% and is ineffective in subjects with...
pre-existing HBV infection. This underscores the importance of drugs used to treat chronic hepatitis B. Interferon alpha (IFN-α) is the standard treatment for chronic HBV. Lamivudine is currently being introduced into clinical practice as an alternative for IFN-α. The aim of this study is to use a decision analysis model to estimate the cost-effectiveness of alternative therapeutic strategies for the management of chronic hepatitis B (CHB) in Poland.

**Epidemiology**

From 1986 to 1990, the registered annual incidence of hepatitis B in Poland was 14,000 to 15,000 [4,5], and the prevalence of the disease was 37 to 40 per 100,000. Introduction of mandatory vaccination against hepatitis B in 1994 resulted in a significant reduction in incidence from 4000 to 5000 in 1997 to 3800 in 1999 [4,5]. In 1997 and 1998, the prevalence was 15 to 18 per 100,000, and then declined below 10 per 100,000 in 1999. According to data from the National Institute of Hygiene, the prevalence of HBV carriers in Poland population is 1% to 1.5% [4]. Thus, the number of subjects infected with HBV in Poland is between 380,000 and 500,000.

**The Need for Causal Treatment for Hepatitis B in Poland**

Elimination of HBeAg can occur spontaneously in up to 20% of infected patients [6] and in most studies occurs in 9% to 14% of untreated patients [7–12]. Assuming that 13% of carriers may spontaneously eliminate HBV and chronic hepatitis will develop in as many as 20%, then 80,000 to 85,000 patients, including 35% to 40% of children (28,000–32,000) required antiviral therapy in the past 10 years in Poland. IFN-α has been available in Poland since 1993. From 1993 to 1999, about 1500 adults and 2500 children infected with HBV have undergone the therapy within the confines of the program financed by the Ministry of Health, which accounts for only 5% of those requiring treatment. Given that the drugs may be purchased by individual patients and nongovernmental institutions such as research programs, which provide treatment to an additional 500 to 700 patients, the number of HBV-infected patients receiving the therapy in Poland is approximately 5000. So far, continuous response to IFN-α therapy (disappearance of HBSAg and loss of HBV DNA) does not exceed 39% [13] or about 2000 patients. Thus, at least 3000 patients previously treated with IFN-α require retreatment. Once added to the number of untreated patients requiring therapy, the number of Polish patients eligible for antiviral treatment is 78,000 to 83,000. This number is projected to increase by at least 8000 patients per year for the next 10 years.

**Therapy for Chronic Hepatitis B**

CHB infection is a result of nonelimination of HBV and includes those cases in which HBV persists for more than 6 months after infection. Therapy should be provided to patients with CHB and symptomatic liver disease including risk of progression of liver disease (evidence for viral replication), extrahepatic disease symptoms (glomerulonephritis, vasculitis), relapse of the disease, advanced disease (decompensated hepatic cirrhosis), and development of infection in the patients after liver transplantation. The aim of therapy is inhibition of HBV replication as indicated by HBeAg seroconversion (disappearance of HBeAg and appearance of HBeAb) and improvement of liver function as indicated by normalization of serum alanine aminotransferase (ALT) levels and slowing or stopping of hepatic cirrhosis.

Two drugs have been licensed worldwide for treatment of CHB: IFN-α and lamivudine. The mechanism of action of the two drugs is different as is patient selection for treatment. Both drugs have been investigated extensively in monotherapy and as combination therapy. In Poland, IFN-α is part of standard drug therapy for CHB [13]. The recommended dose is 5 to 10 million IU subcutaneously three times weekly for 3 to 6 months [1,14]. Lamivudine is a synthetic nucleoside analog exhibiting anti-HIV and anti-HBV activity. The standard dose of lamivudine is 100 mg orally once a day for 1 years [15]. In contrast to IFN-α, lamivudine turns out to be a useful drug in HBV-infected patients before liver transplantation [16]. It is a highly effective agent in patients with precore-mutant strains of HBV [17] and exhibits beneficial activity in patients with decompensated hepatic cirrhosis [18].

**HBeAg seroconversion after IFN-α treatment.** Clinical trials indicate that IFN-α induces elimination of HBeAg in 20% to 40% of individuals with chronic hepatitis B [19–26]. A meta-analysis of results from 15 randomized clinical trials in a total of 837 white patients has revealed that IFN-α administered for 3 to 6 months and follow-up for 6 to 12 months stimulate loss of HBV replication in about 20% more patients receiving IFN-α compared to control [27]. A lower response rate (15–21%) has been found among Asian patients who often become infected
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during childhood and in patients infected with HBV precore mutants, which do not produce HBeAg [28–32]. The less stringent end point, loss of HBeAg rather than HBeAg seroconversion, is likely to increase seroconversion rates in both treated and untreated patients. An analysis of patients from 10 randomized controlled trials, in which IFN-α was administered to HBsAg- and HBeAg-positive patients, revealed that in the IFN-α group, the HBeAb appearance factor was 1.64, while HBeAg disappearance factor was 1.8 [33]. Response to IFN-α therapy depends on baseline patient characteristics. Although the relative response is similar for all patients, those with elevated pretreatment transaminases and low baseline HBV DNA levels get the greatest absolute benefit from IFN-α therapy [21,27,33].

HBeAg seroconversion after lamivudine treatment. Treatment with lamivudine 100 mg p.o. daily for 1 year results in HBeAg seroconversion in 16% to 21% [15,34–36] and is significantly higher for lamivudine than for placebo [15,36]. The disappearance rate of HBeAg after 1 year is higher than seroconversion rate: 17% to 33% in the lamivudine-treated group and 7% to 13% in the placebo group [15,34–36]. In each phase III clinical trial, loss of HBV DNA was observed in a majority of patients who seroconverted from HBeAg to HBeAb. This suggests that lamivudine-induced seroconversion is associated with suppression of HBV replication [15,34–36]. As for IFN-α, elevated baseline ALT is the strongest predictor of lamivudine-induced HBeAg seroconversion. Multivariate analysis showed that both ALT and the histologic activity index (HAI) were significantly correlated with HBeAg seroconversion, although the contribution of HBV DNA to the predicted response was negligible [37]. Lamivudine increases the response rate by a factor of less than 2 when ALT is less than two times the upper limit of normal (ULN), but rises to 4 when ALT is less than five times the ULN [35,38].

Lamivudine versus IFN-α. In comparative clinical trials of lamivudine versus IFN-α monotherapy, the difference in seroconversion rates after daily oral lamivudine 100 mg for 1 year versus 10 million IU IFN-α subcutaneous three times a week after 4 months was not statistically significant [35,39]. The rate of HBeAg disappearance (22%) was identical in both groups [39]. Indirect comparison between lamivudine and IFN-α monotherapy compared to placebo confirms that there is no significant difference in efficacy of these drugs [27,36]. In comparative trials of lamivudine versus IFN-α monotherapy in patients with baseline ALT ≥ 2 × ULN, HBeAg seroconversion rates were 26.5 and 23.8, respectively, which is not significantly different [39].

Duration of response. IFN-α-induced HBeAg seroconversion is sustained in around 90% of patients [20,21,26,29,40,41]. Analysis of randomized, placebo-controlled trials has indicated that HBeAg seroconversion induced by lamivudine is durable in most patients. It persists for 6 months after cessation of therapy in 91% of patients and for 15 months in 83% of patients [34,42]. Persistence of seroconversion at 21 months has been found in 86% of patients previously treated with lamivudine [43], although the surrogate marker, loss of HBeAg, was used in this study to assess seroconversion. Worse results for lamivudine therapy have been associated with a shorter (up to 12 months) treatment period [44].

Based on current data one may conclude that persistence of HBeAg seroconversion after lamivudine or IFN-α monotherapy is equally durable, and HBeAg seroconversion or disappearance of HBeAg is a suitable time to discontinue lamivudine therapy, as long-lasting therapeutic effects are ensured.

Improvement of Liver Histology

Histologic improvement is defined as a reduction of at least 2 points and worsening as an increase of at least 2 points in the necroinflammatory score. One year of lamivudine therapy significantly reduced the HAI score and prevented progression to fibrosis in HBeAg (+) patients [15,35,36,45–47]. Lamivudine shows histologic benefit in about 50% of patients, whereas IFN-α does in 45% [36]. The difference between these treatments is clearer when disease progression is taken as the outcome measure: worsening of histology was noted in 7% to 11% patients treated with lamivudine, whereas IFN-α and placebo were associated with worsening of histology in about 30% patients [15,35]. Pooled results of data from three clinical studies [15,39,45] provide evidence that treatment with lamivudine reduces the rate of progression to cirrhosis, defined as a score of 4 on the fibrosis component of the Knodell histologic activity index [46]. The frequency of progression to cirrhosis after 1 year was 1.8% (4 of 219 patients), 7.1% (7 of 99 patients), and 9.5% (4 of 42 patients) in those treated with lamivudine 100 mg/day, placebo, and IFN-α, respectively [46].

The difference between lamivudine and IFN-α can be explained in part by the fact that these are
overall results, including responders and non-responders. Patients who received lamivudine monotherapy derived histologic benefit irrespective of their HBeAg seroconversion status, whereas the histologic response after IFN-α treatment is usually observed only in patients who have demonstrated a serologic response [15,35,48]. Fattovich et al. [49] suggests that in patients with CHB and evidence of active viral replication, the 5-year incidence of cirrhosis is 15% to 20%. On the basis of these data, Wong et al. [50] estimated that the annual probability of developing cirrhosis was 1% for patients who had HBsAg and 12.1% for patients who had HBeAg. The other important factor hampering the comparison of histologic results for lamivudine with other therapies in several studies is that all biopsies were taken at the end of lamivudine therapy but 6 months after withdrawal of IFN-α therapy.

**Efficacy of Lamivudine in Patients with YMDD-Variant HBV**

In some patients, lamivudine therapy may lead to emergence of an HBV mutant, YMDD-variant HBV, which is less susceptible to lamivudine activity. After 1 year of lamivudine treatment, YMDD-variant HBV was detected in 14% to 32% of patients [15,35,36], and after 2 and 3 years of therapy, in 42% and 52% of Asian patients, respectively [51,52]. Within 3 to 4 months of stopping therapy, occurrence of YMDD-variant HBV decreased from 32% to 29% [36], from 31% to 21% [35], and from 27% to 21% [34]. Among patients receiving lamivudine, emergence of YMDD-variant HBV decreases, but HBeAg seroconversion is not precluded [15]. After 3 years of therapy with lamivudine, seroconversion had occurred in 22% of patients with, and in 50% of patients without, YMDD-variant HBV [51].

**Tolerability of IFN-α and Lamivudine**

Adverse effects associated with IFN-α therapy include depression, psychoses, suicidal tendencies, severe flu-like symptoms, neutropenia, and transient exacerbation of disease symptoms. These contribute to poor compliance and the need for monitoring during therapy [19]. As many as 20% of patients require dosage reductions and 5% to 10% discontinue IFN-α therapy [53] because of adverse events. Parenteral administration of IFN-α is inconvenient. Lamivudine exhibits a better tolerability than IFN-α, which has a safety profile similar to that observed for placebo [15,45,54,55]. Furthermore, the drug may be given to those patients for whom IFN-α is contraindicated such as in patients with advanced liver disease, receiving immunosuppressive therapy (especially after organ transplantation), or with a history of psychiatric or autoimmune disorders. Because of the oral route of administration, lamivudine may also be used in patients who refuse parenteral therapy.

**Materials and Methods**

**Target Population**

The patient population used in the model was representative of those likely to receive antiviral treatment in Poland. All of the patients were positive for HBeAg (patients with the precore-mutant virus were excluded), had moderately elevated ALT and had chronic hepatitis B initially, had not yet progressed to cirrhosis, and were IFN-α-naïve. It was assumed that patients were between the ages of 30 and 50, and 60% of the population was female.

**Methods**

The model for the Polish health-care context was based on data from published clinical trials, expert opinion, and local data on health-care resource utilization and unit costs. The model was created with Data 3.5 (Version 3.5.5, 1988–2000, TreeAge Software, Inc., Williamstown, MA, USA). The costs and effects for a population of CHB patients were modeled using four strategies based on real-life practice in which patients may receive any of the treatment options available, and a proportion of patients may still receive no treatment because therapy is not suitable. Strategies A and B assumed the availability of both treatment options. In strategy A, all patients eligible for lamivudine are treated with lamivudine. Patients ineligible for lamivudine receive IFN-α or no antiviral treatment if IFN-α therapy is contraindicated due to adverse events. Similarly, for strategy B, all patients are treated with IFN-α if eligible, and those ineligible for IFN-α receive lamivudine or no antiviral treatment if lamivudine therapy is not suitable. Patients in whom adverse events cause cessation of IFN-α receive no further antiviral therapy. In strategy C, the only approved treatment available is IFN-α, which is given only to those patients eligible for IFN-α. Patients ineligible for IFN-α receive IFN-α or no antiviral treatment if lamivudine therapy is not suitable. Patients in whom adverse events cause cessation of IFN-α receive no further antiviral therapy. In strategy D, patients receive no antiviral treatment. Strategy D provides the baseline from which the
incremental costs and outcomes of the introduction of lamivudine can be assessed.

The outcome measures of the model were:

- HBeAg seroconversion, defined as the loss of HBeAg and the appearance of HBsAb;
- Nonprogression to cirrhosis, the surrogate marker for improved survival [56].

The model, as represented in Figure 1, allows for calculation of the cost per patient, the HBeAg seroconversion rate, the proportion of patients not progressing to compensated cirrhosis, and the incremental cost/-effectiveness ratios (ICER). The ICER for cost per cirrhosis case avoided was converted into cost per life-year gained using life tables and estimates (of) the effect of hepatic cirrhosis on mortality.

The perspective of health-care payers and a time horizon of 1 year were adopted.

Probabilities of Events in the Model
Initially, all patients are HBeAg (+). After 1 year, they may be in one of three states of health: seroconversion, chronic hepatitis B without cirrhosis, or compensated hepatic cirrhosis. The proportion of patients eligible for lamivudine therapy (80%; range, 60–90%) and IFN-α (60%; range, 40–70%) were obtained from an expert panel of Polish hepatologists (n = 55), whose clinics manage 90% of patients in Poland treated for CHB. Data were collected using a questionnaire and discussed during a consensus meeting [57]. Based on information obtained from literature [53], it is assumed that discontinuation of IFN-α is required in 10% of patients because of intolerance and occurs halfway through the treatment period. Probabilities of seroconversion after lamivudine administration (0.18) and IFN-α (0.19) were based on results of a randomized, controlled, head-to-head, comparative trial of lamivudine versus IFN-α for 52 weeks [35]. The estimated probability of spontaneous seroconversion after 52 weeks without therapy (0.06) took into account the comparative study of lamivudine versus placebo in white patients, in which the response rate to lamivudine was similar to results obtained in the key trial for lamivudine versus IFN-α [36]. The probability of progression to cirrhosis was based on data from three clinical trials evaluating liver histologic response after administration of lamivudine, IFN-α, and placebo [15,39,45]. Analysis of pooled data from these trials showed that the frequency of progression to cirrhosis at 52 weeks was 1.8, 7.1, and 9.5% in those treated with lamivudine, placebo, and IFN-α, respectively [46]. In the three studies analyzed, all patients who seroconverted, regardless of whether they received lamivudine, IFN-α, or placebo, did not progress to cirrhosis [15,39,45]. Assuming that progression to cirrhosis occurs only in patients who did not seroconvert, the probability of progression is 0.02 for lamivudine, 0.12 for IFN-α, and 0.08 for untreated patients. The differences observed can be explained in part by the fact that those who received lamivudine monotherapy derived histologic benefit irrespective of their HBeAg seroconversion status, whereas the histologic response after IFN-α treatment is usually observed only among patients having demonstrated a serologic response [15,35,48]. The difference between IFN-α and placebo demonstrated by pooled analysis of data from three studies does not appear valid, as it is difficult to assess the relative efficacy of the alternatives without a direct comparison of pooled and individual trial results. Because the probability of progression to cirrhosis among patients treated with IFN-α who failed to seroconvert is 0.12 [46], similar to the annual probability of developing cirrhosis in HBeAg-positive patients estimated by Wong et al. [50], the rate of progression to cirrhosis used in the model is 0.12 both for IFN-α and for no therapy. All baseline probabilities for the model, along with the range of values used in the sensitivity analysis, are given in Table 1.

Costs
Analysis from the health-care payers’ perspective assessed only direct medical costs resulting from the diagnosis of CHB, qualification for treatment, and treatment. Information on current treatment practices (dosage, frequency of consultations, hospitalization, and procedures) was obtained from the expert panel of Polish hepatologists (n = 55). Data were collected using a questionnaire and discussed during a consensus meeting [57]. It was assumed that IFN-α dosing was 5 mIU, three times weekly for 6 months, as per Polish clinical practice recommendations. In head-to-head comparison of lamivudine and IFN-α for 52 weeks, IFN-α was dosed at 10 mIU three times weekly for 4 months versus lamivudine 100 mg tablet once daily for 52 weeks.

Qualifying for therapy with IFN-α or lamivudine requires consultation with a specialist and review of laboratory parameters (HBsAg, HBeAg, HBsAb, DNA polymerase, blood cell count, erythrocyte sedimentation rate, protein fraction pattern platelets, aminotransferases, and bilirubin and for IFN-α-treated patients only, creatinine, blood urea nitrogen, and proteinuria), abdominal ultrasound, and
Figure 1 Decision tree for 1-year model.
Cost-Effectiveness of Lamivudine and IFN-α in CHB

Patients treated with IFN-α are monitored more intensively. Patients are hospitalized initially for 10 days and reviewed a total of 11 times by the specialist, at which time liver function tests, total blood counts, and HBeAg and HBsAg measurements are performed. Two thyroid function tests are performed during the 52-week period. Furthermore, 72 ambulatory visits are required during the treatment period to allow for parenteral administration. Patients treated with lamivudine undergo specialist consultations, liver function tests, full blood counts, and measurement of HBeAg and HBsAg monthly for the first 6 months and every 3 months thereafter. It was conservatively assumed that patients who did not receive any antiviral drug did not receive any medication to treat symptoms of disease and had the same schedule of consultations and tests as patients receiving lamivudine and that those patients who progressed to cirrhosis did so at midyear. Estimated costs of developing compensated cirrhosis were based on expert opinions. During the first 6 months of treatment for these patients, liver biopsy, activated partial thromboplastin time, proteinogram, alpha-fetoprotein, and treatment with essential phospholipids and lactulose are recommended. Specialist consultations and other tests are included in the intensive monitoring associated with antiviral treatment.

Price data for the cost of drugs were obtained from the pharmaceutical wholesale price list 2002 [58] and from the Medical Services Schedule 2002 [59] for the costs of specialist consultations, tests, investigations, and hospitalizations, as summarized in Table 2. All costs were assessed in Polish new zloty (PLN) (1 US$ = 4 PLN). Discounting was not required because of the 1-year analytical horizon. Cost data applied to the model are listed in Table 3.

**Sensitivity Analysis**

One-way sensitivity analyses were used to test the robustness of the study results to changes in clinical and economic parameters by varying:

1. Probabilities of HBeAg seroconversion after lamivudine, IFN-α, and no treatment (upper and lower values from phase III studies in Asian and white patients);
2. The percentage of patients eligible for either lamivudine or IFN-α (upper and lower values from information on questionnaires collected by Polish hepatologists);
3. The percentage of patients discontinuing IFN-α therapy (upper and lower values from published studies);
4. The percentage of progression to cirrhosis in patients treated with either lamivudine or IFN-α or untreated (upper and lower values from clinical studies);
5. The acquisition cost for high-dose IFN-α treatment as per clinical trials;
6. The cost of routine medical management of patients treated with lamivudine or with IFN-α both with and without the cost of hospitalization.

The extreme scenario analysis made use of best estimates of key parameters for IFN-α and worst estimates of these for lamivudine. This scenario is plausible because the probabilities represent upper and lower values derived from questionnaires and from clinical studies.

<table>
<thead>
<tr>
<th>Table 1 Probability of events in the model: values used in the baseline analysis and in sensitivity analyses</th>
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<tbody>
<tr>
<td>Variable</td>
</tr>
<tr>
<td>Eligible for lamivudine therapy</td>
</tr>
<tr>
<td>Eligible for IFN-α therapy</td>
</tr>
<tr>
<td>IFN-α intolerance</td>
</tr>
<tr>
<td>HBeAg seroconversion</td>
</tr>
<tr>
<td>Treated with lamivudine</td>
</tr>
<tr>
<td>Treated with IFN-α</td>
</tr>
<tr>
<td>Untreated</td>
</tr>
<tr>
<td>Progression to cirrhosis</td>
</tr>
<tr>
<td>Patients who seroconverted</td>
</tr>
<tr>
<td>Patients who did not seroconvert</td>
</tr>
<tr>
<td>Treated with lamivudine</td>
</tr>
<tr>
<td>Treated with IFN-α</td>
</tr>
<tr>
<td>Untreated</td>
</tr>
</tbody>
</table>

<sup>a</sup>Upper and lower values from questionnaire collected information from Polish hepatologists.
<sup>b</sup>Upper and lower values from published literature.
<sup>c</sup>Upper and lower values from clinical trials in Asian and white patients, with end point of HBeAg seroconversion.
Table 2 Prices of drugs and some diagnostic and therapeutic procedures used in patients with chronic hepatitis B

<table>
<thead>
<tr>
<th>Resources item</th>
<th>Price (PLN)</th>
<th>Data source</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drugs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lamivudine (acquisition cost of 28 tablets, 0.1 g each)</td>
<td>437.80</td>
<td></td>
</tr>
<tr>
<td>IFN-α (acquisition cost of 1 amp., 5mIU)</td>
<td>170.68</td>
<td></td>
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<tr>
<td>Essentiale forte (acquisition cost of 50 capsules)</td>
<td>33.12</td>
<td>Pharmaceutical wholesale price list, 2002</td>
</tr>
<tr>
<td>Lactulose (acquisition cost of 150 ml)</td>
<td>8.34</td>
<td></td>
</tr>
<tr>
<td><strong>Laboratory tests (per test)</strong></td>
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<td></td>
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<tr>
<td>Serologic examination</td>
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<td></td>
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<tr>
<td>HBsAg</td>
<td>12.0</td>
<td></td>
</tr>
<tr>
<td>HBeAg</td>
<td>36.0</td>
<td></td>
</tr>
<tr>
<td>HBeAb</td>
<td>36.0</td>
<td></td>
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<tr>
<td>DNA polymerase</td>
<td>200.0</td>
<td></td>
</tr>
<tr>
<td>Blood cell count + platelets + blood smear + ESR</td>
<td>24.0</td>
<td></td>
</tr>
<tr>
<td>Proteinogram</td>
<td>17.0</td>
<td></td>
</tr>
<tr>
<td>APTT</td>
<td>5.0</td>
<td>Medical Services Schedule, 2002</td>
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<tr>
<td>Aminotransferases</td>
<td>12.0</td>
<td></td>
</tr>
<tr>
<td>Bilirubin</td>
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<td></td>
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<tr>
<td>Proteinuria</td>
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<tr>
<td>BUN</td>
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<tr>
<td>Creatinine</td>
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<tr>
<td>Thyroid hormones</td>
<td>34.0</td>
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</tr>
<tr>
<td>Abdominal ultrasonography</td>
<td>35.0</td>
<td></td>
</tr>
<tr>
<td>Liver biopsy</td>
<td>120.0</td>
<td></td>
</tr>
<tr>
<td>Ambulatory visits (parenteral administration of drug)</td>
<td>576 (72 x 8)</td>
<td></td>
</tr>
<tr>
<td>Tests</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBsAg, HBeAg, HBeAb</td>
<td>1,008 (12 x 84 PLN)</td>
<td>672 (8 x 84 PLN)</td>
</tr>
<tr>
<td>DNA polymerase</td>
<td>200 (1 x 200 PLN)</td>
<td>200 (1 x 200 PLN)</td>
</tr>
<tr>
<td>Blood cell count</td>
<td>288 (12 x 24 PLN)</td>
<td>192 (8 x 24 PLN)</td>
</tr>
<tr>
<td>Proteinogram</td>
<td>17 (1 x 17 PLN)</td>
<td>17 (1 x 17 PLN)</td>
</tr>
<tr>
<td>Aminotransferases</td>
<td>144 (12 x 12 PLN)</td>
<td>96 (8 x 12 PLN)</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>60 (12 x 5 PLN)</td>
<td>40 (8 x 5 PLN)</td>
</tr>
<tr>
<td>BUN, creatinine, proteinuria</td>
<td>15 (1 x 15 PLN)</td>
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</tr>
<tr>
<td>Thyroid hormones</td>
<td>68 (2 x 34 PLN)</td>
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</tr>
<tr>
<td>Abdominal ultrasonography</td>
<td>35 (1 x 35 PLN)</td>
<td>35 (1 x 35 PLN)</td>
</tr>
<tr>
<td>Liver biopsy</td>
<td>120 (1 x 120 PLN)</td>
<td>120 (1 x 120 PLN)</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>2,500 (1 x 2500 PLN)</td>
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</tr>
<tr>
<td><strong>Total</strong></td>
<td>17,536</td>
<td>7207</td>
</tr>
</tbody>
</table>

Abbreviations: APTT, activated partial thromboplastin time; BUN, blood urea nitrogen; ESR, erythrocyte sedimentation rate.

Table 3 Cost data for the model

(A) Costs associated with antiviral treatment

<table>
<thead>
<tr>
<th>Resource item</th>
<th>Cost per patient for 1 year (PLN)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td></td>
</tr>
<tr>
<td>IFN-α</td>
<td>12,289</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>5691</td>
</tr>
<tr>
<td>No treatment</td>
<td>—</td>
</tr>
<tr>
<td>Specialist consultations</td>
<td>216 (12 x 18 PLN)</td>
</tr>
<tr>
<td>(administration of drug)</td>
<td>144 (8 x 18 PLN)</td>
</tr>
</tbody>
</table>
| (B) Additional costs associated with progression to cirrhosis
| Liver biopsy                                | 120 (1 x 120 PLN)                 |
| Hospitalization                             | 2,500 (1 x 2500 PLN)              |
| **Total**                                   | 17,536                            |

Note: Values in parentheses indicate the number of counting units and unit price of resources used.

Abbreviations: APTT, activated partial thromboplastin time; BUN, blood urea nitrogen.
Cost-Effectiveness of Lamivudine and IFN-α in CHB

Results

Base-Case Analysis

Based on the decision tree in Figure 1 it is expected that introduction of lamivudine will result in a much higher proportion of CHB patients being treated than the actual situation in which IFN-α is the only approved drug treatment (92% in strategy A and B vs. 60% in strategy C). It is expected that 80% of CHB patients would be treated with lamivudine if lamivudine were the drug of choice (strategy A) and that 32% of patients would receive lamivudine if IFN-α were the drug of choice (strategy B). The proportion of patients completing treatment with IFN-α (and accounting for IFN-α intolerance was 10.8% in strategy A and 54% in both strategies B and C.

Introduction of lamivudine results in a higher number of patients who seroconvert and a consequent delay in disease progression. HBeAg seroconversion rates for strategies A, B, C, and D were 0.17, 0.169, 0.13, and 0.06, respectively, as summarized in Table 4. The higher HBeAg seroconversion rates for patients in strategies A and B were due to the higher proportion of patients who received active treatment, as efficacies for both lamivudine and IFN-α in terms of seroconversion rates were assumed to be comparable (0.18 vs. 0.19). Table 5 indicates the proportion of patients who did not progress to cirrhosis with strategies A, B, C, and D, and were 0.97, 0.93, 0.9, and 0.89, respectively.

As indicated in Tables 4 and 5, the total costs per patient treated according to strategies B and C were higher than total costs for strategy A. This is directly attributable to the drug acquisition cost and to costs of consultations and monitoring during treatment, which are much higher for IFN-α than for lamivudine as summarized in Table 3.

Because of higher costs and lower effectiveness, strategies B and C are dominated by strategy A. Tables 4 and 5 show the outcome of comparison of strategy A with strategy D: an incremental cost of 57,855 PLN per extra seroconversion and of 79,550 PLN per cirrhosis avoided.

Conversion of Proxy Outcomes to Life-Years Gained

Nonprogression to cirrhosis is the surrogate marker with predictive value for improved survival [60]. Because the outcome of interest in a cost-effectiveness analysis is life-years gained (LYG), information on cirrhosis cases avoided should be translated into life expectancy. To calculate life-years gained under a health program that prevents progression to cirrhosis, the life expectancy of persons with and without hepatic cirrhosis is estimated, starting with the age of the patient at the initiation of the program. This method requires information

### Table 4 Summary of the results of the model

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Effectiveness (HBeAg seroconversion rate)</th>
<th>Incremental effectiveness</th>
<th>Cost (PLN)</th>
<th>Incremental cost (PLN)</th>
<th>ICER (PLN per extra HBeAg seroconversion)</th>
</tr>
</thead>
<tbody>
<tr>
<td>D</td>
<td>0.06</td>
<td></td>
<td>1,562</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>0.13</td>
<td>0.07</td>
<td>10,644</td>
<td>9082</td>
<td>129,743</td>
</tr>
<tr>
<td>B</td>
<td>0.169</td>
<td>0.039</td>
<td>12,453</td>
<td>1,809</td>
<td>46,385</td>
</tr>
<tr>
<td>A</td>
<td>0.17</td>
<td>0.001</td>
<td>7,926</td>
<td>-4527</td>
<td>-4,527,000</td>
</tr>
</tbody>
</table>

Strategies B and C are dominated by strategy A.

### Table 5 Summary of the results of the model

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Effectiveness (nonprogression to cirrhosis)</th>
<th>Incremental effectiveness</th>
<th>Cost (PLN)</th>
<th>Incremental cost (PLN)</th>
<th>ICER (PLN per cirrhosis case avoided)</th>
</tr>
</thead>
<tbody>
<tr>
<td>D</td>
<td>0.06</td>
<td></td>
<td>1,562</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>0.90</td>
<td>0.01</td>
<td>10,644</td>
<td>9082</td>
<td>908,200</td>
</tr>
<tr>
<td>B</td>
<td>0.93</td>
<td>0.03</td>
<td>12,453</td>
<td>1,809</td>
<td>60,300</td>
</tr>
<tr>
<td>A</td>
<td>0.97</td>
<td>0.04</td>
<td>7,926</td>
<td>-4527</td>
<td>-113,175</td>
</tr>
</tbody>
</table>

Strategies B and C are dominated by strategy A.

*The alternative strategies are ranked according to their effectiveness (HBeAg seroconversion rate).
published in life tables and estimates of the effect of hepatic cirrhosis on mortality.

According to data from literature, patients with CHB and hepatic cirrhosis have a 5-year survival rate of 55% \[56\] or 45% mortality over 5 years. Assuming a constant annual probability of dying from hepatic cirrhosis after disease occurrence, the following calculations are performed.

The estimated annual probability of dying from hepatic cirrhosis \((h)\), is given by the equation

\[
h = 1 - (1 - 0.45)^{1/5} = 0.1127.
\]

Life expectancy of a \(k\)-year-old person \((E_k)\) was estimated using this equation and assumes that almost all patients die by age 100 years:

\[
E_k = 0.5 + \sum_{n=k}^{100} z(n) = 0.5 + \sum_{n=k}^{100} \left(\prod_{i=k}^{n}(1-d(i))\right),
\]

where \(z(n)\) is the portion of the initial population that survives to year \(n\).

For a person without hepatic cirrhosis, \(z(n)\) is expressed with the formula

\[
z(n) = \prod_{i=k}^{n}(1-d(i)),
\]

where \(d(i)\) is annual probability of dying at age \(i\).

Similarly, but taking into account excess mortality from the disease, \(z(n)\) for a person with hepatic cirrhosis occurring at age \(k\) is expressed as

\[
z(n) = \prod_{i=k}^{n}((1-d(i)) \times (1-h))
\]

giving

\[
E_k = 0.5 + \sum_{n=k}^{100} \left(\prod_{i=k}^{n}(1-d(i)) \times (1-h)\right)
\]

\[
= 0.5 + \sum_{n=k}^{100} \left(1-h \prod_{i=k}^{n}(1-d(i))\right),
\]

where \(h\) is the annual probability of dying from hepatic cirrhosis and \(d(i)\) is the annual probability of dying from other causes at age \(i\).

Expected life-years lost, if hepatic cirrhosis occurs at age \(k\), is calculated as the difference in expected life-years.

\[
\text{Loss in life expectancy} = \sum_{n=k}^{100} \left(\prod_{i=k}^{n}(1-d(i)) - (1-h) \prod_{i=k}^{n}(1-d(i))\right)
\]

\[
= \sum_{n=k}^{100} \left(1 - (1-h)^{n-k+1}\right) \prod_{i=k}^{n}(1-d(i)),
\]

Results of these calculations are listed in Table 6. Assuming that 60% of the population is female, hepatic cirrhosis reduces estimated life expectancy by 37.76 years, if occurring in 30-year-old individuals, and by 20 years in 50-year-olds.

**Determining Cost-Effectiveness (Cost per Life-Years Gained)**

Table 5 compares strategy A with strategy D and gives the incremental cost of 79,550 PLN per cirrhosis case avoided. Because hepatic cirrhosis reduces estimated life expectancy in the population under study by 37.76 years if it occurs in a 30-year-old person, and by 20 years in a 50-year-old person, the incremental cost-effectiveness ratio comparing strategies A and D is 2105 PLN per LYG for a population at age 30 and 3978 PLN per LYG for a population at age 50. Comparing this result with the suggested threshold for cost-effectiveness, calculated on the basis of 1 year of hemodialysis treatment at a cost of 62,400 PLN, it can be concluded that strategy A offers substantial benefit at reasonable cost to the Polish health-care system.

**Sensitivity Analyses**

To test the robustness of the model, parameters in two categories, probability and cost, were varied and are indicated in Tables 7 and 8. In all cases, parameters that were not varied remained at the

Table 6 Life expectancy for \(k\)-year-old men and women and the effect of hepatic cirrhosis in \(k\)-year-old men and women on life expectancy (\(k = 30\) and \(k = 50\))

<table>
<thead>
<tr>
<th>Population</th>
<th>Life expectancy without hepatic cirrhosis (years)</th>
<th>Life expectancy after progression to hepatic cirrhosis (years)</th>
<th>Loss of life expectancy because of hepatic cirrhosis (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-year-olds</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>49.02</td>
<td>8.26</td>
<td>40.76</td>
</tr>
<tr>
<td>Men</td>
<td>41.32</td>
<td>8.10</td>
<td>33.26</td>
</tr>
<tr>
<td>50-year-olds</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>30.11</td>
<td>7.8</td>
<td>22.31</td>
</tr>
<tr>
<td>Men</td>
<td>23.90</td>
<td>7.26</td>
<td>16.64</td>
</tr>
</tbody>
</table>
base-case values. The sensitivity of the model was based on the change in the dominance report and the incremental cost-effectiveness ratios when comparing strategies A and D. In most cases, changing the value of key drivers for sensitivity analysis across the range described above did not have any significant effect on the dominance report nor on the incremental cost-effectiveness ratios. The least favorable ICER when comparing these strategies is when the probability of progression to cirrhosis in lamivudine-treated patients who failed seroconversion is 0.12, as indicated in Table 8. This is due to a marked reduction in the incremental effectiveness ratio in terms of nonprogression to cirrhosis for strategies A and D, in which case the incremental cost per cirrhosis case avoided increases to 483,964 PLN. Therefore, the cost per life-year gained is 3302 PLN for a 30-year-old person and 6225 PLN for a 50-year-old person and remains within the range of cost-effectiveness.

When the probability of HBeAg seroconversion is altered from the base value to 0.21 for IFN-α or to 0.16 for lamivudine, the best effectiveness, in terms of HBeAg seroconversion rate, is achieved...
with strategy B. The incremental cost per HBeAg seroconversion when comparing strategy B to strategy A is 628,706 PLN when the probability of seroconversion after IFN-α is 0.21, 554,783 PLN when the probability of seroconversion after lamivudine is 0.16, and 269,441 PLN when the probability of seroconversion is adjusted for both drugs (0.21 for IFN-α; 0.16 for lamivudine). These incremental cost-effectiveness ratios are less favorable than when scenario A is compared to scenario D, as indicated in Table 7.

The aim of extreme scenario analysis is to examine the sensitivity of the results under the most optimistic and clinically plausible assumption about the effect of IFN-α treatment and the most pessimistic assumption about the effect of lamivudine treatment. The probabilities represent upper and lower values from questionnaire-collected information and from clinical studies. It was assumed that 70% of patients were eligible for IFN-α therapy; that all were treated; that 60% of patients were eligible for lamivudine therapy; that the probability of HBeAg seroconversion was 0.21 and 0.16 after IFN-α and lamivudine, respectively; and that the probability of progression to cirrhosis after IFN-α and lamivudine was 0.12. In this case,
Cost-Effectiveness of Lamivudine and IFN-α in CHB

the best effectiveness in terms of HBeAg seroconversion and nonprogression to cirrhosis was achieved with strategy B. Strategy C was dominated by a combination of strategies A and B. The incremental cost-effectiveness ratios for strategies B and A, as indicated in Tables 7 and 8, were 206,531 PLN per additional seroconversion and 1,721,093 PLN per cirrhosis case avoided. Thus, cost per life-year gained is 45,580 PLN for a 30-year-old person and 86,055 PLN for a 50-year-old. Comparing this result with the suggested threshold for cost-effectiveness, calculated on the basis of 1 year of hemodialysis treatment at a cost of 62,400 PLN, it can be concluded that, for a 50-year-old population, strategy B is not a cost-effective alternative to strategy A. When comparing strategies A and D, the incremental costs per additional seroconversion and per cirrhosis case avoided are 77,404 PLN and 645,034 PLN, respectively. As in the base-case analysis, strategy A remains the cost-effective alternative to no treatment. The results of the sensitivity analyses indicate that, in terms of the magnitude of the ICER and of dominance, the model is robust over the very wide range of parameter values mentioned above.

Budgetary Impact Analysis

Based on Polish epidemiologic data it was determined that, within the next 10 years, at least 8000 patients with CHB annually should receive treatment. Extrapolation of model results for this population led to the tentative conclusion that use of strategy A rather than strategy B or strategy C could save between 36,216,000 PLN and 21,747,200 PLN per year. Additional benefit is associated with the greater effectiveness of strategy A. Of the 8000 individuals following strategy A, B, or C, the numbers of patients seroconverting would be 1360, 1352, and 1040, respectively, and the numbers of patients not progressing to cirrhosis would be 7760, 7440, and 7200, respectively. Because of the greater number of patients who seroconverted and who did not progress to cirrhosis following strategy A, compared to strategies B and C, a reduction of potential expenditures associated with antiviral retreatment and progression of the disease is implied.

Discussion

The increased pressure on health-care budgets in most countries has emphasized the need to demonstrate the value for money of new health technologies. New drugs and new drug indications must be assessed for cost-effectiveness over and above safety and efficacy. Because this information is considered an important part of the decision-making process, specifically reimbursement, the key requirement for any cost-effectiveness report is that assumptions used in models reflect real-life practice.

Chronic hepatitis B usually follows a slow course, and it is difficult to carry out long-term, prospective, clinical-economic studies to estimate costs and effects associated with administration of different antiviral agents. In such cases, the decision model developed is based on data obtained from reliable, controlled, randomized clinical trials; the natural history of the disease; expert panels; information collected on questionnaires; current treatment practices; patient characteristics; etc.

Previous models for the treatment of CHB [50,61,62] used hypothetical cohorts of patients treated or not with IFN-α. Only in one model was an attempt made to reflect real-life practice—one hypothetical cohort of patients received lamivudine, IFN-α, or no treatment (scenario A); another received either IFN-α or no treatment (scenario B); while the third cohort received no treatment (scenario C) [63]. The authors based their model on patients, treatment practices, and costs in Australia. In the model presented here, hypothetical cohorts of patients received one of the available antiviral drugs or no treatment (strategies A and B), IFN-α or no treatment (strategy C), or no treatment (strategy D), attempting thereby to reflect real-life practice in Poland. As in the Australian study, the proportions of patients eligible for lamivudine and IFN-α therapy were obtained from expert panels and supported by data from the questionnaire distributed to hepatologists. There are some population differences—patients in Australia are predominantly migrants from southeast Asia and have been shown to be more resistant to IFN-α—and differences in treatment practices. The different conclusions from the Australian and the Polish studies may be due to the use of two strategies, A and B, in the Polish study. Strategies A and B and scenario A in the Australian study assumed the availability of lamivudine, but differed in terms of first-line therapy, thereby allowing one to determine which should be the drug of choice. Strategies C and D were relevant to scenarios B and C in the Australian study. The availability of lamivudine as per strategies A and B (Polish) and scenario A (Australian) increases the proportion of patients receiving antiviral therapy and the rates of seroconversion and of nonprogression to cirrhosis. In the Australian study, this benefit was achieved for a small overall increase
in health-care costs. The incremental cost-effectiveness ratio for lamivudine (scenario A) was A$3341 per additional seroconversion and A$5272 per cirrhosis avoided, compared to the scenario in which IFN-α is the only available treatment [63]. A similar situation occurred when strategy B (IFN-α as the drug of choice) was compared to strategy C (only IFN-α is available) in the Polish study: the incremental cost-effectiveness ratio was 46,385 PLN per additional seroconversion and 60,300 PLN per avoided cirrhosis. In the case where strategy A (lamivudine as first-line treatment) was the alternative to strategy C, better outcome and cost savings were possible. Because of higher costs and lower effectiveness, strategies B and C were dominated by strategy A. Compared to no treatment, lamivudine was the cost-effective drug of choice when benchmarked against other currently funded health-care programs in Poland.

The results of this pharmacoeconomic analysis should be interpreted within the limitations of the model and data on which they are based. The time horizon was restricted to 1 year. Because of lack of real long-term cost data for management of subsequent stages of CHB, it was impossible to apply a long-term Markov model. Conversion of the ICER for cost per cirrhosis case avoided into cost per LYG based on 1-year treatment costs alone was possible. Efficacy of IFN-α and lamivudine was based on results of current randomized, controlled, international, clinical trials limited to 1-year follow-up. If new data become available, the analysis may require verification. The proportion of patients receiving IFN-α and lamivudine was based on information from Polish experts in hepatology. Presumably, these data reflect the current situation in Poland, but it might be worthwhile conducting a national survey to confirm this.

In the model it was assumed that IFN-α dosage was 5 mIU, three times weekly for 6 months, based on the recommendations of Polish National Specialists of Infectious Diseases and on clinical practice in Poland. The approved dosage is 5 to 10 mIU, three times weekly for 4 to 6 months. In comparative clinical trials of IFN-α versus lamivudine, IFN-α was given at a dose of 10 mIU, three times weekly for 4 months. This dose was tested in sensitivity analysis and did not have any significant effect on the ICER.

Because the rate of HBeAg seroconversion is a key driver in the model, patients with HBeAg (-) HBV (precore mutant) were not taken into account in the analysis. In some countries, up to 30% of patients have developed precore mutant HBV. In this group, a lower response rate and higher rate of recurrence have been observed after IFN-α therapy [40,64], while the response rate (loss of HBV DNA and normalization of ALT level) after lamivudine was the same as that observed in patients infected with the wild-type virus [17]. Including these patients in the analysis would benefit lamivudine therapy, but an end point, other than HBeAg seroconversion, should be included.

The emergence of YMDD-mutant HBV is the other clinically relevant aspect of lamivudine therapy. The YMDD mutant corresponds to sustained amino acid sequence in HBV DNA polymerase, the enzyme that is highly sensitive to lamivudine. Its inhibition leads to arrest of viral replication. Substitution of isoleucine (YIDD) or valine (YVDD) for methionine may result in decreased lamivudine activity after its emergence. Clinical studies indicate that YMDD mutant may occur in 14% to 32% of patients receiving lamivudine therapy for 1 year [15,35,36]. YMDD mutant does not replicate strongly compared to wild-type HBV, and therefore, lamivudine therapy in patients infected with YMDD mutant still causes reduction of viral DNA, and in some patients HBeAg seroconversion may occur [65,66]. Clinically relevant data regarding YMDD HBV are readily available, and therefore, its influence on the results of lamivudine therapy in this model was not considered. It seems, however, that this does not change the conclusions, because even patients with YMDD mutant have reduced viral replication after lamivudine therapy compared to no treatment and also experience improvements in liver histology.

In the present model, the perspective of the health-care payer was taken. Analysis from the societal perspective should also consider indirect costs, but estimation of these in Poland is impossible without adequate studies. Considering that the availability of lamivudine increases the proportion of treated patients with a consequent increase in the rate of HBeAg seroconversion, lost productivity in the group receiving lamivudine should be lower than in patients receiving only IFN-α therapy or no treatment. This suggests that indirect costs alone may increase the benefits of lamivudine therapy with the result that incorporation of indirect costs into the model should provide additional evidence for the cost effectiveness of lamivudine.

**Conclusions**

This model demonstrates the costs and benefits relevant to the introduction of lamivudine in clinical
Cost-Effectiveness of Lamivudine and IFN-α in CHB

practice. Strategy A (lamivudine as first-line treatment) yields the best results in terms of HBeAg seroconversion rate and nonprogression to cirrhosis. Strategy B (IFN-α as the drug of choice) and strategy C (only IFN-α) are dominated by strategy A, which ensures a greater effectiveness at lower cost. Strategy A is cost-effective when compared to no treatment when benchmarked against other currently funded health-care programs in Poland. The one-way sensitivity analysis and extreme scenario analysis revealed that changing the value of key drivers and parameters did not have any significant effect on the results.

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