Southampton Health Technology Assessments Centre (SHTAC)

ERG comments on the BMS Pharmaceuticals Ltd response to the ACD
7th May 2008

Based on the ERG appraisal the Appraisal Committee noted that the HBeAg-negative model in the original manufacturer's submission did not represent NHS practice with respect to

a) prevalence of existing active cirrhosis in patients first considered for treatment with anti-HBV therapy;
b) continuation of treatment with active therapy when patients progress to compensated cirrhosis.

The Appraisal Committee also noted that the lifetime version of the model is appropriate for estimating the cost effectiveness of entecavir (ETV) in patients with HBeAg-negative chronic hepatitis B (CHB).

In response to the request from the Appraisal Committee, the manufacturer has provided a revised estimate of the cost effectiveness of ETV compared to lamivudine (LAM) in treatment of people with HBeAg-negative CHB (section 2 of the manufacturer's response to ACD) that seems to have included:

a) a lifetime-treatment duration and continuation of treatment with ETV when patients progress to compensated cirrhosis (CC) and
b) a mixed cohort of cirrhotic / non-cirrhotic patients starting with ETV to reflect NHS practice in terms of prevalence of existing active cirrhosis

The revised life-time HBeAg-negative model comparing ETV with LAM is said to incorporate treatment of patients who enter the compensated cirrhosis state. The manufacturer correctly adjusted the progression rate from compensated to decompensated cirrhosis using the same rate of 1.8% (also used in the ERG scenario analysis) for both treatment arms. *The ERG considers the manufacturer's arguments suggesting an additional differential treatment effect associated with the slower progression of ENT cirrhotic patients to the decompensated cirrhosis state as compared to LAM cirrhotic patients to be poorly justified, as these are based entirely on the results of the study of a comparator (i.e. LAM) in Asian patients (Liaw et al, 2004).* The ERG asserts that in the absence of the data on the rate of progression to decompensated cirrhosis in patients receiving ENT monotherapy or a combination of ENT+adefovir, the same rate of progression to decompensated cirrhosis should be applied to both the ENT and the comparator arm.

One of the ERG scenario analyses was conducted to emphasise the inappropriateness of the manufacturer's implicit assumption that patients who progressed to compensated cirrhosis state should no longer receive any anti-HBV therapy. The revised base case analysis presented by the manufacturer reasonably includes the cost of initial active therapy and the cost of salvage therapy received by the patients who developed resistance to active treatment either before progressing to compensated cirrhosis or during the time in this state. *However, in their response to the ACD the manufacturer does not report either the estimates of the rates of developing resistance in patients in the compensated cirrhosis state or the source of the clinical evidence for these estimates.*

The manufacturer also indicated that in order to estimate precisely the cost of both the initial and salvage treatment in patients in the compensated cirrhosis state (CC), the existing CC state was split into two: "a CC state for patients who become resistant to their first-line therapy and require salvage treatment; and a CC state for patients who are still receiving first line monotherapy and become resistant over time whilst in this state" (p.4 of the MS response to the ACD). *It appears that the original structure of the model has been further complicated by introduction of another cirrhotic state in addition to the inactive cirrhosis state and the decompensated cirrhosis state. The ERG has already questioned the clinical rationale for the inactive cirrhosis state in the original model and the values of transition probabilities associated with this state (p81-82 of the ERG report). The ERG report stated that the impact of these structural assumptions on the results of cost-effectiveness analysis is unclear.*

In response to the concerns raised in the ERG report, the manufacturer also modified the original model to include "a range of assumptions relating to the proportion of patients presenting with cirrhosis at treatment initiation" (p.5 of the MS response to the ACD). The manufacturer has reasonably assumed the similar efficacy of ENT in cirrhotic and non-cirrhotic patients (Table 2 of the MS response to the ACD).

The table below presents the ICER estimate reported in the original submission, the exploratory analysis results presented in the ERG scenario analyses and the estimated ICERs as reported in the revised version of the model.

Table. Base case cost effectiveness analysis results of ETV compared to LAM (HBeAg negative patients)

Assumed ratio of non-cirrhotic to cirrhotic patients at the baseline	ICER from the lifetime treatment duration scenario analysis in the MS original model	Results of the exploratory ERG scenario analyses	ICER from the analyses of the MS revised model[a]
1/0	£16,850[b]	£27,124[c]	£20,463/£15,531
0.9/0.1	Not estimated	£34,006[d]	£24,335/£17,083
0.8/0.2	Not estimated	£42,608[d]	£29,176/£19,023

[a]The manufacturer provided two sets of the estimated ICERs with and without the "CC state split". The first estimate effectively assumes that patients in the CC state who develop resistance to the initial treatment continue to receive this treatment but not the salvage therapy.

[b]The estimate does not include the cost of either initial or salvage treatment of patients in the CC state

[c]The estimate was calculated to demonstrate sensitivity of the original ICER to the MS' unreasonable assumption of no treatment of patients in the CC state. It includes additional cost of continuation with the initial treatment but does not include cost of the salvage therapy.

[d]The estimate was calculated to demonstrate sensitivity of the original ICER to the MS' unreasonable assumption of the 1/0 ratio of non-cirrhotic to cirrhotic patients at the baseline. It did not include any other alternative assumptions to the MS original model, such as additional cost of treatment of CC patients.

At the first glance, the estimates based on the "no CC state split" version of the model appear reasonable, although as the manufacturer pointed out, imprecise. However, the same can not be said in relation to results of the "CC state split" version of the model as it is based on the alternative structural assumptions that seem to have been introduced to the original model. Therefore it is not possible for the ERG to verify the new estimates of cost effectiveness of ETV in comparison to LAM reported in the manufacturer's response to the ACD.

The ERG assumed that in line with the AC recommendations the manufacturer's revised cost effectiveness estimates are based on the life time treatment duration version of the model in HBeAg-negative patients. However, it should be kept in mind that there are no long term ENT efficacy data and in the model the low rates of resistance (0.2% in ENT vs 28% in LAM) are extrapolated for up to 60 years of treatment duration.