Response to the Appraisal Consultation Document **Confidential information is highlighted and underlined, e.g.** Baraclude	
Approved Name of Medicinal Product:	Entecavir
Brand Name:	Baraclude®
Company:	Bristol-Myers Squibb Pharmaceuticals Ltd
Submitted by:	CIC REMOVED
Position:	Director, External Affairs & Market Access
Date:	30th April 2008

1. Summary

Bristol-Myers Squibb (BMS) welcomes the preliminary recommendation from the Appraisal Committee (AC) that ETV is both cost and clinically effective for the treatment of HBeAg positive chronic hepatitis B (CHB) patients. BMS notes that both the Evidence Review Group (ERG) and the AC recognised the clinical effectiveness and value of ETV in the HBeAg negative population and is pleased to provide further clarification on the cost and clinical effectiveness of ETV in HBeAg negative patients as requested by the Committee:

1) The consideration of alternative treatment strategies in particular:
   a) Using a typical cohort of patients starting with ETV that represents NHS practice in terms of prevalence of existing active cirrhosis.
   b) The continuation of treatment with ETV when patients progress to compensated cirrhosis.
   c) Lifetime-treatment duration.
2) The relative effectiveness of ETV in people with compensated cirrhosis.
3) The relationship between the surrogate outcomes used and the final effectiveness outcomes of the model.

The revised BMS base case results show that ETV is cost-effective in HBeAg negative patients allowing for a mix of cirrhotic/non-cirrhotic patients starting treatment and when therapy is continued in patients who develop compensated cirrhosis, and lifetime treatment duration is considered.

The incremental cost per QALY (Quality Adjusted Life Year) ratio for ETV in the revised base case is £20,463 when salvage therapy costs (omitted in the ERG scenario analysis) are applied to patients who develop resistance prior to developing compensated cirrhosis. Incorporating a mixed non-cirrhotic / cirrhotic patient population starting on therapy into the revised base case analysis, results in incremental cost per QALYs for ETV versus lamivudine ranging from £24,335 for a 90%:10% non-cirrhotic/cirrhotic split to £29,176 for a 80%:20% split. These incremental cost per QALYs reduce further when salvage therapy costs are included for **all** patients who develop resistance to between £17,083 and £19,023 for the 90%:10% and 80%:20% splits respectively.

BMS requests that the Appraisal Committee recommends entecavir in HBeAg negative patients, based on the supplemental analyses of cost effectiveness and the comments that follow in this response.

BMS would first like to respond to the four questions posed by the Institute, followed by the detailed response to the ACD.

i) Do you consider that all of the relevant evidence has been taken into account?

In this response BMS has referred to two recently published conference abstracts reporting five year resistance rates for the 901 study referenced in the original submission[1] and the results of a new study[2] reporting resistance data for entecavir (ETV).

ii) Do you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence, and that the preliminary views on the resource impact and implications for the NHS are appropriate?

The summaries of clinical and cost effectiveness data in the Appraisal Consultation Document (ACD) are reasonable interpretations of the data presented in the original BMS submission. A revised base case cost effectiveness estimate based on alternative treatment strategies is provided by BMS for consideration by the AC. In this revised base case it is assumed that patients who become resistant to lamivudine therapy subsequently require add-on adefovir salvage therapy, as this is in line with clinical practice in the UK and previous NICE guidance.[3] It is apparent that the ERG's scenario analysis (page 97 of the ERG report) for ETV in the HBeAg negative population omits salvage therapy costs for lamivudine resistant patients who develop compensated cirrhosis (CC). Instead, the ERG's calculation of treatment costs in the CC state rests upon the assumption that all patients would remain on lamivudine monotherapy regardless of resistance status. This is unlikely to be the case in actual clinical practice. This approach has introduced a significant bias into the ERG's estimates of cost effectiveness of ETV by underestimating the drug treatment costs for patients in the lamivudine arm following the development of resistance, and produced incremental cost effectiveness ratios (ICERs) that favour lamivudine over ETV. The ICERs estimated by the ERG are, therefore, neither an accurate nor a clinically reasonable reflection of the cost effectiveness of ETV relative to lamivudine.

iii) Do you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS?

BMS welcomes the provisional recommendation from the Appraisal Committee that ETV is both cost and clinically effective for the treatment of HBeAg positive CHB patients. However, BMS requests that the Appraisal Committee recommends entecavir in HBeAg negative patients. The additional analyses presented in this response show that ETV is a cost effective therapy in the HBeAg negative population based on lifetime treatment duration, continuation of treatment for patients who have developed CC, and a mixed cirrhotic/non-cirrhotic population starting therapy.

iv) Are there any equality related issues that need special consideration that are not covered in the ACD?

None.

2. Cost-Effectiveness of ETV in HBeAg Negative Patients

In response to the request from the Appraisal Committee (AC) (section 1.3 of ACD), Bristol-Myers Squibb (BMS) has provided below further clarification on the cost effectiveness of entecavir (ETV) for the treatment of people with HBeAg-negative chronic hepatitis B (CHB) on the following issues:

- Consideration of two alternative treatment strategies in a revised base case:
  1. Lifetime-treatment duration and continuation of treatment with ETV when patients progress to compensated cirrhosis (CC)
  2. Treatment strategy above modified to include a mixed cohort of cirrhotic / non-cirrhotic patients starting with ETV to reflect NHS practice in terms of prevalence of existing active cirrhosis

2.1 Lifetime treatment (including compensated cirrhosis)

In revising the base case estimates of cost effectiveness for the HBeAg negative population, BMS has made a number of changes to the analysis presented in the original submission.

Duration of therapy

Although there is evidence showing that virological remission can be maintained after therapy discontinuation in a selected subgroup of HBeAg-negative CHB patients successfully treated for 4 to 5 years,[4] the optimal duration of therapy for these patients is still unknown. Lifetime duration of therapy was assumed, consistent with the assumptions of the Evidence Review Group (ERG) in their scenario analysis reported on page 97 of their report.

Continuation of therapy for compensated cirrhotic patients

To allow patients in the economic model to continue therapy once they have developed compensated cirrhosis (CC), the progression rate from compensated to decompensated cirrhosis (DCC) needs to be adjusted, as the rate used in the original submission represents an untreated rate of progression. As data on rates of progression from CC to DCC with ETV versus lamivudine do not exist, the 1.8% rate[5] as suggested by the ERG (page 97 of ERG report) was used and progression is assumed to be independent of therapy. However, it must be emphasised that this progression rate is likely to significantly overestimate the incremental cost per QALY (Quality Adjusted Life Year) for ETV, as there is recent trial evidence showing that progression of cirrhosis in hepatitis B patients is linked with drug resistance.[6] In this study of CHB patients with advanced fibrosis and cirrhosis, disease progression was assessed by a worsening in Child-Pugh scores and was observed in 7% of lamivudine-treated subjects with genotypic resistance (YMDD mutations) compared with less than 1% in lamivudine-treated patients without resistance. Thus the number of patients that experienced a progression of their cirrhosis was seven times higher amongst resistant compared with non-resistant patients. ETV is more likely to slow cirrhosis progression compared with lamivudine as it is associated with very low rates of resistance (approximately 1% of patients over 5 years)[1] whereas lamivudine is

associated with significantly higher (67% after 4 years) rates of genotypic resistance[7]. However, for simplicity, the revised base case estimates assume the same rate of progression from compensated to decompensated cirrhosis (1.8%) for both ETV and lamivudine, and therefore underestimates the benefit of ETV.

Salvage therapy

In the revised base case, patients who become resistant and require salvage therapy before developing CC are assumed to continue on the same therapy once they develop CC. This assumption is consistent with clinical practice in the UK and previous NICE guidance, where adefovir is recommended for use in combination with lamivudine when treatment with lamivudine has resulted in resistance. Maintaining patients on salvage therapy in the CC state is especially important as the goal is to prevent progression to decompensation through sustained viral suppression and low resistance.[8] Following clarification from the ERG (10th, 14th, 23rd April 2008), it appears that this assumption was not made in the ERG's scenario analysis (page 97 of the ERG report). In the ERG's analysis, patients on salvage therapy of lamivudine plus adefovir combination because they have developed resistance to lamivudine monotherapy prior to entering the CC health state, are incorrectly and inappropriately switched back to lamivudine monotherapy once they enter this state. The omission of salvage therapy costs in the ERG's scenario analysis, introduces a significant bias in favour of lamivudine into the cost effectiveness estimates.

The cost of salvage therapy (an additional cost of £3,833 per patient per year) was incorporated into the model for patients who develop resistance prior to developing CC, by estimating an indicative mean drug cost for individuals in the model, based on the number of patients who become resistant and require salvage therapy at the end of each cycle before entering the CC state. As this analysis does not take into account patients who develop lamivudine resistance whilst in the CC state, an additional scenario analysis (Salvage costs for all resistant patients) was also undertaken, as these patients should also be treated with salvage therapy. This scenario analysis required splitting the existing CC state 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. This alternative approach allows for treatment costs in each arm to be more precisely estimated.

Revised base case results

Table 1 presents the results for the revised base case analyses as well as the ERG estimates. Including the costs of salvage therapy for patients who become resistant prior to developing cirrhosis only reduces the ICER from £27,124 (ERG estimate) to £20,463 for the comparison of ETV to lamivudine. Splitting the compensated cirrhosis state into two states – resistant and non-resistant patients with compensated cirrhosis – reduces the ICER further to £15,531.

Table 1: Cost effectiveness of ETV compared with LVD assuming lifetime duration and continuation of treatment in cirrhotic patients

	ICERs
ERG scenario analysis (Costs of salvage therapy omitted)	£27,124
BMS revised base case:	
- Salvage therapy costs for pre-cirrhotic resistant patients only	£20,463
- Salvage therapy costs for all resistant patients (CC state split by resistance status)	£15,531

2.2 Inclusion of mixed cirrhotic/non-cirrhotic patients starting therapy into revised base case

To provide further clarification to the AC on the cost effectiveness of ETV in HBeAg negative CHB patients, a mixed cirrhotic/non-cirrhotic population at baseline was modelled using the same methodology as used by the ERG. The efficacy of ETV in cirrhotic patients was assumed to be similar to that demonstrated in non-cirrhotic patients, as supported by the sub-analysis from the 027 trial shown in Table 2. The HBeAg negative model was re-run using a range of assumptions relating to the proportion of patients presenting with cirrhosis at treatment initiation. The non-cirrhotic to cirrhotic split was explored for the following scenarios - 100%/0%, 90%/10%, 85%/15%, 80%/20%.

Table 2: Percentage of patients with HBV-DNA<300 at Week 48 (027 trial)

	ETV	LVD	Difference (95% CI)
CIC REMOVED			
All patients	90%	72%	18.3 (12.3, 24.2)

The results of the revised base case including a mixed non-cirrhotic/cirrhotic population starting treatment, as well as the ERG's cost effectiveness estimates are presented in Table 3. The table shows that the revised base case estimates increase from £20,463 and £15,531 to £29,176 and £19,023 respectively, as the non-cirrhotic/cirrhotic mix increases from 100% non-cirrhotic to a mix of 80% non-cirrhotics and 20% cirrhotics. These ICERs indicate that ETV is a cost effective use of NHS resources.

Table 3: Cost effectiveness of ETV compared with LVD in a mixed cirrhotic and non-cirrhotic HBeAg negative population

Ratio non-cirrhotics/ cirrhotics	**ERG scenario analysis**	**BMS revised base case**	
	No salvage therapy	**Salvage therapy costs for pre-cirrhotic resistant patients only**	**Salvage therapy costs for all resistant patients (CC state split by resistance status)**
1/0	£27,124	£20,463	£15,531
0.9/0.1	£34,006	£24,335	£17,083
0.85/0.15	n/a	£26,613	£17,996
0.8/0.2	£42,608	£29,176	£19,023

3. Other comments

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ACD Section 4.9 – Relationship between surrogate outcomes used and the final effectiveness outcomes of the model

The ACD stated that the Committee would also welcome further information regarding the relationship between surrogate outcomes used in the model and the final effectiveness outcomes, and comparison of the model results with that observed in observational studies (section 4.9 of ACD). The use of HBV DNA levels as a surrogate marker for effectiveness is increasing in clinical practice. International and national clinical guidelines[8] are increasingly referring to viral load as one of the criteria to initiate and monitor therapy. To help clarify this relationship, additional analyses are presented below of the number of events for both ETV and lamivudine, and the number of events avoided by treating with ETV.

Results on final effectiveness outcomes of the model, i.e. number of cirrhosis and hepatocellular carcinoma cases, are reported in Table 4 for both the HBeAg positive and negative populations. All results correspond to the number of new events per 1,000 individuals. For the HBeAg negative population, lifetime treatment duration and continuation of treatment when patients progress to compensated cirrhosis (1.8% progression rate per year from compensated to decompensated cirrhosis for both ETV and lamivudine) was assumed in line with the ERG scenario analysis. In the HBeAg positive population, the base case was unchanged from BMS's original submission dated 26 November 2007.

Table 4: Estimated number of Cirrhosis and HCC events with ETV and LVD in both HBeAg negative and positive models

	Cirrhosis Incidence (per 100,000 person-years)			**HCC Incidence (per 100,000 person-years)**		
	LVD	**ETV**	**Difference (events avoided)**	**LVD**	**ETV**	**Difference (events avoided)**
HBeAg negative disease						
100% Non-cirrhotics	223.8	110.4	113.4	178.1	132.8	45.3
90%:10% cirrhotics to Non-cirrhotics	201.4	99.4	102.0	207.9	167.1	40.8
80%:20% cirrhotics to Non-cirrhotics	179.0	88.3	90.7	237.7	201.4	36.2
HBeAg positive disease						
100% Non-cirrhotics	517.5	483.0	34.5	271.6	259.4	12.2
90%:10% cirrhotics to Non-cirrhotics	511.9	480.9	31.0	299.4	288.4	11.0
80%:20% cirrhotics to Non-cirrhotics	506.4	478.8	27.6	327.1	317.3	9.8

There is a dearth of long-term observational studies that correlate surrogate markers such as viral load to long-term outcomes, number of cases of cirrhosis and hepatocellular carcinoma. The largest natural history study to date, REVEAL-HBV[9,10], is a 13-year prospective, population-based cohort study in Taiwan of 3,653 CHB patients. This study showed that HBV DNA levels are an important predictor of the risk of HCC and cirrhosis. The results from the REVEAL-HBV study are corroborated by those in a smaller prospective study of 70 Caucasian Italians with a 25-year follow up.[11] The number of cases of cirrhosis and hepatocellular carcinoma from these studies is presented in tables 5 and 6 below.

Table 5: Incidence rates for cirrhosis and HCC in individuals with CHB (reproduced from REVEAL-HBV)

Serum HBV-DNA level, copies/mL	Incidence of Cirrhosis (per 100,000 person-years) 100% non-cirrhotic	Incidence of HCC (per 100,000 person-years) 98% non-cirrhotic
300-(9.9 X 10^4)	339 -774	108 -297
(1.0-9.9) X 10^5	1879	962
≥1 million	2498	1152

The number of cases of cirrhosis and hepatocellular carcinoma from the Fattovich study is presented in table 6 below.

Table 6: Incidence rates for cirrhosis and HCC in individuals with CHB (reproduced from Fattovich et al)

Serum HBV-DNA level, copies/mL	Incidence of Cirrhosis (per 100,000 person-years)	Incidence of HCC (per 100,000 person-years)
	89% non-cirrhotic	
Mixed Cohort: ▪ 57% with HBV-DNA upto 1.4 X 10^5 ▪ 43% with ≥ 10^4	575	320

In general, the incidence of cirrhosis and HCC cases reported in observational studies are higher than the incidence generated by the model for both populations. This would be expected as the observational studies reported in tables 5 and 6 analyse untreated patients who would be expected to have a higher incidence rate of both cirrhosis and HCC incidence than the treated patient cohorts analysed in the economic model.

In the HBeAg positive model, individuals are treated for two years only and revert to the natural history of CHB for the remaining time in the model. Therefore, it would be expected that the incidence of cirrhosis and HCC cases from the observational studies would be closer to that predicted by the economic model for this population, as treatment is given for two years and not lifetime. In contrast, in the HBeAg negative model, patients are treated for lifetime and viral load is continually suppressed; therefore, a lower incidence of cirrhosis and HCC would be expected.

ACD Section 4.6 – Resistance

In section 4.6, the ACD stated that the low rates of resistance reported for ETV were biologically plausible. However, it is also stated that the Committee remained unconvinced that this low rate of resistance could be expected to be maintained over the long term.

In the original submission, BMS submitted data on patients who were originally enrolled in the 022 and 027 studies and continued on ETV treatment in the 901 rollover study. These data showed that for patients treated with ETV for up to four years, there was a cumulative probability of virological breakthrough due to ETV genotypic resistance of less than 1.2%. BMS now has five year data on the same cohort of patients. These data shows that patients continue to demonstrate low resistance, with no additional patients reporting genotypic resistance. Thus, the cumulative rate of genotypic resistance at 5 years remains at 1.2% (Figure 1).

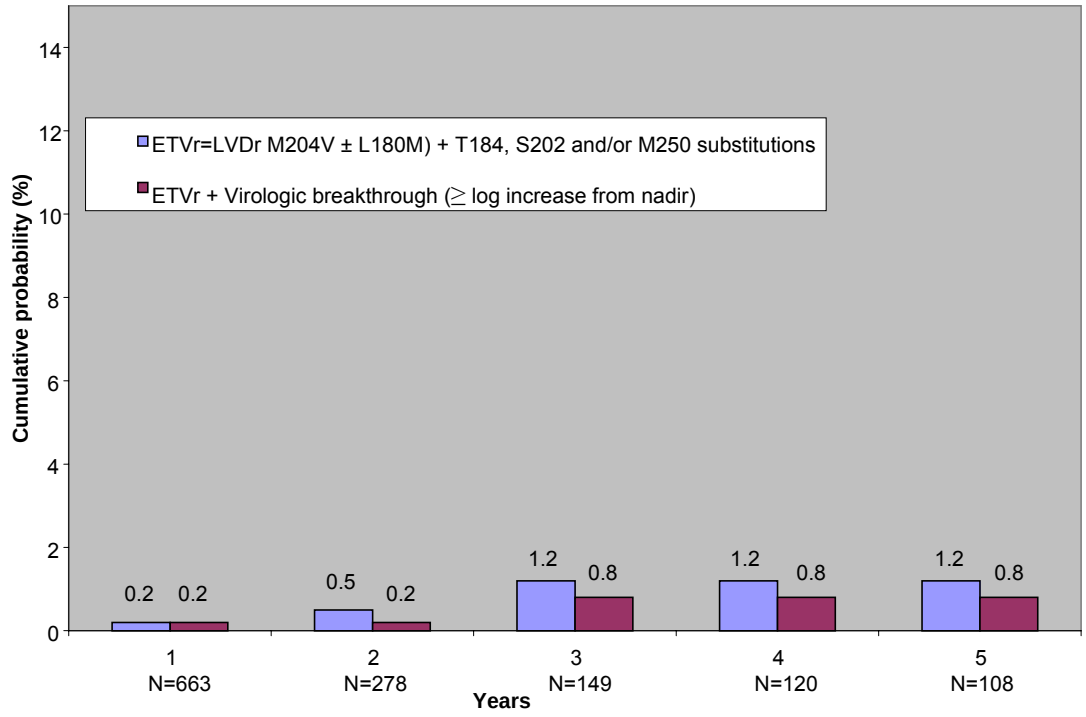

Figure 1: Cumulative probability of ETV resistance over 5 years in nucleoside-naïve cohort (HBeAg positive and HBeAg negative patients)

BMS recognizes that the resistance data from the 901 rollover study is not based on an intention to treat population, as responders were not followed up. However, there is no clinical reason to believe that the resistance rates in responders would be higher than that of partial and non-responders if they had likewise been followed-up for 5 years. The results of a recently-reported Japanese study independently confirm the findings from the 5 year resistance monitoring programme presented above. This study monitored resistance in a cohort of 66 nucleoside-naïve patients who received ETV

(0.5mg) for 3 years. Only one patient showed evidence of ETV resistance substitutions at year 3 (1.7% cumulative probability).

ACD Section 7.2 – Proposed date for review of guidance

BMS notes that the guidance on ETV is proposed to be considered for review in February 2009. However, BMS would suggest that this review date is too early since no significant new evidence is likely to be available at this point. CIC REMOVED. Therefore, BMS would like the review date for this guidance to be scheduled for 2012 when new data will be available and guidance on ETV can be meaningfully reviewed.

References

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