1 Appraisal Committee's preliminary recommendations

1.1 Tenofovir disoproxil used as monotherapy is recommended, within its marketing authorisation, as an option for adults with HBeAg-positive or HBeAg-negative chronic hepatitis B in whom antiviral treatment is indicated.

Gilead fully supports the Appraisal Committee's preliminary recommendation that tenofovir be used within it marketing authorisation and we acknowledge that the current body of evidence supports first line use of tenofovir as monotherapy.

However, we request the removal of "used as monotherapy" as this wording does not appear in our marketing authorisation[1] and could therefore be perceived as a restricted recommendation.

As discussed at the public hearing the EASL guidelines recommend tenofovir and entecavir as the preferred first line NUCs.[2]

The EASL guidelines clearly state there are circumstances where combination therapy be used:

"In case of resistance, an appropriate rescue therapy should be initiated with the most effective antiviral effect and the minimal risk to induce multiple drug-resistant strains.

- Lamivudine resistance: add tenofovir (add adefovir if tenofovir not yet available).
- Adefovir resistance: it is recommended to switch to tenofovir if available and add a second drug without crossresistance. If an N236T substitution is present, add lamivudine, entecavir or telbivudine or switch to tenofovir plus emtricitabine (in one tablet). If an A181T/V substitution is present, add entecavir (the safety of the tenofovir–entecavir combination is unknown) or switch to tenofovir plus emtricitabine.
- Telbivudine resistance: add tenofovir (add adefovir if tenofovir not yet available). The long-term safety of these combinations is unknown.
- Entecavir resistance: Add tenofovir (the safety of this combination is unknown).
- Tenofovir resistance: resistance to tenofovir has not been described so far. It is recommended that genotyping and phenotyping be done by an expert laboratory to determine the cross-resistance profile. Entecavir, telbivudine, lamivudine or emtricitabine could be added (the safety of these combinations is unknown)."[2]

If the wording of the NICE guidance is interpreted as an absolute restriction to the use of tenofovir combination therapy this would be contrary to EASL guidelines and good clinical practice.

Finally, it should be noted that NICE did not explicitly state entecavir only be "used as monotherapy". Inclusion of the monotherapy wording for tenofovir could be perceived as a restriction and would be inconsistent with previous NICE guidance for a drug with an identical licence indication.[3]

3.3 The manufacturer's submission presented evidence on the clinical effectiveness of tenofovir disoproxil from two randomised controlled trials (RCTs) that compared tenofovir disoproxil with adefovir dipivoxil. The protocol for both studies specified that the populations would be people who had not previously received nucleotide analogue therapy.

The protocol for our pivotal HBeAg negative study allowed recruitment of patients with prior experience of lamivudine or emtricitabine.[4]

17% of patients who received tenofovir from baseline and 18% of patients who received adefovir for the first 48 weeks had previous treatment experience with lamivudine or emtricitabine.[4]

Tenofovir produced a similar HBV DNA response in patients who had previously received lamivudine and in those who had not.

"An evaluation of the treatment response in subgroups defined by baseline characteristics showed no significant interactions at the alpha level. Among patients treated with tenofovir, 90% of patients who had received lamivudine versus 88% of those who had not received lamivudine had HBV DNA suppression to less than 400 copies per millilitre".[4]

Please note that the findings of 102 and 103 have now been published in the New England Journal of Medicine.[4]

3.6 The incidence of severe, life-threatening or disabling adverse events was similar between treatment groups, with no deaths reported in either study. However, statistically significantly more participants had at least one treatment-related adverse event in the tenofovir disoproxil treatment group in one study (p = 0.018). The incidence of arthralgia was statistically significantly higher for the group receiving tenofovir disoproxil in the other study (p = 0.003).

As discussed in our submission and the ERG report please qualify that the "statistically significantly" difference was due to "mild nausea".

The Marcellin NEJM 2008 publication states:

"The safety profiles observed in both studies (102 & 103) were consistent with the known safety profiles for tenofovir in patients with HIV infection and for the safety profiles for adefovir dipivoxil in patients with HBV infection. Nausea was the only adverse event that consistently occurred more frequently in the group of patients who received tenofovir than in the group of patients who received adefovir dipivoxil (9% vs. 3%). Among the cases of nausea that were considered to be related to tenofovir, nausea was mild except for one case of grade 2 (moderate) nausea."[4]

4.4 The Committee expressed concern that the results for tenofovir disoproxil in the indirect mixed-treatment comparison were not similar to those in individual RCTs, but this would be expected given that tenofovir disoproxil was linked by only one comparator.

We would like to provide the following clarification regarding this misunderstanding:

The absolute estimate figures have been confused with the relative difference figures, which had the impact of exaggerating the difference: a 90% absolute estimate from the meta-analysis was contrasted with a 20-fold relative difference observed in the trial. The meta-analysis actually suggests that around 94% of patients receiving tenofovir will achieve undetectable HBV DNA and that the odds of responding to tenofovir are 27 times as high as those of responding to adefovir (vs. a 20-fold difference observed in study 103).

The absolute probability of responding to treatment differed from those observed in clinical trials because the probability of viral suppression with tenofovir was calculated from the log-odds ratio (OR) for tenofovir relative to lamivudine (and the odds of responding to lamivudine) rather than being based on the absolute proportion of patients who achieved undetectable HBV DNA with tenofovir. This was conducted because analyses on relative treatment effects have been shown to be more robust and much less prone to bias than those based on absolute outcomes in individual trials; subsequently, it is generally recommended that indirect comparisons should be based on the log-OR rather than the absolute outcomes observed in each trial.

Although the mean odds ratio for response with tenofovir relative to adefovir that was calculated in the MTC (26.93) is higher than the odds ratio observed in study 103 (20.3), comparisons of relative efficacy should in fact be based on the log-odds ratios (on which the MTC was based), which are extremely similar between the MTC (log-OR for tenofovir vs adefovir=3.051) and study 103 (log-OR for tenofovir vs adefovir=3.010). It is appropriate to compare measures of relative effect based on the log-OR rather than ORs because the MTC was based on log-ORs and because the exponent of the mean log-odds ratio is not equal to the mean odds ratio. We attach data on the log-OR and OR output from the MTC.

References

1. Viread Summary of Product Characteristics

    4.1 Therapeutic indications

    Hepatitis B infection: Viread is indicated for the treatment of chronic hepatitis B in adults with compensated liver disease, with evidence of active viral replication, persistently elevated serum alanine aminotransferase (ALT) levels and histological evidence of active inflammation and/or fibrosis.

    This indication is based on histological, virological, biochemical and serological responses mainly in adult nucleoside naïve patients with HBeAg positive and HBeAg negative chronic hepatitis B with compensated liver function

2. EASL Clinical Practice Guidelines: Management of chronic hepatitis B. Journal of Hepatology 50 (2009) 227–242

3. Baraclude Summary of Product Characteristics

    4.1 Therapeutic indications

    Baraclude is indicated for the treatment of chronic hepatitis B virus (HBV) infection in adults with compensated liver disease and evidence of active viral replication, persistently elevated serum alanine aminotransferase (ALT) levels and histological evidence of active inflammation and/or fibrosis.

    This indication is based on clinical trial data in nucleoside naive patients with HBeAg positive and HBeAg negative HBV infection. With respect to patients with lamivudine-refractory hepatitis B,

4. Patrick Marcellin, M.D., E. Jenny Heathcote, M.D., Maria Buti, M.D et al. Tenofovir Disoproxil Fumarate versus Adefovir Dipivoxil for Chronic Hepatitis B. N Eng J Med 2008; 359: 2442-2455,