Anti-Infective Subcommittee of PTAC meeting

held 11 December 2008

(minutes for web publishing)

Anti-Infective Subcommittee minutes are published in accordance with the *Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) and PTAC Subcommittees 2008*:

Note that this document is not necessarily a complete record of the Anti-Infective Subcommittee meeting; only the Minutes relating to Anti-Infective Subcommittee discussions about an application that contain a recommendation in relation to an application are published.

The Anti-Infective Subcommittee may:

(a) recommend that a pharmaceutical be listed by PHARMAC on the Pharmaceutical Schedule and the priority it gives to such a listing;
(b) defer a final recommendation, and give reasons for the deferral (such as the supply of further information) and what is required before further review; or
(c) recommend that PHARMAC decline to list a pharmaceutical on the Pharmaceutical Schedule.

Contents

1 Darunavir (Prezista) for HIV

1.1 The Subcommittee reviewed the application from Janssen-Cilag for the listing of darunavir (Prezista) for the treatment of patients with HIV infection. Members noted that darunavir, a new Protease Inhibitor (PI), had a slightly greater effect compared to other PI's. Members noted that darunavir showed a better resistance profile compared to other PI's.

1.2 The Subcommittee noted the tabled 96 week data from the pooled analysis of POWER 1 and 2 trials. Members considered the data to be of good quality. Members noted that there was a virological failure rate of 11-13% if darunavir was used last line in heavily treatment experienced patients.

1.3 The Subcommittee noted the tabled 96 week pooled data from studies POWER 1, 2 and 3 (Yeni et al 2007). Members noted that there was good safety profile with no new safety concerns arising at 96 weeks.

1.4 The Subcommittee noted that the supplier gave patient figures of 30 new patients annually. Members considered that this figure accurately reflected the number of eligible patients in New Zealand.

1.5 The Subcommittee considered that the current aim of HIV-1 treatment is to ensure complete viral suppression as this has been shown to reduce viral escape and hence resistance. Members noted that patients who achieve complete viral suppression are likely to remain that way as long as complete adherence is maintained.

1.6 The Subcommittee considered that there was an unmet clinical need for patients who develop multiple class resistance to currently available antiretroviral treatment. Members noted the importance of not adding darunavir as a single additional agent to a failing antiretroviral regimen. Members **recommended** that darunavir be listed at the same time as raltegravir to ensure optimal usage.

1.7 The Subcommittee **recommended** that darunavir be listed on the Pharmaceutical Schedule with a high priority via Special Authority criteria to indicate that darunavir is second line treatment and should be restricted to use for multi-drug resistant HIV-1.

2 Raltegravir (Isentress) for HIV

2.1 The Subcommittee reviewed the application from Merck Sharp and Dohme (New Zealand) Limited for the listing of raltegravir (Isentress) on the Pharmaceutical Schedule for the treatment of HIV-1 infection in combination with optimised background therapy (OBT). Members noted that the application was for a listing

of either second line treatment after initial treatment failure or as a treatment for multiple class resistant patients.

2.2 The Subcommittee noted that raltegravir was a novel HIV pharmaceutical; an inhibitor of HIV integrase strand transfer, which is normally required for HIV replication.

2.3 The Subcommittee noted the tabled data for clinical trials evaluating the efficacy of raltegravir in combination with OBT for the treatment of HIV. The Subcommittee noted that two of the trials were phase three trials and two were phase two trials. The Subcommittee considered that the clinical evidence provided on raltegravir was of good quality. Members noted however that the follow-up of patients in the clinical trials was limited to 48 weeks.

2.4 The Subcommittee noted the tabled BENCHMRK 1 and 2 combined analysis data. Members noted that there was a good safety profile at 48 weeks. Members considered that the published data showed complete viral suppression at 48 weeks of 62.1% in patients randomised to raltegravir versus 32.9% in the placebo group ($p<0.001$). Members considered that the published response rates in the placebo group were lower than expected with current treatments in the New Zealand setting. One member considered that New Zealand patients would not be as treatment experienced as the BENCHMRK study cohorts and would therefore have less resistance mutations, allowing the possibility of better outcomes than were obtained in the published studies. The Subcommittee considered that, in the absence of longer term data, the patient population experiencing complete viral suppression could reduce by 5-10% per year.

2.5 The Subcommittee considered that raltegravir should be currently restricted to multiple class resistant patients. Members considered that resistance should be defined as demonstrated genotypical resistance and virological failure (> 1000 copies per mL). Members considered that raltegravir would be used before enfuvirtide.

2.6 The Subcommittee noted that there was a low genetic barrier to resistance so raltegravir would need to be used in combination with other antiretroviral agents. Members noted that the trial population was not reflective of the New Zealand population and that less resistance would be expected to develop due to less heavily treatment experienced patients.

2.7 The Subcommittee considered that there was an unmet clinical need for patients who develop multiple class resistance to currently available antiretroviral treatment. Members considered that raltegravir would be used before enfuvirtide in the treatment of multiple class resistant patients, but realised the importance of not adding raltegravir as a single additional agent to a failing antiretroviral regimen. Members **recommended** that raltegravir be listed at the same time as darunavir to ensure optimal usage

2.8 The Subcommittee **recommended** that raltegravir be listed on the Pharmaceutical Schedule with a high priority via Special Authority criteria to indicate that raltegravir is second line treatment and should be restricted to use for multi-drug resistant HIV-1.

3 Tenofovir (Viread) for Chronic Hepatitis B

3.1 The Subcommittee reviewed an application from Gilead Sciences New Zealand for the listing of tenofovir (Viread) on the Pharmaceutical Schedule for the treatment of chronic hepatitis B (CHB).

3.2 The Subcommittee noted the tabled 96 week data from studies 0102 and 0103; phase 3 randomised double blind evaluations of tenofovir 300 mg daily versus adefovir 10 mg daily in patients with hepatitis B early antigen-negative and antigen-positive CHB respectively.

3.3 The Subcommittee noted that at week 96 there was an increase in the percentage of patients with HBV DNA copies < 400 copies per ml after switching to tenofovir from adefovir at 48 weeks during open label prescribing. Members noted that viral suppression on adefovir was maintained after switching to tenofovir.

3.4 The Subcommittee noted that tenofovir was generally well tolerated over 96 weeks and that the safety profile between 48 and 96 weeks was consistent with results observed over the first 48 weeks. Members noted there was no detectable resistance to tenofovir monotherapy at 96 weeks.

3.5 The Subcommittee noted that tenofovir was category B and considered that it would be the treatment of choice for pregnant hepatitis B patients.

3.6 The Subcommittee considered that there would be a reduction in the need for blood tests for HBV DNA load from every 3 months to every 6 months in patients undergoing tenofovir treatment compared to adefovir or lamivudine treatment. Members considered that there would be a reduction in the number of liver biopsies preformed if tenofovir was funded and that patients would switch from adefovir to tenofovir.

3.7 The Subcommittee considered that there was an unmet clinical need for hepatitis B treatment and that new more potent pharmaceuticals were required to achieve complete virologic response or seroconversion. Members noted that if patients underwent e-antigen seroconversion and remained so for 6 to 12 months then it is unlikely they would require ongoing treatment.

3.8 The Subcommittee **recommended** that tenofovir should be listed in the Pharmaceutical Schedule with high priority via Special Authority criteria appropriate for the following four indications: treatment-naïve CHB; lamivudine resistant CHB; adefovir resistant CHB; entecavir resistant CHB.

TENOFOVIR IN TREATMENT-NAÏVE CHRONIC HEPATITIS B

Initial application only from a gastroenterologist, infectious disease specialist, or general physician. Approvals valid without further renewal unless notified for applications meeting ALL of the following pre-treatment criteria:

1. Patient has confirmed Hepatitis B infection (HBsAg positive for more than 6 months); and
2. Patient is Hepatitis B treatment-naïve; and
3. Any of the following:
    3.1 ALT greater than upper limit of normal; or
    3.2 Bridging fibrosis of cirrhosis (≥ Metavir Stage F3);
4. Any of the following:
    4.1 HBeAg positive; or
    4.2 serum HBV DNA ≥ 2,000 IU/ml and significant fibrosis (≥ Metavir Stage F2);
5. All of the following:
    5.1 No continuing alcohol abuse or intravenous drug use; and
    5.2 Not co-infected with HCV or HDV; and
    5.3 Neither ALT nor AST greater than 10 times upper limit of normal; and
    5.4 No history of hypersensitivity to tenofovir.

TENOFOVIR IN LAMIVUDINE-RESISTANT CHRONIC HEPATITIS B

Initial application only from a gastroenterologist, infectious disease specialist, or general physician. Approvals valid for 1 year for applications meeting ALL of the following criteria:

1. Patient has confirmed Hepatitis B infection (HBsAg positive for more than 6 months); and
2. Patient has had previous lamivudine therapy; and
3. Documented resistance to lamivudine, defined as all of the following:
    3.1 ALT greater than upper limit of normal; or ≥ Metavir Stage F3; and
    3.2 HBV DNA greater than 20,000 IU/mL or increased ≥ 10 fold over nadir; and
    3.3 Detection of M204I/V mutation.

Renewal only from a gastroenterologist, infectious disease specialist or general physician. Approvals valid for 2 years for applications where in the opinion of the treating physician, treatment remains appropriate and patient is benefiting from treatment.

TENOFOVIR IN ADEFOVIR-RESISTANT CHRONIC HEPATITIS B

Initial application only from a gastroenterologist, infectious disease specialist, or general physician. Approvals valid for 1 year for applications meeting ALL of the following criteria:

1. Patient has confirmed Hepatitis B infection (HBsAg positive for more than 6 months); and
2. Patient has had previous Adefovir therapy; and
3. Documented resistance to Adefovir, defined as all of the following:
    3.1 ALT greater than upper limit of normal; or ≥ Metavir Stage F3; and
    3.2 HBV DNA greater than 20,000 IU/mL or increased ≥ 10 fold over nadir; and
    3.3. detection of A181T/V or N236T mutation.

Renewal only from a gastroenterologist, infectious disease specialist or general physician. Approvals valid for 2 years for applications where in the opinion of the treating physician, treatment remains appropriate and patient is benefiting from treatment.

TENOFOVIR IN ENTECAVIR-RESISTANT CHRONIC HEPATITIS B

Initial application only from a gastroenterologist, infectious disease specialist, or general physician. Approvals valid for 1 year for applications meeting ALL of the following criteria:

1. Patient has confirmed Hepatitis B infection (HBsAg positive for more than 6 months); and
2. Patient has had previous entecavir therapy; and
3. Documented resistance to entecavir, defined as all of the following:
    3.1 ALT greater than upper limit of normal; or ≥ Metavir Stage F3; and
    3.2 HBV DNA greater than 20,000 IU/mL or increased ≥ 10 fold over nadir; and
    3.3 detection of relevant mutations which confer resistance to Entecavir including I169T, L180M T184S/A/I/L/G/C/M, S202C/G/I, M204V or M250I/V.

Renewal only from a gastroenterologist, infectious disease specialist or general physician. Approvals valid for 2 years for applications where in the opinion of the treating physician, treatment remains appropriate and patient is benefiting from treatment.

Notes for Tenofovir:

- Tenofovir should be stopped 6 months following HBeAg seroconversion for patients who were HBeAg positive prior to commencing this agent.
- The recommended dose of tenofovir for all three indications is 300 mg once daily.
- In patients with renal insufficiency (calculated creatinine clearance less than 50ml/min), tenofovir dose should be reduced in accordance with the datasheet guidelines.
- Tenofovir is not approved for use in children.