Anti-Infective Subcommittee of PTAC

Meeting held 1 March 2012

(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 relevant portions of the minutes relating to Anti-Infective Subcommittee discussions about an Application or PHARMAC staff proposal that contain a recommendation are generally published.
- that any part of the minutes relating to hospital pharmaceuticals and the establishment of a national Preferred Medicines List (PML) will be released, in a complete publication with the original Hospital Pharmaceuticals Subcommittee minutes and final recommendations made by PTAC, once PTAC have reviewed each therapeutic group.

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.

These Subcommittee minutes were reviewed by PTAC at its meeting on 10 & 11 May 2012, the record of which will be available in July 2012.

1 Clinically recommended action points

1.1 The Subcommittee **recommended** that PHARMAC

1.1.1 Widen funded access with a high priority to lamivudine to include prophylaxis for patients receiving R-CHOP or those receiving a liver transplant;

1.1.2 Amend the that the Special Authority relating to tenofovir for use in pregnancy for postpartum care;

1.1.3 Amend the Special Authorities where the metavir staging was required to include the alternative option of “moderate fibrosis”

1.1.4 amend with a high priority the Special Authority criteria applying to pegylated interferon with ribavirin for hepatitis C patients with genotype 2 or 3 following liver transplant;

1.1.5 list posaconazole on the Pharmaceutical Schedule for the prophylaxis of aspergillus, with high priority, and seek further advice from Haematologists as to patient numbers and the appropriateness of the proposed indications

1.1.6 fund valganciclovir for CMV prophylaxis for up to 6 months in lung transplant recipients, and up to 90 days in other transplant recipients.

2 Therapeutic Group review

Lamivudine

2.1 The Subcommittee noted an application for the funding of lamivudine for Hepatitis B prophylaxis in patients receiving cytotoxic chemotherapy. Members noted that chemotherapy treatment regimes with high dose steroids (20 mg of prednisone for at least seven days) resulted in an increased risk of Hepatitis B reactivation.

2.2 The Subcommittee considered that patients who were Hepatitis B core antibody positive (anti-HBc+ve) have occult HBV infection with evidence of very low levels of intrahepatic HBV replication. Members noted that this group would typically only develop reactivated HBV infection and active liver disease if they become severely immunocompromised, following development of immunodeficiency or intensive immunosuppression

2.3 The Subcommittee noted that patients with natural immunity to HBV from previous exposure (i.e. were anti-HBc+ve and HBsAg-ve) who were receiving R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone) had a 20-25% reactivation rate without lamivudine prophylaxis. Members noted that approximately 12% of the population is Hepatitis B core antibody positive (anti-HBc+ve), but in Maori, Polynesian and Asian populations this figure was higher at around 50%.

2.4 The Subcommittee considered that in HBsAg neg/anti-HBc+ve patients receiving R-CHOP it would likely be more cost effective to provide lamivudine prophylaxis rather than monitor and provide pre-emptive treatment when patients became HBsAg+ve. Members noted that lamivudine was off patent and the price would likely reduce.

2.5 The Subcommittee noted that some patients may receive rituximab in combination with high dose steroids outside of the oncology setting, such for Rheumatoid Arthritis, and members considered that both HBsAg+ve patients and HBsAg neg/anti-HBc+ve patients would also be at risk of reactivation without lamivudine prophylaxis.

2.6 The Subcommittee noted that transplanting a anti-HBc+ve liver from an HBsAg neg/anti-HBc+ve donor into an HBV-naïve recipient carried a high risk of hepatitis B infection in the recipient. The Subcommittee considered that lamivudine prophylaxis would be appropriate for these patients, but not other transplant groups as the risk of transmission was lower.

2.7 The Subcommittee **recommended,** with a high priority, widening funded access to lamivudine to include prophylaxis for HBsAg -ve/anti-HBc+ve patients receiving R-CHOP or for HBV-naive patients receiving a liver transplant from an HBsAg neg/anti-HBc+ve donor. Members recommended that the Special Authority criteria applying to lamivudine funding be amended as follows (additions in bold, deletions in strikethrough):

Initial application only from a gastroenterologist, infectious disease specialist, paediatrician or general physician. Approvals valid for 1 year for applications meeting the following criteria:
Both:
1 Any of the following:
1.1 All of the following:
1.1.1 HBsAg positive for more than 6 months; and
1.1.2 HBeAg positive or HBV DNA positive defined as > 100,000 copies per ml by quantitative PCR at a reference laboratory; and
1.1.3 ALT greater than twice upper limit of normal or bridging fibrosis or cirrhosis (Metavir stage 3 or 4 or equivalent) on liver histology or clinical/radiological evidence of cirrhosis; or
1.2 HBV DNA positive cirrhosis prior to liver transplantation; or
1.3 HBsAg positive and have had a liver, kidney, heart, lung or bone marrow transplant; or
1.4 Hepatitis B virus naïve patient who has received a liver transplant from an anti-HBc (Heptatits B Core antibody) positive donor; or
1.4**5** Hepatitis B surface antigen positive (HbsAg) **positive** patient who is receiving chemotherapy for a malignancy, or high dose steroids (at least 20mg/day for at least 7 days) or who has received such treatment within the previous two months; **or**
1.6 Hepatitis B core antibody (anti-HBc) positive patient who is receiving rituximab plus high dose steroids (e.g. R-CHOP)

2 All of the following:
2.1 No continuing alcohol abuse or intravenous drug use; and
2.2 Not coinfected with HCV or HDV; and
2.3 Neither ALT nor AST greater than 10 times upper limit of normal; and
2.4 No history of hypersensitivity to lamivudine; and
2.5 No previous lamivudine therapy with genotypically proven lamivudine resistance.

Renewal only from a gastroenterologist, infectious disease specialist, paediatrician or general physician. Approvals valid for 2 years for applications meeting the following criteria:

Either:
Renewal for patients who have maintained continuous treatment and response to lamivudine
3 All of the following:
3.1 Have maintained continuous treatment with lamivudine; and
3.2 Most recent test result shows continuing biochemical response (normal ALT); and,
3.3 HBV DNA < 100,000 copies per ml by quantitative PCR at a reference laboratory: or.
Renewal when given in combination with adefovir dipivoxil for patients with cirrhosis and resistance to lamivudine
4 All of the following
4.1 lamivudine to be used in combination with adefovir dipivoxil; and
4.2 patient is cirrhotic; and
Documented resistance to lamivudine, defined as:
4.3 patient has raised serum ALT (> 1 x ULN); and
4.4 patient has HBV DNA greater than 100,000 copies per mL, or viral load = 10 fold over nadir; and
4.5 detection of M204I or M204V mutation; or

Renewal when given in combination with adefovir dipivoxil for patients with resistance to adefovir dipivoxil
5 All of the following
5.1 lamivudine to be used in combination with adefovir dipivoxil; and
Documented resistance to adefovir, defined as:
5.2 patient has raised serum ALT (> 1 x ULN); and
5.3 patient has HBV DNA greater than 100,000 copies per mL, or viral load = 10 fold over nadir; and
5.4 detection of N236T or A181T/V mutation

Tenofovir

2.8 The Subcommittee noted that the current Special Authority for funding of tenofovir or prevention of vertical transmission in HBsAg+ve pregnant patients was restricted to a maximum of four months treatment for each pregnancy. The Subcommittee noted that the current Special Authority was consistent with its previous advice from its 8 April 2010 meeting.

2.9 The Subcommittee considered that tenofovir would be required throughout the pregnancy as there were potential safety issues with using, or switching back to, entecavir in pregnancy as shown in animal studies. The Subcommittee considered that patients receiving entecavir treatment for chronic hepatitis B (CHB) infection should be switched to tenofovir as soon as possible when pregnant and continued on tenofovir until eight weeks post-partum or until the patient has finished breastfeeding whichever is longer.

2.10 The Subcommittee noted that there was good evidence for the use of lamivudine or telbivudine for prevention of vertical transmission of hepatitis B. Members noted a telbivudine study from China which showed the risk of vertical transmission reduced from 10% to 0% (1.2% on intention to treat) when telbivudine was provided as prophylaxis.

2.11 Members considered that as tenofovir was more potent than lamivudine, and had a good safety record due to its use in the HIV population during pregnancy, it was likely to be more effective in than lamivudine in the CHB setting.

2.12 The Subcommittee considered that pregnant women who were Hepatitis B E antigen positive (HBeAg+ve) with 8 log copies per ml (≥7 log IU per ml) HBV DNA

had a risk of vertical transmission of around 10%. Members noted that this risk rate primarily related to women from South East Asian, Chinese and Tongan communities.

2.13 The Subcommittee considered that this patient group should receive tenofovir for prophylaxis of vertical transmission throughout pregnancy and until 8 weeks post partum. Members noted that there was a risk of viral flare when antivirals are ceased so recommended continuing therapy for 8 weeks postpartum.

2.14 The Subcommittee noted that tenofovir disoproxil fumurate (the prodrug of tenofovir) was not expressed in the breast milk and although the active moiety tenofovir (PMEA) was, the concentrations were at very low level (2% maternal levels). Tenofovir has very poor bioavailability due to charged anionic state and therefore tissue exposure in the infant is negligible. Therefore the Subcommittee considered that patients who receive tenofovir during pregnancy and who wish to breastfeed should remain on tenofovir during throughout the pregnancy and breastfeeding period. Members noted that there was significant safety experience with the use of tenofovir in breastfeeding due to its use in the HIV setting.

2.15 The Subcommittee considered that patients with high HBV DNA levels (>7 $\log_{10}$ IU/mL) and persistently normal liver function test prior to pregnancy, who were initiated on tenofovir for prevention of vertical transmission should received funded tenofovir throughout pregnancy until eight weeks after delivery. Members noted there was no clinical reason to extend treatment beyond eight weeks in this patient group. However, patients should be monitored closely after tenofovir withdrawal as between 20 and 40% will have a transient acute hepatitis flare and 10% will need to recommence antiviral therapy. Members considered that it would be appropriate for the New Zealand Gastroenterology Society to provide guidelines to all Lead Maternity providers to ensure that there was understanding of the requirement to assess liver function tests in pregnancy.

2.16 The Subcommittee **recommended** that the Special Authority relating to tenofovir for use in pregnancy be amended with a high priority as follows (deletions in strike through, additions in bold)

> Initial application - (Pregnant **Active hepatitis B)** only from a gastroenterologist, infectious disease specialist or general physician. Approvals valid for **12**4 months for applications meeting the following criteria:
> Both:
> 1 Patient is HBsAg positive and pregnant; and
> ~~2~~ ~~Either:~~
> 2~~.1~~ HBV DNA > 20,000 IU/mL and ALT > ULN; ~~or~~
> ~~2.2 HBV DNA > 100 million IU/mL and ALT normal~~.
>
> Renewal - (Subsequent Pregnancy **or Breastfeeding**, **Active hepatitis B)** only from a gastroenterologist, infectious disease specialist or general physician. Approvals valid for **12**4 months for applications meeting the following criteria:
> Both:
> 1 Patient is HBsAg positive and pregnant or breastfeeding; and
> ~~2~~ ~~Either:~~
> 2~~.1~~ HBV DNA > 20,000 IU/mL and ALT > ULN; ~~or~~
> ~~2.2 HBV DNA > 100 million IU/mL and ALT normal~~.

Initial application - (Pregnant, **prevention of vertical transmission)** only from a gastroenterologist, infectious disease specialist or general physician. Approvals valid for **6**~~4~~ months for applications meeting the following criteria:
Both:
1 Patient is HBsAg positive and pregnant; and
~~2~~ ~~Either:~~
~~2.1 HBV DNA > 20,000 IU/mL and ALT > ULN; or~~
2.~~2~~ HBV DNA > **2**0 million IU/mL and ALT normal.

Renewal - (Subsequent Pregnancy, **prevention of vertical transmission)** only from a gastroenterologist, infectious disease specialist or general physician. Approvals valid for **6**~~4~~ months for applications meeting the following criteria:
Both:
1 Patient is HBsAg positive and pregnant; and
~~2 Either:~~
~~2.1 HBV DNA > 20,000 IU/mL and ALT > ULN; or~~
2.~~2~~ HBV DNA > ~~10~~**20** million IU/mL and ALT normal.

Interferon

2.17 The Subcommittee noted that the Special Authority for pegylated interferon alpha 2A and ribavirin for the treatment of Hepatitis C was amended in 2009 and no longer required that patients undergo liver biopsy. However, members noted that the guidelines in the Pharmaceutical Schedule relating to the use of interferon alpha 2A and 2B in the treatment of hepatitis C still included a requirement for liver biopsy. Members considered that the guideline should be amended as follows (deletion in strikethrough):

Guidelines for the use of interferon in the treatment of hepatitis C:
Physicians considering treatment of patients with hepatitis C should discuss cases with a gastroenterologist or an
infectious disease physician. All subjects undergoing treatment require careful monitoring for side effects.
Patients should be otherwise fit.
Hepatocellular carcinoma should be excluded by ultrasound examination and alpha-fetoprotein level.
Criteria for Treatment
a) Diagnosis
- Anti-HCV positive on at least two occasions with a positive PCR for HCV-RNA and preferably confirmed by a supplementary RIBA test; or
- PCR-RNA positive for HCV on at least 2 occasions if antibody negative; or
- Anti-HCV positive on at least two occasions with a positive supplementary RIBA test with a negative PCR for HCV RNA but with a liver biopsy consistent with 2(b) following.

b) Establishing Active Chronic Liver Disease
- Confirmed HCV infection and serum ALT/AST levels measured on at least three occasions over six months averaging > 1.5 x upper limit of normal. (ALT is the preferable enzyme).~~; or~~
~~- Liver biopsy showing significant inflammatory activity (active hepatitis) with or without cirrhosis. This is not a necessary requirement for those patients with coagulopathy. (Some patients have active disease on histology with normal transaminase enzymes).~~

Exclusion Criteria
a) Autoimmune liver disease. (Interferon may exacerbate autoimmune liver disease as well as other autoimmune diseases such as thyroid disease).
b) Pregnancy.
c) Neutropenia (<2.0 x 109) and/or thrombocytopenia.
d) Continuing alcohol abuse and/or continuing intravenous drug users.
Dosage

The current recommended dosage is 3 million units of interferon alpha-2a or interferon alpha-2b administered subcutaneously three times a week for 52 weeks (twelve months).
Exit Criteria
The patient's response to interferon treatment should be reviewed at either three or four months. Interferon treatment should be discontinued in patients who do not show a substantial reduction (50%) in their mean pre-treatment ALT level at this stage.

2.18 The Subcommittee noted that entecavir, lamivudine and pegylated interferon alpha-2A with have a requirement for Metavir staging in the Special Authority. Members considered that this should be amended as most District health Board (DHB) Hospitals now routinely used Fibroscan in place of bioposy as it was less invasive.

2.19 The Subcommittee **recommended** that where the metavir staging was required an alternative option of "moderate fibrosis" would be appropriate with the Special Authority wording amended as follows "Metavir stage 3 or greater, **or moderate fibrosis**".

Peglyated interferon

2.20 The Subcommittee noted a request to widen funding for pegylated interferon and ribavirin to include post liver transplant patients. Members considered that a potential extension would be for Hepatitis C Genotype 2 or 3 patients only as all other genotypes already have access to funding for up to 48 weeks under the current Special Authority.

2.21 The Subcommittee noted that studies in liver transplant patients receiving pegylated interferon and ribavirin were for 48 weeks treatment regardless of genotype. Members considered that it was standard of care to provide 48 weeks of therapy for these patients.

2.22 The Subcommittee **recommended** with a high priority that the Special Authority criteria applying to pegylated interferon with ribavirin for hepatitis C be amended as follows (additions in bold):

Initial application - (chronic hepatitis C - genotype 1, 4, 5 or 6 infection or co-infection with HIV **or genotype 2 or 3 post liver transplant**) from any specialist. Approvals valid for 18 months for applications meeting the following criteria:
Both:
1. Either:
1.1 Patient has chronic hepatitis C, genotype 1, 4, 5 or 6 infection; or
1.2 Patient has chronic hepatitis C and is co-infected with HIV; ~~and~~ **or**
1.3 Patient has chronic hepatitis C genotype 2 or 3 and has received a liver transplant; and
2. maximum of 48 weeks therapy
Notes
- Consider stopping treatment if there is absence of a virological response (defined as at least a 2-log reduction in viral load) following 12 weeks of treatment since this is predictive of treatment failure.
- Consider reducing treatment to 24 weeks if serum HCV RNA level at Week 4 is undetectable by sensitive PCR assay (less than 50IU/ml) AND Baseline serum HCV RNA is less than 400,000IU/ml

2.23 The Subcommittee considered that, if funding was widened as recommended an additional 3 to 5 patients per annum would be eligible for 48 weeks treatment (and additional 5 months therapy compared with current funding).

3 Posaconazole

3.1 The Subcommittee noted the November 2010 PTAC minute regarding the funding of posaconazole for prophylaxis of invasive aspergillus in immunocompromised patients. Members noted that the clinical opinion on when to use posaconazole for prophylaxis was based on the heterogeneity of patient risks notably environmental and clinical diagnosis and different clinical approaches. The Subcommittee noted that the risk of aspergillus infection differs between DHB hospitals due to environmental factors, for example filtration systems, construction work etc.

3.2 The Subcommittee considered there was a clinical need to have accurate information technology infrastructure in the hospital setting to monitor outcomes and audit the effectiveness of treatments including use of pozaconazole for aspergillus prophylaxis.

3.3 The Subcommittee considered that posaconazole prophylaxis would be very effective in highly immunocompromised patients at high risk for infection such as patients with acute myeloid leukemia (AML) and selected patients undergoing bone marrow transplant (BMT).

3.4 The Subcommittee considered that patients receiving treatment for acute lymphoblastic leukemia (ALL) were not at such a high risk and that invasive fungal infections were handled differently. Members considered that these patients should be treated in rooms with HEPA filtration and given fluconazole prophylaxis with an invasive fungal infection being treated with liposomal amphotericin.

3.5 The Subcommittee considered that patients undergoing solid organ transplantation did not commonly require posaconazole prophylaxis early post transplant. Members noted that posaconazole was not well absorbed early post transplant. Members considered there may be a place for posaconazole prophylaxis for selected high risk patients.

3.6 The Subcommittee noted the recommendations of Slavin et al (Internal Medicine Journal 2008; 38: 468-476) for antifungal prophylaxis in patients with haematological malignancy or profound neutropenia lasting more than 10 days. Members considered that posaconazole prophylaxis would be appropriate for patients with AML undergoing intensive induction, or re-induction, chemotherapy, or high dose consolidation chemotherapy.

3.7 The Subcommittee considered that the risk factors for AML patients should be reviewed following induction. The Subcommittee considered that the cost effectiveness of primary prophylaxis would vary in certain situations and that unrestricted use may have significant cost implications. The Subcommittee considered it may be more appropriate to recommend posaconazole prophylaxis during consolidation cycles for those patients scheduled to proceed to allogeneic stem cell transplant and that those patients who were not likely to receive a transplant may not require ongoing prophylaxis during consolidation treatment.

3.8 The Subcommittee **recommended** that posaconazole should be listed on the Pharmaceutical Schedule for the prophylaxis of aspergillus, with high priority, subject to Special Authority criteria as follows:

> Initial Application from Haematologist or Infectious Disease Physician
> Approvals valid for 6 weeks for patients meeting the following criteria:
> Both:
> 1 Either:
> 1.1 Patient has acute myeloid leukemia; or
> 1.2 Patient is planned to receive a stem cell transplant and is at high risk for aspergillus infection; and
> 2 Patient is to be treated with high dose Remission Induction therapy
>
> Renewal Application from Haematologist or Infectious Disease Physician
> Approvals valid for 6 weeks for patients meeting the following criteria:
> Both
> 1 Patient has previously received posaconazole prophylaxis during Remission Induction therapy; and
> 2 Any of the following:
> 2.1 Patient is to be treated with high dose Remission Re-induction therapy; or
> 2.2 Patient is to be treated with high dose Consolidation therapy; or
> 2.3 Patient is receiving a high risk stem cell transplant.

3.9 The Subcommittee considered that approximately 150 patients per annum would be eligible for posaconazole prophylaxis during induction/re-induction therapy.

3.10 The Subcommittee noted that current practice was to try to transplant all high risk AML patients. The Subcommittee also noted that some intermediate risk AML patients would also be considered for transplant and therefore approximately 30-40% of all AML patients would be considered for transplant. The Subcommittee considered that this would equate to 40-50 patients nationally being eligible for posaconazole prophylaxis during transplant and consolidation per annum.

3.11 The Subcommittee recommended that more accurate figures be requested regarding numbers of eligible cases nationally from the Haematology Society of Australia & New Zealand (HSANZ). The Subcommittee recommended that this minute be circulated to HSANZ for comment and to request proposals for indications/cases that would be recommended for primary prophylaxis with posaconazole.

4 Valganciclovir

4.1 The Subcommittee noted the PTAC minute relating to valganciclovir for prophylaxis of cytomegalovirus (CMV) following transplant. The Subcommittee recommended that the PTAC recommendation for 21 day approval indications for CMV prophylaxis not be funded. The Subcommittee agreed with PTAC's recommendation to fund valganciclovir for up to 90 days prophylaxis for most transplant indications with a high priority.. However, members considered that a longer duration of treatment was warranted in lung transplant recipients.

4.2 The Subcommittee noted that CMV prophylaxis was required for patients who received a transplant following acute liver failure and patients undergoing re-transplantation regardless of serostatus.

4.3 The Subcommittee noted evidence supporting use of more than 6 months prophylaxis in patients undergoing lung transplant where the recipient was CMV positive or there was a donor mismatch (Zamora et al American Journal of transplantation, 2004: 4: 1635-1642). The Subcommittee noted that there was a statistically significant difference in CMV disease in patients receiving 6, 9 or 12 months of valganciclovir prophylaxis compared with those receiving less than 6 months.

4.4 The Subcommittee **recommended** that valganciclovir for CMV prophylaxis should be funded for up to 6 months in lung transplant recipients where the recipient was CMV positive or there was a donor mismatch, and up to 90 days in other transplant recipients. Members gave this recommendation a high priority.