Anti-Infective Subcommittee of PTAC meeting held 8 April 2010

(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 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.

Some material has been withheld, in accordance with the Official Information Act 1982 (OIA) in order to protect the privacy of natural persons (section 9(2)(a)).

These Subcommittee minutes were reviewed by PTAC at its meeting on 5 & 6 August 2010, the record of which is available on the PHARMAC website.

Contents

1 Azithromycin

1.1 Members noted the current limit of two packs per Practitioner Supply Order (PSO) for azithromycin. Members noted that current clinical practice was to secure a greater amount of azithromycin than this in General Practice clinics and replace stock as it was used. Members considered that increasing the limit from two to four packs and maintaining the current endorsement would still restrict azithromycin usage for the treatment of *Chlamydia trachomatis* infections rather than respiratory indications. The Subcommittee **recommended** the PSO limit be increased to four packs.

2 Vancomycin for C. difficle

2.1 The Subcommittee noted that vancomycin capsules were not listed on the Pharmaceutical Schedule. Members considered that vancomycin injections could be compounded to an acceptable formulation for oral usage, but that there was a palatability issue with this formulation. Members noted there would be a maximum of 50 patients per annum requiring oral vancomycin for *C. difficle* treatment. Members noted that if vancomycin was the same price per mg in either formulation then the capsules would be the preferred formulation. Members **recommended** that vancomycin capsules be listed if cost-neutral to the injections.

3 Fluconazole for systemic candidiasis prophylaxis

3.1 The Subcommittee noted the letter from the Paediatric Society of New Zealand, requesting funding of fluconazole liquid for prophylaxis in immunocompromised children. Members noted the difficulties in restricting a product to an age group. Members considered that if fluconazole liquid was listed more than the 50 patients the Paediatric Society estimated would access therapy. Members noted that the required volume of liquid would ensure that liquid usage remained low. The Subcommittee **recommended** listing fluconazole under the following Special Authority:

> Initial application- from a relevant practitioner. Approvals valid for 6 weeks where the patient requires prophylaxis for, or treatment of, systemic candidiasis and the patient is unable to swallow capsules.
>
> Renewal - Approvals valid for 6 weeks where the patient continues to requires prophylaxis for, or treatment of, systemic candidiasis and the patient is unable to swallow capsules

4 HIV non-occupational prophylaxis

4.1 The Subcommittee reviewed the request from AMTAC to amend the proposed Special Authority for HIV non-occupational prophylaxis (HIV-nPEP). Members noted that the 18 September 2007 minute discussed the risk of transmission levels and that HIV-nPEP was intended to be used for risk levels of >1 in 300. Members considered that the proposed Special Authority should be amended as follows (additions in **Bold**):

> Initial application - (post-exposure prophylaxis following non-occupational exposure to HIV) only from a named specialist. Approvals valid for 4 weeks for applications meeting the following criteria:
> Both:
> Treatment course to be initiated within 72 hours post exposure; and
> Either:
> Patient has had **unprotected** receptive anal intercourse with a known HIV positive person; or
> Patient has had shared intravenous injecting equipment with a known HIV positive person.
>
> Renewal - (second or subsequent post-exposure prophylaxis) only from a named specialist. Approvals valid for 4 weeks for applications meeting the following criteria:
> Both:
> Treatment course to be initiated within 72 hours post exposure; and
> Either:
> Patient has had **unprotected** receptive anal intercourse with a known HIV positive person; or
> Patient has had shared intravenous injecting equipment with a known HIV positive person.
>
> Renewal - (second or subsequent percutaneous exposure) only from a named specialist. Approvals valid for 6 weeks where the patient has percutaneous exposure to blood known to be HIV positive.

4.2 The Subcommittee noted that clinicians utilising HIV-nPEP would take into account the HIV positive patient's viral load, as exposure to a patient with a suppressed viral load posed a lesser risk of transmission. Members noted that HIV-nPEP did not provide access to funding for prophylaxis for rape as this received funding from the Accident Compensation Corporation (ACC).

4.3 The Subcommittee noted that PHARMAC had received Tender bids for generic antiretrovirals in the 2009/10 Tender. Members noted the correspondence from AMTAC regarding the fragility of this patient group. Members considered that any brand switch in this patient group should be communicated to patients as early as possible with a clear and coherent description of the change.

4.4 The Subcommittee noted the subsidy reductions that PHARMAC typically achieved when a products patent life expired and a tender occurred. Members considered the price of therapy was a lesser factor compared with efficacy and side effect profile in deciding which pharmaceutical to use. Members noted that literature supported rationalising regimes to once daily therapy as this improved compliance (possibly by up to 2.3%) when compared to twice daily dosing.

4.5 The Subcommittee considered that when the combination zidovudine with lamivudine' patent expired it would be possible to persuade prescribers to consider price in treatment

decisions. Members considered that as this is a closed prescriber group that the named antiretroviral prescribers should be involved in discussion with the goal of agreeing on a treatment paradigm.

5 Tenofovir for post-liver transplantation prophylaxis

5.1 The Subcommittee noted the tabled correspondence from [withheld under s9(2)(a) of the OIA] requesting the funding of tenofovir for post-liver transplantation prophylaxis in combination with lamivudine. Members noted that adefovir for this indication had received a medium priority at the December 2008 meeting. Members noted that adefovir or tenofovir for this indication would reduce the use of Hepatitis B Immunoglobulin (HBIg).

5.2 Members noted the Teperman et al (2010) slides presented at the European Association for the Study of the Liver, regarding tenofovir for post-liver transplantation hepatitis B prophylaxis. Members noted that the trial involved tenofovir in combination with emtracitabine, but considered that lamivudine was equivalent to emtracitabine. Members noted that no patient had recurrence of hepatitis B after discontinuation of HBIg and continuation of tenofovir and emtrictabine. Members **recommended** funding tenofovir for post-liver transplantation hepatitis B prophylaxis.

5.3 The Subcommittee considered that the proposed Special Authority should be amended as follows (additions in **Bold,** deletions in ~~strikethrough~~):

SA0997 Special Authority for Waiver of Rule
Initial application - (Drug-Resistant Chronic Hepatitis B) only from a gastroenterologist, infectious disease specialist or general physician. ~~Approvals valid for 1 year for applications meeting the following criteria:~~

1 Patient has any of the following

1.1 Patient has confirmed Hepatitis B infection (HBsAg positive for more than 6 months); and all of the following

1.1.1 Patient has had previous lamivudine, adefovir or entecavir therapy; and

1.1.2 HBV DNA greater than 20,000 IU/mL or increased = 10 fold over nadir; and

1.1.3 Any of the following:

1.1.3.1 Lamivudine resistance - detection of M204I/V mutation; or

1.1.3.2 Adefovir resistance - detection of A181T/V or N236T mutation; or

1.1.3.3 Entecavir resistance - detection of relevant mutations including I169T, L180M T184S/A/I/L/G/C/M, S202C/G/I, M204V or M250I/V.

1.2 Patient is either listed or has undergone liver transplantation for HBV

1.3 Patient is HBsAg positive and pregnant and has one of the following:

1.3.1 HBV DNA>20,000 IU/mL and ALT >ULN. *Tenofovir is indicated to treat active CHB and should be continued until delivery, following which switch to another agent such as lamivudine or entecavir should be considered*

1.3.2 HBV DNA >10^8 IU/mL and ALT normal. *Patient does not have active CHB and Tenofovir is indicated to prevent vertical transmission from mother to baby (>30% risk despite neonatal vaccination and HBIG immunoprophylaxis). Tenofovir should be delayed until the mother enters the third trimester and continued until*

delivery. It should then be stopped but mother's LFTs should be monitored for next 3 months to ensure that rebound hepatitis flare does not ensue (unlikely)

~~Renewal - (Drug-Resistant Chronic Hepatitis B) only from a gastroenterologist, infectious disease specialist or general physician. Approvals valid for 2 years where in the opinion of the treating physician, treatment remains appropriate and patient is benefiting from treatment~~
Note
Tenofovir should be stopped 6 months following HBeAg seroconversion for patients who were HBeAg positive prior to commencing this agent and 6 months following HBsAg seroconversion for patients who were HBeAg negative 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.

6 Tenofovir/emtricitabine/efavirenz (Atripla) and tenofovir/emtricitabine (Truvada) for HIV

6.1 The Subcommittee reviewed applications from Gilead Sciences (NZ) for the listing of Tenofovir/ emtricitabine / efavirenz (Atripla) & tenofovir/ emtricitabine (Truvada) on the Pharmaceutical Schedule for the treatment of HIV infection.

6.2 The Subcommittee noted that the individual medications for each of the products were available under the current Special Authority for Antiretrovirals (tenofovir by endorsement if co-prescribed with funded antiretrovirals). Members noted that all the products in the combination products were one tablet once daily medications.

6.3 Members noted the tabled letter from [withheld under s9(2)(a) of the OIA], on behalf of the AIDS Medical and Technical Advisory Committee (AMTAC) requesting Atripla and Truvada for juveniles and adolescents to assist them with improved compliance. Members noted the evidence provided from [withheld under s9(2)(a) of the OIA] time at St Marys Hospital in London regarding fixed dose combination antiretrovirals in adolescents and young adults.

6.4 The Subcommittee noted the tabled data from the Mathias et al bioequivalence study for Atripla and the tabled data from the unpublished bioequivalence study GS-US-104-0172 for Truvada. Members considered these bioequivalence studies to be of good quality.

6.5 The Subcommittee noted the tabled data from the Parienti et al paper comparing once to twice daily antiretroviral regimens. Members noted the 2.3 % increase in compliance in this study. Members considered there was no evidence that reducing pill burden improved compliance. Members considered from their clinical experience that a one tablet regime may improve compliance in a small cohort of patients.

6.6 The Subcommittee considered that antiretroviral therapy required very good compliance (possibly as high as 95%) to be effective, although compliance rates at 80% may be acceptable with the medications with a high barrier to resistance and if patients had already achieved an undetectable viral load. Members considered that Atripla and Truvada offered a convenient dosage form but there was no evidence provided to show

improved compliance in any patient group. Members considered that clinical motivation and explanation from a Doctor could provide improved compliance.

6.7 The Subcommittee noted that the tablet size for Atripla was large but comparable with other combination antiretrovirals e.g. Kaletra. Members considered that some of the compliance benefits of a single pill may be diminished due to this tablet size.

6.8 The Subcommittee considered the number of patients who would use Atripla and Truvada to be underestimated in the proposal. Members considered that almost 100% of patients on the individual components would switch to the fixed dose combination therapy. Members considered that at least 20% of patients on other combination therapies may be changed to Atripla or Truvada. Members considered that it was likely that 70-80% of new patients would be initiated on Atripla or Truvada if they were available.

6.9 Members noted that 90% of patients on current treatment have an undetectable viral load and therefore would derive no benefit from using Atripla or Truvada because they were already compliant. The Subcommittee considered that fixed dose combination antiretroviral therapy would provide a benefit to less than 5% of the treatment population; although the benefit may be higher in adolescents and young adults. Members noted that this subgroup of patients represent approximately 1-2% of all patients receiving treatment. Members noted that only a small percentage, approximately 4%, of patients were adolescents. Members noted the difficulty in restricting a product on the basis of age. The Subcommittee noted there may be requests for off-licence use of Truvada in the Hepatitis B patient population.

6.10 The Subcommittee noted that the patents for the individual products expire significantly earlier than the fixed dose combination products. The Subcommittee noted there was no clinical reason not to list Atripla or Truvada.

6.11 The Committee recommended that there were no clinical reason not to fund Atripla, and further **recommended** that Atripla for HIV only be listed on the Pharmaceutical Schedule if cost-neutral to the Pharmaceutical Schedule for the life of the Atripla patent.

6.12 The Committee recommended that there were no clinical reason not to fund Truvada, and further **recommended** that Truvada for HIV only be listed on the Pharmaceutical Schedule if cost-neutral to the Pharmaceutical Schedule for the life of the Truvada patent.

7 Initiation of antiretroviral therapy

7.1 The Subcommittee noted the tabled December 2009 Department of Health and Human Services Panel (DHHS) updated Guidelines for the use of antiretroviral agents in HIV-1 Infected Adults and Adolescents.

7.2 The Subcommittee noted that the DHHS guidelines recommended that initiation of antiretroviral therapy was appropriate for patients with a CD4 count $\leq$500 cells/mm3. Members considered that initiation was not a significant issue as symptomatic patients

could have therapy initiated regardless of CD4 count. Members noted however that the association between some symptoms and HIV/AIDS were tenuous and that there may be variability among clinicians as to how the word “symptomatic” is used.

7.3 The Subcommittee considered that antiretroviral therapy should be initiated in infants (aged less than 1 year) at diagnosis regardless of CD4 count.

7.4 Members considered there were approximately 400 people infected with HIV who were not currently receiving antiretroviral therapy. Members considered that if the CD4 count requirement was raised to ≤500 cells/mm3 or removed altogether then approximately 20-50 patients of these 400 people may access therapy earlier than they currently would.

7.5 The Subcommittee considered that earlier initiation of antiretroviral therapy would reduce both AIDS defining and non-AIDS defining illnesses. Members noted that initiation at the time of diagnosis may provide a public health benefit as it would reduce transmission of HIV. Members considered there may be neuroprotective benefits in obtaining an undetectable viral load at an earlier stage in infants and the elderly and that earlier initiation could provide greater benefit.

7.6 The Subcommittee considered that there would be compliance issues for some patients if treatment was initiated earlier, and that earlier initiation should only occur if the treating physician considered the patient likely to be compliant. Members noted that a non-compliant patient should not initiate therapy as this may increase the likelihood of resistance developing. Members noted that there may be some long term toxicity issues with earlier initiation; however, this was considered less likely with the currently preferred antiretrovirals.

7.7 The Subcommittee noted that active Hepatitis B requiring treatment in HIV co-infected should be considered a reason for initiating therapy. Members also considered that active Hepatitis C requiring therapy in HIV co-infection should also be considered a reason for earlier initiation. Members noted that many clinicians already considered these as symptomatic patients.

7.8 The Subcommittee **recommended** amending the Special Authority for antiretrovirals as follows (additions in **Bold**, deletions in ~~strikethrough~~):

Special Authority for Subsidy - Form SA0779
Initial application - (Confirmed HIV/AIDS) only from a named specialist. Approvals valid without further renewal unless notified for applications meeting the following criteria:
Both:
1 Confirmed HIV infection; and
2 Any of the following:
- 2.1 Symptomatic patient; or
- 2.2 Patient aged 12 months and under; or
- 2.3 Both:
  - 2.3.1 Patient aged 1 to 5 years; and
  - 2.3.2 Any of the following:
    - 2.3.2.1 CD4 counts < 1,000 cells/mm3; or
    - 2.3.2.2 CD4 counts < 0.25 x total lymphocyte count; or
    - 2.3.2.3 Viral load counts > 100,000 copies per ml; or
- 2.4 Both:
  - 2.4.1 Patient aged 6 years and over; and
  - 2.4.2 CD4 counts < ~~350~~ **500** cells/mm3~~.~~ **or**

2.5 Co-infection with Hepatitis B or Hepatitis C

Note
Tenofovir disoproxil fumarate prescribed under endorsement for HIV/AIDS is included in the count of up to 3 subsidised antiretrovirals.
Subsidies for a combination of up to three anti-retroviral medications~~, including a maximum of two protease inhibitors~~. Combinations including ritonavir plus indinavir or atazanavir will be counted as one protease inhibitor for the purpose of accessing funding to anti-retrovirals.

8 Optimised Background therapy in HIV

8.1 The Subcommittee noted the previous PTAC minutes from April 2009 and April 2008 with respect to Optimised Background Therapy (OBT). Members noted that the minute provided by PTAC was clinically appropriate, but did not reflect the commercial situation faced by PHARMAC. Members reiterated that the clinical need for darunavir remained.

8.2 Members noted that the listing of raltegravir had caused therapeutic problems for a subgroup of patients (four patients in total) who were receiving raltegravir as their fourth antiretroviral. Members also noted that the Auckland Infectious Disease department had several patients receiving compassionate supply of darunavir who required ritonavir as a booster and that ritonavir was not funded under the current Special Authority restriction in this patient group.

8.3 The Subcommittee noted that the trials for all new antiretrovirals were in combination to OBT. Members considered that the evidence supports the use of four antiretrovirals to achieve a suppressive regimen. Members noted that there was no current evidence to support reducing the number of antiretrovirals once an undetectable HIV viral load has been achieved.

8.4 The Subcommittee noted the tabled paper by Yazdanpanah et al. Members noted that in a subgroup analysis that there was no difference in the efficacy of raltegravir, darunavir/ritonavir and etravirine whether used without OBT, a low potency OBT or a high potency OBT. Members considered that ongoing clinical studies may provide evidence for the use of this combination i.e. raltegravir, darunavir/ritonavir and etravirine without OBT, but this was not clinically appropriate at this stage.

8.5 The Subcommittee considered that OBT was a historical term as previously there was no resistance testing, and with the advent of genotypic testing the terminology should be ‘active drugs’. The Subcommittee considered with genotypic resistance testing that targeted treatment was possible and that prescribing three fully active drugs on the basis of genotypic testing was possible.. Members noted that the combination of two fully active drugs and two partly active drugs was highly likely to achieve virological suppression.

8.6 The Subcommittee considered that there would be no requirement for patients in New Zealand to access more than four antiretrovirals (excluding ritonavir as a booster). Members noted that under current special authority criteria, a fourth antiretroviral enfuvirtide was already funded for salvage therapy. It was also noted that this was significantly more expensive than other antiretroviral therapies. Members considered that

if access was not widened to allow 4 antiretrovirals to be prescribed, enfuvirtide usage would inevitably increase.

8.7 The Subcommittee considered that if therapy was extended to allow 4 antiretrovirals to be prescribed an initial 20 patients would access this number of antiretrovirals and this would increase by five to ten patients annually.

8.8 The Subcommittee **recommended** amending the Special Authority for antiretrovirals with a high priority as follows (additions in **Bold**, deletions in ~~strikethrough~~):

> Special Authority for Subsidy - Form SA0779
> Initial application - (Confirmed HIV/AIDS) only from a named specialist. Approvals valid without further renewal unless notified for applications meeting the following criteria:
> Both:
> 1 Confirmed HIV infection; and
> 2 Any of the following:
> 2.1 Symptomatic patient; or
> 2.2 Patient aged 12 months and under; or
> 2.3 Both:
> 2.3.1 Patient aged 1 to 5 years; and
> 2.3.2 Any of the following:
> 2.3.2.1 CD4 counts < 1,000 cells/mm3; or
> 2.3.2.2 CD4 counts < 0.25 x total lymphocyte count; or
> 2.3.2.3 Viral load counts > 100,000 copies per ml; or
> 2.4 Both:
> 2.4.1 Patient aged 6 years and over; and
> 2.4.2 CD4 counts < 350 cells/mm3.
> Note
> Tenofovir disoproxil fumarate prescribed under endorsement for HIV/AIDS is included in the count of up to ~~3~~**4** subsidised antiretrovirals.
> Subsidies for a combination of up to ~~three~~ **four** anti-retroviral medications, ~~including a maximum of two protease inhibitors~~. Combinations including ritonavir plus indinavir or atazanavir will be counted as one protease inhibitor for the purpose of accessing funding to anti-retrovirals.