Haematology Subcommittee of PTAC

Meeting held on 6 August 2012

(minutes for web publishing)

The Haematology 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 Haematology Subcommittee meeting; only the relevant portions of the minutes relating to Haematology Subcommittee discussions about an application or PHARMAC staff proposal that contain a recommendation are generally published.

The Haematology 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 a 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 14 and 15 February 2013, the record of which is available in on the PHARMAC website.

Recommendations for the Record of the Haematology Subcommittee of PTAC Meeting held on 6 August

Location of Recommendation	Recommendation
1. Therapeutic Group Review	1.4. The Subcommittee recommended that the guidelines for the perioperative management of dabigatran and guidelines for its management in the event of bleeding be revised as there is currently more clinical experience with the product following its listing in July 2011. The Subcommittee noted that it appears that the rate of adverse events observed with dabigatran has reduced, which is possibly reflective of prescribers being more experienced with the treatment and prescribing it more appropriately.
2. Eculizumab in Paroxysmal nocturnal haemoglobinuria	2.2 The Subcommittee **recommended** that the eculizumab be listed in the Pharmaceutical Schedule with a low priority subject to criteria limiting it to patients with paroxysmal nocturnal haemoglobinuria who: • Have a clone size >50%, have systemic symptoms (for example severe abdominal pain, fatigue and shortness of breath) and there is evidence of active haemolysis; OR • Have developed thrombosis despite adequate treatment (for example anticoagulation).
3. Eltrombopag in idiopathic thrombocytopenic purpura	3.2. The Subcommittee **recommended** that eltrombopag is funded with medium priority and restricted by the following Special Authority criteria: **Initial application - (idiopathic thrombocytopenic purpura – post-splenectomy)** from a haematologist. Approvals valid for 6 weeks for applications meeting the following criteria: All of the following: 1.1 Patient has had a splenectomy; 1.2 Patient has failed 2 immunosuppressive therapies after therapy of 3 months each (or 1 month for rituximab); and 1.3 Any of the following: 1.3.1 Patient has a platelet count of ≤20,000 platelets per µL and has evidence of active bleeding; or 1.3.2 Patient has a platelet count of

	≤10,000 platelets per µL. **Initial application - (idiopathic thrombocytopenic purpura – preparation for splenectomy)** from a haematologist. Approvals valid for 6 weeks for patients requiring eltrombopag treatment as preparation for splenectomy. **Renewal application – (idiopathic thrombocytopenic purpura – post-splenectomy)** from a haematologist. Approvals valid for 12 months where the patient has obtained a response* from treatment during the initial approval or subsequent renewal periods and further treatment is required. ***Response to treatment is defined as a platelet count of >30,000 platelets per µL
4. Posaconazole for the prophylaxis of invasive fungal infection	4.2. The Subcommittee **recommended** that posaconazole is funded with high priority and restricted to the following patient groups through the following Special Authority restriction: **Initial application** only from a Haematologist or Infectious Disease Physician. Approvals valid for 6 weeks for patients meeting the following criteria: Any of the following: 1. Patient has acute myeloid leukaemia and is to be treated with high dose remission induction, re-induction or consolidation chemotherapy; or 2. Patient has received a stem cell transplant and has graft versus host disease (GVHD) on significant immunosuppressive therapy*. **Renewal application** only from a Haematologist or Infectious Disease Physician. Approvals valid for 6 weeks for patients meeting the following criteria: Any of the following: 1. Patient has acute myeloid leukaemia and is to be treated with high dose remission induction, re-induction or consolidation therapy; or 2. Patient has received a stem cell transplant and has GVHD on significant immunosuppression* and requires ongoing posaconazole treatment. * GVHD on significant immunosuppression is defined as acute GVHD, grade II to IV, or extensive chronic GVHD, or if they were being treated with intensive immunosuppressive therapy consisting of either high-dose corticosteroids (≥1 mg per kilogram of body weight per day for patients with acute GVHD or ≥0.8 mg per kilogram every other day for patients with chronic GVHD), antithymocyte globulin, or a combination of two or more immunosuppressive agents or types of treatment.

4. Posaconazole for the prophylaxisof invasive fungal infection	4.3. The Subcommittee **recommended** that the funding application for posaconazole use in aplastic anaemia and acute lymphoblastic leukemia (ALL) be declined.
5. Hospital Pharmaceutical Review	5.12. The Subcommittee **recommended** that filgrastim be subject to recommendation by haematologists and oncologists. Members noted that while others, such as renal physicians, do prescribe filgrastim, it is usual and appropriate for them to seek advice from haematologists or oncologists before prescribing. 5.15. The Subcommittee **recommended** that pegfilgrastim not be included in a national PML. The Subcommittee noted that individual patients would be able to have pegfilgrastim funded under NPPA, and considered that this would be appropriate.
6. Treatments for HIT	6.2. The Subcommittee **recommended** that bivalirudin, danaparoid and fondaparinux are included on the national Preferred Medicines List for the management of heparin-induced thrombocytopenia.
7. Rituximab for ITP and autoimmune haemolytic anaemia	7.2. The Subcommittee **recommended** that rituximab is included in the national Preferred Medicines List for the treatment of cold haemagglutinin disease (CHD) with high priority and warm autoimmune haemolytic anaemia with medium priority. 7.3. The Subcommittee also **recommended** that rituximab is included in the hospital Preferred Medicines List for the treatment of refractory idiopathic thrombocytopenic purpura (ITP) (platelet count <20,000 per µL) where there is evidence of clinically significant bleeding. 7.4. The Subcommittee **recommended** that for these indications, it would be appropriate to restrict rituximab prescribing in hospitals to haematologists.
8. Rituximab for haemophilia with inhibitors	8.2. The Subcommittee **recommended** that rituximab is included on the national Preferred Medicines List for the treatment of: 9.2.1. Mild congenital haemophilia, complicated by inhibitors with high priority; 9.2.2. Severe congenital haemophilia in patients who have failed immune tolerance therapy with medium priority; and 9.2.3. Acquired haemophilia with low priority. 8.3. The Subcommittee **recommended** that for these indications, it would be appropriate to restrict rituximab prescribing in hospitals to haematologists.

Record of the Haematology Subcommittee of PTAC meeting

held at PHARMAC on 6 August 2012

Present from the Haematology Subcommittee:

Mark Weatherall (Chair, PTAC member)

Tim Hawkins

Paul Ockelford

Paul Harper

Nyree Cole

Nigel Patton

John Carter

1 Therapeutic Group Review

1.1 The Subcommittee noted that the use of aspirin 100mg has been steadily increasing. The Subcommittee noted that a recent study found a 40% relative risk reduction of venous thromboembolism (VTE) recurrence in patients who were treated with aspirin versus placebo for VTE secondary prevention and could lead to further increase in use.

1.2 The Subcommittee noted that rivaroxaban will likely be reviewed by PTAC in November 2012. The Subcommittee noted that experience in the clinical trial setting suggests that it potentially could have a better safety profile than dabigatran, especially in patients with renal impairment. In the trials for rivaroxaban in the VTE treatment indication, there was also no need to use bridging anticoagulation with enoxaparin. The Subcommittee considered that if funded, guidelines for the perioperative management of rivaroxaban and management of bleeding should be put together in a timely manner.

1.3 The Subcommittee also noted that apixaban and edoxaban are other Factor Xa inhibitors in the pipeline. The Subcommittee noted that there might be clinical merit in not having too many types of these agents available to avoid confusion which could lead to prescribing or dispensing errors.

1.4 The Subcommittee recommended that the guidelines for the perioperative management of dabigatran and guidelines for its management in the event of bleeding be revised as there is currently more clinical experience with the product following its listing in July 2011. The Subcommittee noted that it appears that the rate of adverse events observed with dabigatran has reduced, which is possibly reflective of prescribers being more experienced with the treatment and prescribing it more appropriately.

1.5 The Subcommittee noted that the trial investigating the benefits of iron chelation for iron overload in myelodysplasia (MDS) is ongoing and there has been no new evidence for iron chelation in MDS.

1.6 The Subcommittee noted that a new iron injection - ferric carboxymaltose (Ferinject) was recently registered in New Zealand and there is increasing use of it over the intramuscular injection in hospitals given its ease of administration where an intravenous bolus can be given and as it can replenish iron stores prior to surgery and reduces the requirement for blood transfusions.

1.7 The Subcommittee noted that enoxaparin is increasingly being used in residential care facilities for VTE prophylaxis in patients who are immobile but it is not currently funded for this indication. The Subcommittee considered that if it was more widely available then usage in this patient population, about 25,000 people, could increase and the evidence for enoxaparin in this indication shows that it could result in more complications than benefit.

1.8 The Subcommittee noted that PHARMAC had received many Named Patient Pharmaceutical Assessment (NPPA) or Exceptional Circumstances applications for enoxaparin. The Subcommittee noted that there are financial risks associated with removing the enoxaparin Special Authority restrictions. The Subcommittee noted that there is currently insufficient evidence to support the use of enoxaparin for VTE prophylaxis during long haul flights. The Subcommittee considered that the risk of VTE during long haul flights is relatively small and there is uncertainty around what the optimal dose of enoxaparin in this setting is. The Subcommittee considered that it would be appropriate to widen access to enoxaparin for the following patient groups:

1.8.1 Patients with proven intolerance to warfarin;

1.8.2 Patients with malabsorption syndromes (especially those who have had a small bowel resection);

1.8.3 Patients who develop thromboses despite adequate anticoagulation with warfarin; and

1.8.4 Infants who require anticoagulation and treatment with warfarin is not clinically appropriate or practically feasible (especially where the infant is being breastfed).

2 Eculizumab in Paroxysmal Nocturnal Haemoglobinuria

Application

2.1 The Subcommittee reviewed an application from Alexion Pharmaceuticals for the listing of eculizumab (Soliris) on the Pharmaceutical Schedule for the treatment of paroxysmal nocturnal haemoglobinuria (PNH).

Recommendation

2.2 The Subcommittee **recommended** that the eculizumab be listed in the Pharmaceutical Schedule with a low priority subject to criteria limiting it to patients with paroxysmal nocturnal haemoglobinuria who:

- Have a clone size >50%, have systemic symptoms (for example severe abdominal pain, fatigue and shortness of breath) and there is evidence of active haemolysis; OR

- Have developed thrombosis despite adequate treatment (for example anticoagulation).

2.3 The Subcommittee considered that given the high cost of treatment, an advisory panel may be required to administer the treatment eligibility criteria.

2.4 The Decision Criteria particularly relevant to this recommendation are: *(i) The health needs of all eligible people within New Zealand; (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; and (iv) The clinical benefits and risks of pharmaceuticals and (vi) The budgetary impact of any changes to the Pharmaceutical Schedule.*

Discussion

2.5 The Subcommittee noted that this application had been reviewed by PTAC at its February 2012 meeting and has recommended that it be declined due to its high cost and the uncertainty around survival benefit with the treatment. The Subcommittee also noted that the supplier and Professor Peter Hillmen have provided feedback to some of the points raised by PTAC for review by the Subcommittee.

2.6 The Subcommittee noted that paroxysmal nocturnal haemoglobinuria (PNH) is an extremely rare disease characterised by complement-mediated haemolysis resulting in haemolytic anaemia, venous thromboembolisms and the associated symptoms. The Subcommittee noted that there is a range of treatments currently available but they are not very efficacious except for warfarin prophylaxis and supportive care with blood transfusion, iron and folate replacement.

2.7 The Subcommittee noted that the efficacy of eculizumab was investigated in 3 trials – the TRIUMPH study (Hillmen P et al. N Engl J Med 2006; 355(12): 1233-1243), the SHEPHERD study (Brodsky R et al. Blood 2008; 111(4): 1840-1847) and the Kelly et al study (Blood 2011; 117(25): 6786-92). The Subcommittee considered that the evidence was of medium strength and quality. The Subcommittee considered that the evidence available indicates that eculizumab is effective in reducing blood transfusion requirements and thrombosis rates.

2.8 The Subcommittee considered that the evidence of survival benefit with eculizumab was limited but it is likely to be associated with a survival benefit. The Subcommittee acknowledged that there were weaknesses associated with the Kelly et al study (Blood 2011; 117(25): 6786-92), namely that the lack of information regarding whether the treatment and control groups were matched adequately. The Subcommittee noted the response from Professor Peter Hillmen in regards to PTAC's comments on the French cohort study (de Latour et al. Blood 2008; 112: 3099) and considered that it was reasonable to conclude that the 92% 10-year survival rate estimate was probably too high given none of these patients (cohort diagnosed after 1996) were followed up for 10 years and only 18 of the 83 patients were followed up for 5 years. The Subcommittee also noted the response from Professor Peter Hillmen to PTAC's concerns regarding the 7-year study timeframe chosen in the Kelly et al study (Blood 2011; 117(25): 6786-92) and considered that his response was appropriate. The Subcommittee noted that previous studies have shown a median survival rate of 10 years for patients treated with best supportive care (Hillmen P et al. N Engl J Med. 1995;333(19):1253-1258) but considered that best supportive care including recommended warfarin anticoagulation is now better given that thrombosis is the largest risk factor in the patient population.

2.9 The Subcommittee noted that there would be an increased risk of serotype B meningococcal disease with eculizumab use and clinicians as well as patients would

need to be vigilant of this increased risk, and establish prophylaxis and treatment algorithms.

2.10 The Subcommittee considered that there would be a small number of patients with a clone size of >50%, approximately 3 patients per million population. The Subcommittee considered that there is a high clinical need in this group of patients given the limited effective treatment alternatives. The Subcommittee considered that the patient group most likely to benefit from treatment with eculizumab would be patients who have developed thrombosis despite adequate treatment (anticoagulation) or those who have a clone size >50% with systemic symptoms (for example severe abdominal pain, fatigue and shortness of breath) and in whom there is evidence of active haemolysis.

2.11 The Subcommittee however noted the high drug cost for this treatment which resulted in its poor cost-effectiveness although evidence indicates it is an effective treatment. The Subcommittee noted that this is a significant issue especially given it is a long term treatment. The Subcommittee noted that this is the reason why the Canadian Agency for Drugs and Technologies in Health (CADTH) and Scottish Medicines Consortium did not recommend it for use within their jurisdictions.

2.12 The Subcommittee considered that there is no clinical reason why eculizumab should not be listed on the Pharmaceutical Schedule and recommended its listing with a low priority due to its extremely high cost. The Subcommittee also considered that if funded, patient compliance with treatment would need to be stressed.

3 Eltrombopag in Idiopathic Thrombocytopenic Purpura

Application

3.1 The Subcommittee reviewed an application from GlaxoSmithKline for the listing of eltrombopag (Revolade) on the Pharmaceutical Schedule for the treatment of idiopathic thrombocytopenic purpura (ITP).

Recommendation

3.2 The Subcommittee **recommended** that eltrombopag is funded with medium priority and restricted by the following Special Authority criteria:

Initial application - (idiopathic thrombocytopenic purpura – post-splenectomy) from a haematologist. Approvals valid for 6 weeks for applications meeting the following criteria:

All of the following:

1.4 Patient has had a splenectomy;

1.5 Patient has failed 2 immunosuppressive therapies after therapy of 3 months each (or 1 month for rituximab); and

1.6 Any of the following:

1.6.1 Patient has a platelet count of ≤20,000 platelets per µL and has evidence of active bleeding; or

1.6.2 Patient has a platelet count of ≤10,000 platelets per µL.

Initial application - (idiopathic thrombocytopenic purpura – preparation for splenectomy) from a haematologist. Approvals valid for 6 weeks for patients requiring eltrombopag treatment as preparation for splenectomy.

Renewal application – (idiopathic thrombocytopenic purpura – post-splenectomy) from a haematologist. Approvals valid for 12 months where the patient has obtained a response* from treatment during the initial approval or subsequent renewal periods and further treatment is required.

***Response to treatment is defined as a platelet count of >30,000 platelets per µL.

3.3 The Decision Criteria particularly relevant to this recommendation are: *(i) The health needs of all eligible people within New Zealand; (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals; (v) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publically funded health and disability support services and (vi) The budgetary impact of any changes to the Pharmaceutical Schedule.*

Discussion

3.4 The Subcommittee noted that PTAC had reviewed this application at its meeting in February 2012 and had deferred making a recommendation until the application was reviewed by this Subcommittee, including for further advice on any Special Authority criteria.

3.5 The Subcommittee noted that idiopathic thrombocytopenic purpura (ITP) was associated with an incidence of 4 to 5 per 100,000 with the incidence of severe cases being perhaps 10 per year. The Subcommittee considered that first-line treatments in New Zealand are corticosteroids and intravenous immunoglobulin (IVIG). The Subcommittee considered that if patients failed on these treatments, splenectomy would be the next option followed by immunosuppressant therapies like danazol, azathioprine, cyclosporin and rituximab. The Subcommittee considered that approximately 75% of patients have an initial response to splenectomy and about 60% of patients achieve long-term remission (Schwartz et al. Am J Haematology 2003; 72(2): 94-98, Akwari et al. Annals of Surg 1987; 206(4): 529). The Subcommittee considered that approximately 60% of patients do not require any subsequent treatments following a splenectomy.. The Subcommittee considered that patients would likely be less responsive to rituximab following a splenectomy.

3.6 The Subcommittee noted that there were two Phase III trials for eltrombopag in addition to standard care in ITP compared to placebo (RAISE study - Cheng et al. Lancet 2011; 377: 393-402 and Bussel et al. Lancet 2009; 373: 641-648). The Subcommittee considered that the evidence for eltrombopag in this indication was of good strength and quality. The Subcommittee noted that versus placebo, eltrombopag was effective at increasing platelet counts but the Subcommittee noted that the response to treatment was not sustained and long-term treatment with eltrombopag was required. The Subcommittee noted that there is no head-to-head trial of eltrombopag versus other treatments like rituximab. The Subcommittee noted that there is limited evidence for the efficacy of other treatments in ITP and the evidence for eltrombopag in this indication being better than the other treatments except for splenectomy. The Subcommittee considered that if given the choice patients may choose to be treated with long-term eltrombopag rather than undergo a splenectomy.

3.7 The Subcommittee noted that in the RAISE study, patients on eltrombopag still had a higher thrombosis risk despite those at increased risk being excluded from the trial. The Subcommittee also noted that eltrombopag had an impact on liver function. The Subcommittee noted that there was currently no available evidence on the long-term safety of eltrombopag, for example the risk of bone marrow fibrosis with prolonged treatment. The Subcommittee considered that the overall mortality rate with ITP is low.

3.8 The Subcommittee considered that it was difficult to quantify the risk of bleeding at the different platelet levels as requested by PTAC. The Subcommittee considered that in view of the benefits and risks, the patients most likely to benefit from eltrombopag would be those who have had a splenectomy and failed at other treatments with evidence of significant bleeding (for example wet purpura) or for short-term use in patients as a bridge to splenectomy. The Subcommittee considered that a response to treatment should be seen within 6 weeks of commencing therapy. The Subcommittee considered that non-responders would not obtain any benefit from continued treatment with eltrombopag and should cease treatment.

3.9 The Subcommittee noted that there was a lack of comparator studies against other available pharmaceutical options. It also noted that the evidence was against standard care but that this is variable between treatment centres and clinicians.

3.10 The Subcommittee considered that if restricted to the patient group outlined above, the patient numbers accessing treatment would be approximately half of that proposed by the supplier. The Subcommittee considered that it was difficult to estimate the baseline mortality rate from bleeding in ITP due to the small patient numbers but the Subcommittee considered that the 1.3% estimate per annum used by NICE was reasonable.

3.11 The Subcommittee noted that romiplostim was another thrombopoietin receptor agonist indicated for use in ITP in other countries but it is not registered in New Zealand and PHARMAC had not received a funding application.

4 Posaconazole for prophylaxis of invasive fungal infection

Application

4.1 The Subcommittee reviewed a memorandum from PHARMAC staff for the listing of posaconazole (Nofaxil) on the Pharmaceutical Schedule for the prophylaxis of invasive fungal infections.

Recommendation

4.2 The Subcommittee **recommended** that posaconazole is funded with high priority and restricted to the following patient groups through the following Special Authority restriction:

> **Initial application** only from a Haematologist or Infectious Disease Physician. Approvals valid for 6 weeks for patients meeting the following criteria:
>
> Any of the following:
>
> 1. Patient has acute myeloid leukaemia and is to be treated with high dose remission induction, re-induction or consolidation chemotherapy; or
>
> 2. Patient has received a stem cell transplant and has graft versus host disease (GVHD) on significant immunosuppressive therapy*.
>
> **Renewal application** only from a Haematologist or Infectious Disease Physician. Approvals valid for 6 weeks for patients meeting the following criteria:

Any of the following:

1. Patient has acute myeloid leukaemia and is to be treated with high dose remission induction, re-induction or consolidation therapy; or

2. Patient has received a stem cell transplant and has GVHD on significant immunosuppression* and requires ongoing posaconazole treatment.

* GVHD on significant immunosuppression is defined as acute GVHD, grade II to IV, or extensive chronic GVHD, or if they were being treated with intensive immunosuppressive therapy consisting of either high-dose corticosteroids (≥1 mg per kilogram of body weight per day for patients with acute GVHD or ≥0.8 mg per kilogram every other day for patients with chronic GVHD), antithymocyte globulin, or a combination of two or more immunosuppressive agents or types of treatment.

4.3 The Subcommittee **recommended** that the funding application for posaconazole use in aplastic anaemia and acute lymphoblastic leukemia (ALL) be declined.

The Decision Criteria particularly relevant to this recommendation are: *(i) The health needs of all eligible people within New Zealand; (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals; (v) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publically funded health and disability support services and (vi) The budgetary impact of any changes to the Pharmaceutical Schedule.*

Discussion

4.4 The Subcommittee noted that posaconazole has previously been reviewed by PTAC and the Anti-Infective Subcommittee of PTAC at its November 2010 and March 2012 meetings respectively. The Subcommittee noted the tabled minutes from those meetings. The Subcommittee noted that PHARMAC was now seeking this Subcommittee's advice on the proposed Special Authority restriction, an estimate of patient numbers for the patient groups recommended for funding and a priority for the posaconazole funding proposal.

4.5 The Subcommittee considered that the incidence of invasive fungal infections in patients with acute myeloid leukemia (AML) is high at about 14%. The Subcommittee considered that the evidence for fungal prophylaxis in this clinical setting is well-established. The Subcommittee considered that AML is associated with a high cure rate of almost 50% with treatment and patients who respond are likely to have a normal life expectancy. The Subcommittee considered that there is evidence from Phase III clinical studies for fungal prophylaxis in the stem cell transplant setting but the evidence is not as strong as for its use in AML.

4.6 The Subcommittee noted the application from the Children's Haematology and Oncology Centre (CHOC) for access to posaconazole prophylaxis in AML, allogeneic haemopoietic stem cell transplantation complicated by graft versus host disease (GVHD) and aplastic anaemia (severe and very severe cases only). The Subcommittee noted that the clinicians in Christchurch were concerned about the 2011 earthquake leading to an increased spore count in the centre and a greater risk of invasive fungal infections.

4.7 The Subcommittee agreed with CHOC clinicians that posaconazole prophylaxis should be available for patients who have undergone haemopoietic stem cell transplantation and have developed GVHD. The Subcommittee noted that the Anti-Infective Subcommittee had not considered or recommended posaconazole prophylaxis in aplastic anaemia. The Subcommittee considered that aplastic anaemia was a rare condition. The Subcommittee also considered that there is no good evidence to support the use of posaconazole prophylaxis in aplastic anaemia.

4.8 The Subcommittee agreed with the Anti-Infective Subcommittee that patients receiving treatment for ALL were not at such a high risk. The Subcommittee considered that posaconazole prophylaxis is problematic in patients receiving vinca alkaloid therapy during induction or consolidation for ALL and there is no proven standard of prophylaxis in this patient group. The Subcommittee considered that better strategies are required. The Subcommittee noted that current approaches include:

- treatment with fluconazole as it is the azole with the least potential for drug interactions with vincristine;
- intravenous liposomal amphotericin B (the Subcommittee noted that there is no definitive evidence for its use although a trial is currently ongoing);
- +/- the use of a protected environment (HEPA filtration) although this requires an inpatient stay;
- The use of pre-emptive monitoring and intensive investigation of suspected fungal infection; and
- Mould active azoles could be considered during period of intensive therapy when not on vinca alkaloids although this has not been formally studied in clinical trials.

4.9 The Subcommittee considered that posaconazole was more effective than fluconazole and itraconazole because fluconazole is not effective against moulds and there are clinical issues with the different itraconazole formulations. The Subcommittee considered that voriconazole was a possible alternative treatment for some of the indications above but it was not currently available.

4.10 The Subcommittee considered that patient number estimates for each of the indications above can be better approximated using data available from all New Zealand acute leukaemia and bone marrow transplant centres. The Subcommittee noted that this should include careful estimates of elderly AML patients who should be treated with intensive AML therapy..

5 Hospital Pharmaceuticals Review

5.1 The Subcommittee reviewed a series of recommendations by the Hospital Pharmaceuticals Subcommittee in regards to which pharmaceuticals should be included on a national preferred medicines list (PML). The Subcommittee noted that PHARMAC had invited feedback from relevant colleges and professional societies, and noted the responses that were received.

5.2 The Subcommittee noted that the Hospital Pharmaceuticals Subcommittee had recommended that the prescribing of erythropoietin in DHB hospitals be subject to restrictions that are in line with the Special Authority criteria in the community.

5.3 The Subcommittee noted that the use of erythropoietin as an alternative to blood transfusions for religious reasons is an on-going issue that is not covered by the community criteria.

5.4 Members noted that trials are underway investigating the use of erythropoietin in a pre-surgical setting, which may require consideration in the future.

5.5 The Subcommittee noted that the Hospital Pharmaceuticals Subcommittee had queried whether all currently available presentations of recombinant blood factor products were required in a national PML. The Subcommittee recommended that all of these presentations be included.

5.6 The Subcommittee noted that the Hospital Pharmaceuticals Subcommittee had requested advice on the need for more than one form of low molecular weight heparin to be available in DHB hospitals. The Subcommittee noted that many DHBs currently use enoxaparin only, and that a few use dalteparin. Members noted that historically tinzaparin was used preferentially in obstetrics, but that this was no longer the majority view and that tinzaparin is now not commonly used in DHB hospitals.

5.7 The Subcommittee considered that having more variants of low molecular weight heparin available increased the risk of confusion and therefore overdose.

5.8 The Subcommittee considered that it would be preferable just to list enoxaparin in a national PML, and to exclude dalteparin and tinzaparin. However, the Subcommittee considered that it would be acceptable to include dalteparin also. The Subcommittee recommended that tinzaparin not be included in a national PML.

5.9 The Subcommittee noted that dextrose with sodium citrate and citric acid (acid citric dextrose A) was used in a number of niche indications including as an anticoagulant in stem cell harvest, and recommended that it be included in a national PML.

5.10 The Subcommittee noted that the Hospital Pharmaceuticals Subcommittee has sought advice on the presentations of intravenous heparin infusions that should be included in a national PML. The Subcommittee recommended that only the 100 iu per ml, 250 ml presentation be included for safety reasons.

5.11 The Subcommittee noted that the Hospital Pharmaceuticals Subcommittee has sought advice on the presentations of heparinised saline that should be included in a national PML. The Subcommittee recommended that all three presentations that are currently in use be included.

5.12 The Subcommittee **recommended** that filgrastim be subject to recommendation by haematologists and oncologists. Members noted that while others, such as renal physicians, do prescribe filgrastim, it is usual and appropriate for them to seek advice from haematologists or oncologists before prescribing.

5.13 The Subcommittee noted that the Hospital Pharmaceuticals Subcommittee had recommended including pegfilgrastim in a national PML. The Subcommittee noted that the benefits of pegfilgrastim relate to convenience rather than clinical superiority over filgrastim. The Subcommittee noted that most people however, are able to self-administer filgrastim.

5.14 The Subcommittee considered that, if pegfilgrastim was listed in a national PML, prescribing restrictions would be required, due to the cost difference between it and filgrastim. The Subcommittee considered that defining criteria would be difficult, as they would need to relate to a patient's ability to self-administer filgrastim, and would likely be difficult to enforce.

5.15 The Subcommittee **recommended** that pegfilgrastim not be included in a national PML. The Subcommittee noted that individual patients would be able to have pegfilgrastim funded under NPPA, and considered that this would be appropriate.

5.16 The Subcommittee noted that plerixafor had been used in some DHBs. The Subcommittee considered that this should undergo a formal review by PTAC and the Subcommittee, and recommended that PHARMAC seek a funding application for it.

5.17 The Subcommittee agreed with the Hospital Pharmaceuticals Subcommittee that an oral magnesium preparation also be included in a national PML and considered that the selection of salt is not important.

5.18 The Subcommittee noted and agreed with the recommendation from the Hospital Pharmaceuticals Subcommittee that the prescribing of rasburicase be subject to recommendation by haematologists.

5.19 The Subcommittee noted that there has been some use of imatinib in the treatment of hypereosinophilic syndrome. The Subcommittee noted that this is a rare condition, and considered that it was appropriate for this to be managed through NPPA.

5.20 The Subcommittee noted that the Hospital Pharmaceuticals Subcommittee had recommended that the 150 mcg dose form of desmopressin nasal spray not be listed in a national PML. The Subcommittee noted that this form is not widely used, with desmopressin injection being the predominant formulation used in haematology.

5.21 The Subcommittee noted also that defibrotide is currently being used by major transplant centres for venous occlusive disease prophylaxis in stem cell transplant recipients. The Subcommittee considered that the patient numbers are small (<10 per year). The Subcommittee recommended that defibrotide is included in a national PML and access criteria can be guided by hospital guidelines which are currently being used.

6 Treatments for HIT

Application

6.1 The Subcommittee reviewed a memorandum from PHARMAC staff regarding the inpatient treatments for heparin-induced thrombocytopenia (HIT) including bivalirudin, danaparoid, lepirudin, fondaparinux and argatroban.

Recommendation

6.2 The Subcommittee **recommended** that bivalirudin, danaparoid and fondaparinux are included on the national Preferred Medicines List for the management of heparin-induced thrombocytopenia.

Discussion

6.3 The Subcommittee considered that heparin-induced thrombocytopenia (HIT) was strongly associated with venous thromboembolism (VTE) and arterial thromboembolism as well as an increased risk of warfarin-related tissue necrosis. The Subcommittee considered that haemorrhagic complications are rare even with severe thrombocytopenia (platelets <15 x 109/L) which occurs in 5% of patients. The Subcommittee considered that overall the incidence of HIT is variable depending on the specific patient population and it also depends on the type of heparin used (a greater incidence in bovine versus porcine heparin) and the duration of heparin treatment. The Subcommittee considered that HIT occurs in approximately 2.5% of medical cardiac patients. The Subcommittee also considered that at most 10% of patients with suspected HIT are finally diagnosed with it.

6.4 The Subcommittee noted that thrombotic complications can occur at any time prior/during/after the onset of thrombocytopenia despite the cessation of heparin treatment. The Subcommittee considered that the thrombosis risk is approximately 5-10% per day for the first 1-2 days and the 30-day cumulative risk was about 50%. The Subcommittee also noted that the rate of thrombosis was similar even if heparin was replaced with warfarin. The Subcommittee considered that an alternative anticoagulant was therefore required.

6.5 The Subcommittee noted that the possible alternative anticoagulants include lepirudin, desirudin, bivalirudin, argatroban, danaparoid and fondaparinux. The Subcommittee noted that there is no published evidence with direct head-to-head comparisons of any of these agents. The Subcommittee noted that the PREVENT-HIT study comparing argatroban and desirudin was terminated before full recruitment. The Subcommittee considered that indirect comparison suggests that these treatments are effective.

6.6 The Subcommittee noted that the pivotal studies for argatroban that led to its approval were non-randomised single arm open label studies with untreated historical controls for comparison and serologic confirmation was not required for study inclusion (Lewis et al. Arch Intern Med 2003 Aug 11-25; 163(15): 1849-56 and Lewis et al. Circulation 2001 Apr 10; 103(14): 1838-43). The Subcommittee noted that 36% of those enrolled were antibody negative on post-hoc tests and a subset of patients had a remote history of HIT but no acute disease. The Subcommittee noted that the study results were in favour of argatroban for the primary end point (composite all-cause death, all-cause amputation or new thrombosis in 37 days) with an odds ratio (OR) of 0.61; 95% CI 0.39-0.98; p=0.04. The Subcommittee noted that there was no significant difference in bleeding between argatroban and controls in those trials. The Subcommittee noted that argatroban is metabolised in the liver and therefore caution is required in patients with liver failure. The Subcommittee noted that the American College of Chest Physicians (ACCP) guidelines favour argatroban in patients with renal failure. The Subcommittee noted also that argatroban is not registered in Australia or New Zealand.

6.7 The Subcommittee noted that lepirudin is registered in New Zealand and the evidence for its use in HIT is based on single arm studies with untreated historical controls for comparison however serologic confirmation of diagnosis was required prior to study enrolment. The Subcommittee noted that the study results favoured lepirudin with a reduction in new thromboses (11.9% vs. 32.1%, P = 0.0008)(Lubenow et al. J Thromb Haemost. 2005 Nov;3(11):2428-36) but there was a higher rate of bleeding (29.4% vs. 9.1%, P = 0.0148) which was dose-dependent. The Subcommittee also noted that lepirudin is renally cleared. The Subcommittee noted that approximately half of the patients developed anti-lepirudin antibodies but this is usually not problematic. The Subcommittee however noted that the supplier has discontinued supply of this treatment worldwide since April 2012.

6.8 The Subcommittee noted that bivalirudin is indicated and used mainly in percutaneous intravascular procedures in New Zealand. The Subcommittee noted that the evidence for its use in HIT is mainly from open label single arm studies. The Subcommittee noted that it is currently being used to treat HIT in the cardiac ICU setting in Auckland Hospital. The Subcommittee noted that the ACCP guidelines recommend the use of bivalirudin (Level 2C evidence) in the setting of acute or subacute HIT associated with cardiac surgery.

6.9 The Subcommittee considered that treatment with intravenous danaparoid showed benefit when compared to Dextran 70 (Chong et al. Thromb Haemost 2001 Nov; 86(5): 1170-5). The Subcommittee noted that the ACCP guidelines recommended that danaparoid is used in patients with HIT or HIT with thrombosis who have normal renal function (Level 2C evidence). The Subcommittee noted that it was previously used in

Auckland Hospital but there were was an interruption of supply. The Subcommittee noted that the supply issues are being resolved by the supplier.

6.10 The Subcommittee noted that fondaparinux is given as a subcutaneous injection and it is not registered for use in the treatment of HIT or systematically studied in this indication. The Subcommittee noted that there are several case series. The Subcommittee noted that a pooled analysis of 71 patients showed that none of the patients treated with fondaparinux developed new thrombotic events, major haemorrhage occurred in 4 patients but 3 of these patients had a creatinine clearance level of <30ml/min (Warkentin TE. Expert Review of Haematology 2010; 3(5): 567-581). The Subcommittee noted that there have been a few cases reported where fondaparinux potentially cause HIT but attribution remains uncertain. The Subcommittee noted that given its ease of administration with subcutaneous and once-daily administration, it is increasingly being used in stable patients.

6.11 The Subcommittee considered that the choice of treatment for HIT would be largely dependent on what treatments are actually available and taking into account the different clinical settings. The Subcommittee considered that it would be appropriate to include bivalirudin, fondaparinux and danaparoid on the national Preferred Medicines List for the treatment of HIT.

6.12 The Subcommittee noted that the newer oral anticoagulants like dabigatran and rivaroxaban could be efficacious in HIT but there is currently no evidence for their use in this setting.

7 Rituximab for ITP and autoimmune haemolytic anaemia

Application

7.1 The Subcommittee reviewed a memorandum from PHARMAC staff regarding rituximab for the treatment of autoimmune haemolytic anaemia and idiopathic thrombocytopenic purpura.

Recommendation

7.2 The Subcommittee **recommended** that rituximab is included in the national Preferred Medicines List for the treatment of cold haemagglutinin disease (CHD) with high priority and warm autoimmune haemolytic anaemia with medium priority.

7.3 The Subcommittee also **recommended** that rituximab is included in the hospital Preferred Medicines List for the treatment of refractory idiopathic thrombocytopenic purpura (ITP) (platelet count <20,000 per µL) where there is evidence of clinically significant bleeding.

7.4 The Subcommittee **recommended** that for these indications, it would be appropriate to restrict rituximab prescribing in hospitals to haematologists.

Discussion

7.5 The Subcommittee considered that cold haemagglutinin disease (CHD) is rare, very difficult to treat and there are no other effective treatment options. The Subcommittee noted that currently first-line treatments include steroids and immunosuppressants. Splenectomy and IVIG are additional options and then rituximab. The Subcommittee considered that rituximab may be considered prior to other immunosuppressants in younger patients. The Subcommittee considered that the limited data available

indicates that the response rate to rituximab can be up to 70% and it is also reduces the need for steroids.

7.6 The Subcommittee noted that warm haemagglutinin disease is the most common form of autoimmune haemolytic anaemia and can occur spontaneously or in association with certain disorders including systemic lupus erythematosus (SLE), lymphoma and CLL. The Subcommittee noted that 10-20% of patients with CLL develop haemolytic anaemia and therefore it is not a rare condition. The Subcommittee considered that the evidence for rituximab in haemolytic anaemia associated with CLL is fair. The Subcommittee considered that rituximab is now funded in Section B of the Pharmaceutical Schedule for CLL but not in the context of haemolytic anaemia associated with the disease.

7.7 The Subcommittee considered that <20 patients would access rituximab for cold haemagglutinin disease and warm autoimmune haemolytic anaemia per year as the proportion of patients with severe disease is rare and they are already accessing rituximab in these settings currently. The Subcommittee considered that the dosage for rituximab in these indications would be either 375mg/m2 weekly for four weeks or 100mg weekly for four weeks. The Subcommittee considered there would be some patients would require re-treatment with rituximab in these indications.

7.8 The Subcommittee considered that there are,effective treatment options and clear treatment guidelines for ITP as discussed during the review of eltrombopag in this indication above. The Subcommittee considered that first-line treatments in New Zealand are corticosteroids and intravenous immunoglobulin (IVIG). The Subcommittee considered that if patients failed on these treatments, splenectomy would be the next option followed by immunosuppressant therapies like danazol, azathioprine, cyclosporin and rituximab or if available, eltrombopag. The Subcommittee considered that there is no good quality evidence for the efficacy of rituximab in ITP, only case series. The Subcommittee considered that there is also inconclusive evidence about the appropriate dose for rituximab (375mg/m2 weekly for four weeks versus 100mg weekly for four weeks). The Subcommittee noted the Barcellini et al study (Blood 2012; 119(16): 3691-3697) showed that the lower dose of rituximab resulted in an 82% response rate. The Subcommittee noted however that this was a small study involving only 23 patients with a median follow up of 15 months. For the reasons above, the Subcommittee was unable to recommend the lower dose as the standard of care. The Subcommittee noted that the lower dose is used in Wellington Hospital currently. The Subcommittee however noted that unlike eltrombopag, rituximab is not an ongoing long term treatment.

7.9 Although rituximab could be used to avoid a splenectomy, the Subcommittee noted that only 30% respond and the response is not durable, varying from 12 to 24 months. Therefore, the Subcommittee considered that patients most likely to benefit from rituximab would be patients who have refractory ITP despite a splenectomy and have significant problems with bleeding. The Subcommittee considered that the response rate in this patient group is about 30-40%.

8 Rituximab for haemophilia with inhibitors

Application

8.1 The Subcommittee reviewed a memorandum from PHARMAC staff regarding rituximab for the treatment of haemophilia with inhibitors.

Recommendation

8.2 The Subcommittee **recommended** that rituximab is included on the national Preferred Medicines List for the treatment of:

8.2.1 Mild congenital haemophilia, complicated by inhibitors with high priority;

8.2.2 Severe congenital haemophilia in patients who have failed immune tolerance therapy with medium priority; and

8.2.3 Acquired haemophilia with low priority.

8.3 The Subcommittee **recommended** that for these indications, it would be appropriate to restrict rituximab prescribing in hospitals to haematologists.

Discussion

8.4 The Subcommittee considered that the development of alloantibodies or inhibitors in congenital haemophilia is a very significant problem. The Subcommittee considered that it is associated with increased morbidity, poor quality of life and a significant cost where a bleeding event needs to be treated with bypassing agents. These patients are not on prophylactic treatment and therefore have progressive arthropathies which have long term effect.

8.5 The Subcommittee noted that immune tolerance can be achieved in up to 70% of patients who have severe haemophilia complicated by inhibitors, with immune tolerance therapy (ITT) for which a guideline exists in New Zealand. The Subcommittee considered that the evidence for rituximab in this indication is mainly from case reports and case series. The Subcommittee considered that the most relevant paper in severe haemophilia is the systematic review by Collins et al (J Thromb Haemost 2009; May; 7(5): 787-94) where 40% of 15 patients achieved a negative inhibitor titer and 47% achieved a significant clinical benefit. The Subcommittee noted that 5 patients eventually relapsed. The Subcommittee noted that although this study only involved a small number of patients, it indicated that concomitant treatment with Factor VIII was important for the success of rituximab therapy in severe haemophilia with inhibitors.. The Subcommittee considered that rituximab is currently used in patients who are refractory to ITI and the response rates are about 50% and response tends to be transient.

8.6 The Subcommittee noted that inhibitors are an uncommon complication of mild haemophilia (1% incidence in mild haemophilia A) (Dunkley et al. Haemophilia 2006; 12: 663–667) and patients normally present later in life. The Subcommittee considered that mild haemophilia with inhibitors is a severe disease and these patients have a haemorrhagic tendency. The Subcommittee considered that the evidence available indicates that these patients respond less well to ITI. The Subcommittee noted that observation is a common treatment approach in asymptomatic patients because spontaneous remission is quite common (60%)(Dunkley et al. Haemophilia 2006; 12: 663–667). The Subcommittee noted that Dunkley et al reported successful treatment of mild haemophilia with inhibitors with rituximab in 3 patients.

8.7 The Subcommittee noted that acquired haemophilia was a rare condition, approximately 1 to 4 patients per million per year but when it does occur; it is associated with significant morbidity and mortality. There is a peak in incidence during the postpartum period and in the elderly. The Subcommittee noted that it is idiopathic in 50% of cases. The Subcommittee noted that there are currently no standard protocols for treatment. Current treatment involved treating bleeds and eradicating inhibitors with immune suppression (steroids +/- cyclophosphamide). The Subcommittee however noted that there are significant side-effects with cyclophosphamide. The Subcommittee noted a systematic review involving 65 patients (Franchini M. Crit Rev Oncol Hematol.

2007 Jul;63(1):47-52) showed that the response rate with rituximab treatment in acquired haemophilia was approximately 90% with concomitant immunosuppression.

8.8 The Subcommittee considered that overall, the evidence suggests that rituximab is effective for the treatment of haemophilia with inhibitors and it is relatively safe although longer term data is lacking. The Subcommittee considered however that it is still unknown what the optimal dosing schedule is.