PTAC meeting held 8 & 9 November 2012

(minutes for web publishing)

PTAC 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 PTAC meeting; only the relevant portions of the minutes relating to PTAC 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.

PTAC 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:

(i) protect information where the making available of the information would be likely unreasonably to prejudice the commercial position of the person who supplied or who is the subject of the information (section 9(2)(b)(ii))

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1 Record of PTAC meeting held May 2012

1.1 The Committee reviewed the minutes of the PTAC meeting held on 10 and 11 May 2012 and made the following amendments:

1.1.1 The Committee noted that the minuted action points, specifically surrounding Subcommittee Minutes and Liraglutide, didn't match the document and **recommended** this be reviewed by PHARMAC staff.

2 Correspondence / Matters Arising

2.1 Erythropoietin in Myelodysplasia

2.1.1 The Committee noted that it had recommended that erythropoietin (EPO) be funded for patients with refractory anaemia associated with myelodysplasia (MDS) with low priority at its meeting in August 2012 but noted then that it would only make a recommendation regarding the Special Authority criteria after further analysis by PHARMAC staff. The Committee also noted that the applicants provided some suggested criteria following review of the previous PTAC minutes.

2.1.2 The Committee considered that no other cost factors should be taken into account when considering cost-effectiveness other than the financial costs of blood transfusions avoided.

2.1.3 The Committee considered that the criteria proposed by the applicants were reasonable and largely agreed with them. The Committee **recommended** that erythropoietin be funded for patients with refractory anaemia associated with myelodysplasia with low priority subject to the following Special Authority criteria, with renewal criteria to be finalised at the February 2013 meeting:

Initial application only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 2 months for applications meeting the following criteria:

1. Patient has a confirmed diagnosis of myelodysplasia (MDS); and
2. Has symptomatic anaemia with haemoglobin <100g/L or is red cell transfusion-dependent*; and
3. Patient has very low or low risk MDS based on the WHO classification-based prognostic scoring system for myelodysplastic syndrome (WPSS) ; and
4. Other causes of anaemia such as B12 and folate deficiency have been excluded; and
5. Patient has a serum erythropoietin level of <500 IU/mL; and
6. The minimum necessary dose of erythropoietin would be used and will not exceed 80,000 iu per week.

Renewal application only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 12 months for applications meeting the following criteria:

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1. Any of the following:
   1.1. Patient has had >15g/L rise in haemoglobin level since commencing erythropoietin treatment; or
   1.2. Patient has become transfusion-independent since commencing erythropoietin treatment; or
   1.3. The patient's transfusion requirement has reduced by ≥4 units of red blood cells over 8 weeks since commencing erythropoietin treatment; and

2. Patient who was previously transfusion-independent has not become transfusion-dependent*; and
3. Transformation to acute myeloid leukaemia has not occurred.

*Transfusion dependence is defined as a transfusion requirement of at least 4 units of red cells per month over a period of 4 months.

2.2 Paliperidone Depot Injection

2.2.1 The Committee reviewed correspondence from the supplier (Janssen) of paliperidone depot injection (Invega Sustenna) and clinicians requesting that PTAC re-consider its previous recommendation that it only be listed on the Pharmaceutical Schedule if cost-neutral or cost-saving versus risperidone depot injection.

2.2.2 The Committee noted that all the correspondence failed to highlight that paliperidone is the major active metabolite of risperidone, which is already funded in New Zealand.

2.2.3 The Committee noted that the correspondents considered that PTAC's previous recommendation on the average monthly dose of paliperidone depot injection of 138 mg was too high. The Committee considered that this may be the case; however, the Committee considered the likely average monthly dose of paliperidone remains speculative because the trial populations were different to the likely treated population in New Zealand and because the trials were of relatively short duration. The Committee also considered that when treating people with severe complicated schizophrenia, which is the group who generally receive injectable antipsychotics in New Zealand, there is a tendency to use larger doses over time. The Committee noted that more data on this could now be available from its usage overseas and considered that it would be appropriate for PHARMAC staff to take that information into consideration when evaluating the fiscal impact of listing paliperidone depot injection. The Committee also considered that PHARMAC staff should take into account future incremental dose increases which commonly occur in this therapeutic area. The Committee considered that, if listed, it is likely that paliperidone depot injection would quickly take over the market from risperidone depot injection given the increased convenience in administration.

2.2.4 The Committee noted that although paliperidone depot injection would require monthly rather than fortnightly injections and, therefore, less nursing time for administration of injections, input is generally still needed from other staff in the mental health service in between nursing visits. Therefore, the Committee

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considered that the availability of a monthly injection would be unlikely to result in significant savings to DHBs. The Committee considered that there is no evidence to support the argument that paliperidone depot injection is more clinically efficacious than risperidone depot injection.

2.2.5 The Committee considered that the length of inpatient stay for many people with schizophrenia is not primarily driven by the need to achieve therapeutic doses of treatment. The Committee considered that for a large proportion of patients, there are other issues keeping the patients in hospital, for example the need to sort out housing arrangements and issues like substance dependence. The Committee considered that in trials for paliperidone depot injection, many patients still required cover with other treatments such as benzodiazepines as inpatients. The Committee considered that the recommendation from the Mental Health Subcommittee to assume that paliperidone depot injection may result in a reduction of hospitalisation of one day per patient, on initiation of treatment, is appropriate.

2.2.6 The Committee noted that the Mental Health Subcommittee of PTAC had amended its recommendation in relation to paliperidone depot injection from cost-neutral to medium priority at its meeting in June 2012. The Committee noted that the Subcommittee had not reviewed any new evidence in making this change.

2.2.7 Taking into account all the available evidence and the view of the Mental Health Subcommittee, the Committee again **recommended** that paliperidone depot injection be listed on the Pharmaceutical Schedule only if it was cost-neutral or cost-saving versus risperidone depot injection.

3 Subcommittee Minutes

3.1 Endocrinology Subcommittee – 29 May 2012

3.1.1 The Committee noted and accepted the record of the meeting in relation to items 1 – 2.

3.1.2 Regarding item 3, the Committee noted the Subcommittee's recommendation to change the cabergoline Special Authority and questioned whether the term "relevant prescriber" would result in psychiatrists prescribing it for antipsychotic-induced hyperprolactinaemia. The Committee **recommended** that this be taken to the Mental Health Subcommittee for consideration.

3.1.3 The Committee noted that the remainder of the record related to hospital pharmaceuticals and the establishment of a national Preferred Medicines List (PML). The Committee noted the Subcommittee's recommendations in relation to these items, and noted PTAC would be formally reviewing these items for inclusion in a national PML at its own meeting.

3.2 Mental Health Subcommittee – 8 June 2012

3.2.1 The Committee noted and accepted the record of the meeting in relation to items 1-3 and 5-7.

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3.2.2 Regarding item 4, the Committee noted the Subcommittee recommended paliperidone be funded with medium priority. The Committee maintained its previous recommendation that it should only be listed on the Pharmaceutical Schedule subject to Special Authority criteria similar to those applying to risperidone depot injection only if cost-neutral or cost-saving versus risperidone depot injection (see further discussion detailed in Correspondence/Matters Arising section above).

3.2.3 The Committee noted that the remainder of the record related to hospital pharmaceuticals and the establishment of a national Preferred Medicines List (PML). The Committee noted the Subcommittee's recommendations in relation to these items, and noted PTAC would be formally reviewing these items for inclusion in a national PML at its own meeting.

3.3 Reproductive and Sexual Health Subcommittee – 25 June 2012

3.3.1 The Committee noted and accepted the record of the meeting in relation to items 1-3.

3.3.2 The Committee noted that the remainder of the record related to hospital pharmaceuticals and the establishment of a national Preferred Medicines List (PML). The Committee noted the Subcommittee's recommendations in relation to these items, and noted PTAC would be formally reviewing these items for inclusion in a national PML at its own meeting.

3.4 Neurological Subcommittee – 24 July 2012

3.4.1 The Committee noted and accepted the record of the meeting in relation to items 1-4 and 8.

3.4.2 The Committee noted items 5, 6 and 7 related to the review of fingolimod, natalizumab and multiple sclerosis treatments respectively and that these items would be brought back to PTAC for review in 2013.

3.4.3 The Committee noted that the remainder of the record related to hospital pharmaceuticals and the establishment of a national Preferred Medicines List (PML). The Committee noted the Subcommittee's recommendations in relation to these items, and noted PTAC would be formally reviewing these items for inclusion in a national PML at its own meeting.

3.5 Hospital Pharmaceuticals Subcommittee

3.5.1 The Committee noted minutes for the following meetings of the Hospital Pharmaceuticals Subcommittee:

- 1 March 2011
- 5 April 2011
- 3 May 2011
- 7 June 2011
- 3 April 2012
- 1 May 2012

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- 25 September 2012

3.5.2 The Committee noted that these related to hospital pharmaceuticals and the establishment of a national Preferred Medicines List (PML), and that PTAC would be formally reviewing these items for inclusion in a national PML as part of separate agenda items.

4 Rifaximin – Hepatic Encephalopathy

Application

4.1 The Committee reviewed an application from PHARMAC staff for the listing of rifaximin on the Pharmaceutical Schedule for the treatment of hepatic encephalopathy.

Recommendation

4.2 The Committee **recommended** that rifaximin be listed in the Pharmaceutical Schedule with a **medium** priority with the following Special Authority criteria*:*

> Initial Application only from a gastroenterologist. Approvals valid for six months for applications meeting the following criterion:
>
> 1. Patient has had two previous episodes of hepatic encephalopathy despite an adequate trial of maximum tolerated doses of lactulose.
>
> Renewal application from a gastroenterologist without further renewal for patients continuing to benefit from treatment

4.3 The Decision Criteria particularly relevant to this recommendation are: *(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.*

Discussion

4.4 The Committee noted that hepatic encephalopathy is a syndrome observed in patients with cirrhosis and is defined as a spectrum of neuropsychiatric abnormalities in patients with liver dysfunction. The Committee noted that hepatic encephalopathy is characterised by personality changes, intellectual impairment, and a depressed level of consciousness.

4.5 The Committee noted that the mainstay of therapy has been non-absorbable disaccharides such as lactulose which appears to inhibit intestinal ammonia production by a number of mechanisms including the acidification of the gut lumen and by cathartic action, reducing colonic bacterial load.

4.6 The Committee noted that there was one systematic review (Als-Nielsen et al. BMJ 2004;328:1049) that concluded that there was insufficient evidence to support or refute the use of lactulose for the treatment of hepatic encephalopathy.

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4.7 The Committee considered a meta-analysis of rifaximin versus conventional oral therapy for hepatic encephalopathy (Eltawil KM, et al. World J Gastroenterol. 2012 28;18:767-77). The authors reported that the clinical effectiveness of rifaximin was equivalent to disaccharides or other oral antibiotics but with a better safety profile (odds ratio 0.27; 95% CI: 0.12-59 p = 0.001) with patients receiving rifaximin showing non-statistically significant improvements in serum ammonia levels, mental status and less asterixis. The authors concluded that rifaximin should be used as a second line treatment in hepatic encephalopathy patients who are not responsive to disaccharides and first line if there is intolerance.

4.8 The Committee considered the evidence for rifaximin to prevent (or maintain remission of) hepatic encephalopathy in the form of an industry sponsored study by Bass et al (N Engl J Med. 2010;362:1071-81). The Committee noted that this was a randomised, double-blind, placebo-controlled trial of 299 patients who were in remission from recurrent hepatic encephalopathy who received either rifaximin, at a dose of 550 mg twice daily (n=140), or placebo (n=159) for 6 months. The primary efficacy end point was the time to the first breakthrough episode of hepatic encephalopathy and the secondary end point was the time to the first hospitalization involving hepatic encephalopathy. The Committee noted that rifaximin significantly reduced the risk of an episode of hepatic encephalopathy compared with placebo (hazard ratio with rifaximin, 0.42; 95% confidence interval [CI], 0.28 to 0.64; P<0.001) and the breakthrough episode occurred in 22.1% patients receiving rifaximin vs. 45.9% of patients receiving placebo The Committee noted that hospitalisation rates were lower in the rifaximin group (hazard ratio 0.50; 95% CI, 0.29 to 0.87; P=0.01) and the incidence of adverse events reported during the study was similar between the two groups. The Committee considered that over a 6-month period, rifaximin maintained remission from hepatic encephalopathy more effectively than with placebo and reduced the risk of hospitalisation involving hepatic encephalopathy.

4.9 The Committee noted that rifaximin has a broad spectrum antibacterial activity. The Committee noted that there has been some concern in other countries regarding potential induction of antibiotic resistance (especially the potential to cause resistance to chemically related drugs for M. tuberculosis). The Committee considered that based on limited studies (Brigidi et al J Chemother 2002;14:290-5.) the risk of antibacterial resistance is likely to be low due to the very low systemic bioavailability.

4.10 The Committee considered that there was more evidence for prevention rather than treatment with rifaximin in hepatic encephalopathy. Rifaximin is generally well tolerated and may have less side effects than other treatments. The Committee also noted that rifaximin is not registered with Medsafe.

4.11 The Committee noted that rifaximin has been used in other indications and was efficacious in conditions such as inflammatory bowel diseases and traveller diarrhoea. The Committee considered therefore that strict criteria should be applied to rifaximin.

4.12 The Committee noted that the evidence base for rifaximin was stronger than for lactulose or for l-ornithine and l-aspartate (LOLA) and considered that the availability of rifaximin is likely to markedly reduce LOLA usage. LOLA is currently funded under Discretionary Community Supply for hepatic encephalopathy and could possibly be more expensive than rifaximin.

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4.13 The Committee noted the economic analysis of Huang et al and noted that it was in the setting of managing chronic hepatic encephalopathy with a 14 day course rather than long term prevention of recurrence (for which the evidence is stronger). Members considered that the cost of rifaximin may be lower than the one suggested by PHARMAC staff, and noted the drug is now generic. The Committee considered that given the comparable efficacy of rifaximin and lactulose there was no clinical reason for rifaximin to be used second line to treat hepatic encephalopathy. However, at current pricing, the Committee considered that it may be more cost-effective to use rifaximin following an adequate trial of lactulose. Members noted that rifaximin's place in therapy may vary with price and that at a sufficiently low price using it first line over lactulose may be dominant, providing greater health gains at the same or lower price as current treatment.

5 Preservative Free Eye Drops – Allergy or Chronic Usage

Preservative Free Lubricating Eye Drops

Application

5.1 The Committee reviewed a PHARMAC generated application relating to a potential listing of Preservative Free Lubricating Eye Drops on the Pharmaceutical Schedule for the treatment of severe secretory dry eyes.

Recommendation

5.2 The Committee **recommended** that Preservative Free Lubricating Eye Drops be listed in the Pharmaceutical Schedule with a medium priority, subject to the following Special Authority criteria.

> Initial application from any relevant practitioner
> Approvals valid for 12 months for patients meeting the following criteria:
> Both:
> 1 Confirmed diagnosis by slit lamp of severe secretory dry eye; and
> 2 Either:
> 2.1 Patient is using eye drops more than four times daily on a regular basis and has toxicity associated with the preservative; or
> 2.2 Patient has had a confirmed allergic reaction to preservative in eye drop;
> Renewal from any relevant practitioner
> Approvals valid for 24 months for patients meeting the following criteria:
> Both:
> 1 Confirmed diagnosis by slit lamp of severe secretory dry eye; and
> 2 Either:
> 2.1 Patient is using eye drops more than four times daily on a regular basis; or
> 2.2 Patient has had a confirmed allergic reaction or evidence of toxicity to preservative in eye drop;

5.3 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 publicly funded health and disability support services.*

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Discussion

5.4 The Committee noted that the Ophthalmology Subcommittee of PTAC had considered an application for the funding of Preservative Free Lubricating Eye Drops at its March 2012 meeting and had recommended funding, under a Special Authority, with a medium priority.

5.5 The Committee noted that the Ophthalmology Subcommittee had highlighted the potential corneal toxicity of the preservative benzalkonium chloride to the eye when used for protracted periods and with high dose frequency.

5.6 The Committee noted that non-preserved ocular products are associated with a higher risk of eye infection.

5.7 The Committee noted that there is some but limited evidence on the efficacy of preservative-free lubricating eye drops, and no randomised controlled trials have been undertaken. The Committee noted the Pisella et al. (Br J Ophthalmol. 2002;86:418-23) prospective epidemiological survey of 4107 patients using preserved and preservative-free glaucoma medication.

5.8 The Committee noted that there have been a number of applications for the funding of preservative-free lubricating eye drops under the Named Patient Pharmaceutical Assessment process. It was noted that the majority of applications were for patients with severe secretory dry eye and who were using lubricant eye drops at high daily frequencies.

5.9 The Committee noted that eye ointments, which are by their nature preservative free, are funded. It was considered that these are often unsatisfactory for the patient due to blurring of vision following instillation.

5.10 The Committee considered the number of people with dry eyes would be more than 30% of the general population but the number of people with severe symptoms would be less than 1-5% of this subgroup. The Committee considered that overall approximately 10% of patients with severe dry eye disease are likely to be eligible to receive preservative-free lubricating eye drops under the proposed Special Authority criteria, and of these patients, less than 20% are likely to have severe symptoms causes by the frequent use of eye drops with preservatives.

5.11 The Committee considered that single-use vials are likely to be used multiple times in patients who are frequent users of eye drops.

5.12 The Committee considered that a significant number of patients would use preservative free drops should these be made available. Members noted that currently preservative-free eye drops are significantly more expensive than preserved eye drops. The Committee consider that to reduce the fiscal risk associated preservative free eye drops these should be restricted to patients presenting with documented allergies and/or toxicity to preservatives. The Committee considered there was no reason to define toxicity to preserved eye drops at this time. The Committee noted that PHARMAC had released a Request for Proposals relating to the funding of preservative free eye drops. The Committee noted that this could result in a reduction

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in cost of preservative free eye drops which would reduce the fiscal risk associated with this presentation of eye drops.

Preservative Free Prednisolone Sodium Phosphate eye drops

Application

5.13 The Committee reviewed a recommendation from the Ophthalmology Subcommittee to list Preservative Free Prednisolone Sodium Phosphate on the Pharmaceutical Schedule for the treatment of severe ocular inflammation.

Recommendation

5.14 The Committee **recommended** that the Application for Preservative Free Prednisolone Sodium Phosphate be listed in the Pharmaceutical Schedule under the following Special Authority with a medium priority:

Initial application from Ophthalmologist
Approvals valid for 6 months for patients meeting the following criteria:
1. Patient has severe inflammation; and
2. Patient has a confirmed allergic reaction to preservative in eye drops;

Renewal from Ophthalmologist
Approvals valid for 6 months for patients meeting the following criteria:
1. Patient is benefiting from treatment and continues to require preservative free steroid eye drops

Discussion

5.15 The Committee noted that there were two aspects to this application: one related to the specific salt of prednisolone (acetate or phosphate) and the other related to the preservative free presentation of the phosphate salt.

5.16 The Committee noted that evidence on prednisolone sodium phosphate eye drops is mainly limited to bioavailability studies in rabbits. The Committee noted that the preservative in the currently available formulations, benzalkonium chloride, has been shown to cause animal toxicity with high usage.

5.17 The Committee noted a review article comparing sodium phosphate with sodium acetate (Sousa FJ CLAO Journal 1991;17(4):282-284). It was noted that evidence suggests that the phosphate salt may have less intraocular penetration than the acetate salts, however it is uncertain whether there was a difference between the two salts in terms of effectiveness.

5.18 The Committee noted that there have been a number of applications received through the Named Patient Pharmaceutical Assessment process for prednisolone sodium phosphate eye drops.

5.19 The Committee considered that prednisolone sodium phosphate eye drops should be restricted to those patients who experience an allergy to the preservative.

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5.20 The Committee noted that preservative-free eye drops are associated with increased risk of infection and thus the expiry date and usage and handling instructions should be strictly adhered to.

5.21 The Committee noted that there was a potential concern relating to increasing the risk of glaucoma due to damage to the cornea following heavy exposure to benzalkonium chloride, however this risk remained theoretical. The Committee noted that it would review further evidence if it became available.

6 Priorities Report

6.1 The Committee noted the report on PHARMAC's priorities for new spending. The Committee noted that regular updates are provided to the PHARMAC Board on the Priority lists and status of proposals with a PTAC recommendation of high priority.

6.2 Action points arising from the Committee's discussion are summarised in section 5 above.

7 Hospital Pharmaceuticals Review

8 Rituximab – Refractory SLE

Application

8.1 The Committee reviewed an application from a clinician on behalf of the New Zealand Rheumatology Association for the funding of rituximab (MabThera, Roche Products NZ Limited) for patients with systemic lupus erythematosus (SLE) who have failed conventional therapies.

Recommendation

8.2 The Committee **recommended**, with low priority, that rituximab should be funded for patients with severe, life threatening, SLE that had failed all conventional treatments, under the following Special Authority Criteria:

> Initial Application – (Treatment refractory SLE) – only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 7 months for applications meeting the following criteria:
>
> 1. The patient has severe, immediately life- or organ-threatening, systemic lupus erythematosus (SLE), and
> 2. The disease has proved refractory to treatment with steroids at a dose of at least 1 mg/kg, and
> 3. The disease has relapsed following prior treatment for at least 6 months with maximal tolerated doses of azathioprine, mycophenolate and high dose cyclophosphamide, or cyclophosphamide is contraindicated.
> 4. Maximum of four 1000 mg infusions of rituximab.

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Renewal Application – (Treatment refractory SLE) – only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 3 months for applications meeting the following criteria:

1. Patient's SLE achieved at least a partial response to the previous round of prior rituximab treatment; and
2. The disease has subsequently relapsed, and
3. Maximum of two 1000 mg infusions of rituximab.

8.3 The Decision Criteria particularly relevant to this recommendation are: *(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; (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.*

Discussion

8.4 The Committee noted that this application was prompted by a request from the Rheumatology Subcommittee of PTAC's October 2011 review of off-label uses of biologics.

8.5 The Committee noted that SLE is a chronic inflammatory autoimmune disease that in some patients can have debilitating and life threatening manifestations such as renal, central nervous system and vascular disease. Members noted that standard treatments for SLE include immunosuppressive agents such as high dose corticosteroids, cyclophosphamide, azathioprine and mycophenolate. Members noted that of the clinical manifestations of SLE are mediated directly, or indirectly, by antibody formation and the creation of immune complexes, therefore, through its B-lymphocyte depletion activity there was good biological rationale for the use of rituximab in this disease setting.

8.6 The Committee noted evidence from two relevant randomised controlled studies, the EXPLORER study (Merril 2010) and the LUNAR study (Rovin 2012). Members noted that the EXPLORER study enrolled 257 patients with moderately to severely active SLE (≥1 BILAG A score or ≥2 BILAG B scores despite background immunosuppressant therapy (methotrexate, azathioprine or mycophenolate) which were continued on study. Members noted that EXPLORER enrolled patients with extra-renal disease. Patients were randomised 2:1 to receive (1000 mg) or placebo on days 1, 15, 168, and 182 in addition to prednisone (0.5-1mg/kg tapered to 10mg over 10 weeks) and background immunosuppressant therapy. Members noted the primary endpoint of the study defined as maintained clinical response (BILAG C or better by week 24 with no subsequent flares) by 52 weeks which they considered quite a strict definition of response. Members noted there were no differences between treatment groups in the primary endpoint with a response rate of about 28% in both arms. Members noted there were no differences between placebo and rituximab in any of the endpoints, with the exception of an apparent benefit for rituximab over placebo in the primary endpoint in African-American and Hispanic patients, who comprised approximately 1/3 of the patient population. Members considered this result most likely to be due to the play of chance, noting that one of its implications if real would be that rituximab was actually harmful in other patient groups.

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8.7 The Committee noted that the LUNAR study was a randomized controlled study in 144 patients with class III or class IV lupus nephritis treated concomitantly with mycophenolate and corticosteroids. Patients were randomized 1:1 to receive rituximab (1000 mg) or placebo on days 1, 15, 168, and 182 both in combination with prednisone 0.75 mg.kg tapered to 10 mg over 10 weeks. Members noted that the primary endpoint of the study was renal response status at 52 weeks (with patients who experienced a flare that had resolved by 52 weeks also being deemed responders) which was not as strict as the EXPLORER study. Members noted that the overall (complete and partial) renal response rates were not statistically significant between the two treatment groups (45.8% in the placebo group and 56.9% in the rituximab group (p=0.18)), however, response rates in black patients favoured rituximab (70% vs. 45%).

8.8 The Committee considered that overall the results from the two randomised controlled studies, were of moderate strength and quality and demonstrated no benefit of rituximab over placebo treated patients, in the context of background immunosuppression including high dose corticosteroids.

8.9 The Committee reviewed a number of registry and uncontrolled studies of rituximab in various SLE populations in combination with various other immunosuppressive treatments. Members considered that given the heterogeneity of these studies it was difficult to draw any meaningful conclusions. In general members considered that because most the studies did not recruit 'last line' SLE patients the relevance of the evidence to the application was questionable.

8.10 The Committee considered that despite the absence of any clear evidence of benefit for rituximab in the absence of any other proven treatment it may be a reasonable 'last line' option. Members noted that in this patient group there was a clear unmet health need and significant health costs associated with organ failure. However, members considered that such treatment may not be beneficial, and indeed may be harmful given the known rituximab side effects of infection, risk of PML and leukopaenia, therefore, its funding in this setting should be limited to patients with severe, life or organ threatening SLE that had failed all conventional treatments. Members considered that under such criteria usage would be limited to around 5 new patients per year. Members noted that patients would likely be retreated with rituximab on flare such that overtime as many as 100 patients would be on treatment.

9 Tumour Necrosis Factor (TNF) Inhibitors for Pyoderma Gangrenosum

Application

9.1 The Committee reviewed an application from PHARMAC staff for the listing of TNF Inhibitors on the Pharmaceutical Schedule for the treatment of pyoderma gangrenosum**.**

Recommendation

9.2 The Committee **recommended** that biological treatments for pyoderma gangrenosum be listed in the Pharmaceutical Schedule with a medium priority with the following Special Authority criteria

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Special Authority:

Initial application – any relevant practitioner. Approvals valid for three doses for applications meeting the following criteria:

1. Patient has pyoderma gangrenosum; and
2. Applicant is a Dermatologist or has confirmed the diagnosis with a Dermatologist; and
3. Patient has received three months of conventional therapy including a minimum of three agents (e.g. prednisone, ciclosporin, azathioprine, or methotrexate) and not received an adequate response

Renewal – any relevant practitioner. Approvals valid for three doses for applications meeting the following criteria:

1. Patient has shown clinical improvement; and
2. Patient continues to require treatment.

9.3 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; (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.*

Discussion

9.4 The Committee noted that pyoderma gangrenosum (PG) is an uncommon, ulcerative cutaneous condition of uncertain aetiology. The Committee noted that PG is associated with systemic diseases in at least 50% of patients who are affected. The diagnosis is made by excluding other causes of similar-appearing cutaneous ulcerations, including infection, malignancy, vasculitis, collagen vascular diseases, diabetes, and trauma. The Committee noted that the incidence is 3-10 patients per million per year.

9.5 The Committee noted that PG is an extremely painful disease because of skin failure. The Committee considered that there may be a place for anti-TNF biologic therapy in patients who prove to be refractory and who have tried various other treatments.

9.6 Members noted anecdotally that they had seen long hospitalisations with this disease.

9.7 Members considered that there was potential for misdiagnosis of this dermatological disease.

9.8 The Committee noted that therapy for PG involves the use of local therapies, corticosteroids, standard immunosuppressive agents, and more recently biologic agents.

9.9 The Committee considered the quality of evidence to be poor. The Committee noted that there was one RCT and a limited number of observational studies related to the use of biological agents (most of which are TNF-alpha inhibitors). The Committee considered a study by Brooklyn et al (Gut 2006;55:505-509) which evaluated infliximab for the treatment of PG. The Committee noted that this was a randomised, double blind, placebo controlled trial, where 29 patients received infliximab with 69% (20/29)

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demonstrating a beneficial clinical response. The Committee noted that remission rate at week 6 was 21% (6/29) and that there was no response in 31% (9/29) of patients.

9.10 The Committed considered a study by Regueiro et al (Am J Gastroenterol. 2003;98:1821-6). The Committee noted that this was a multicentre retrospective study of patients with medically refractory PG. The Committee noted that 13 patients with moderate to severe PG were treated with infliximab and all patients demonstrated complete healing of the skin lesions.

9.11 Regarding adalimumab the Committee noted that there were a few case reports The Committee noted a case reported by Hubbard et al (Br J Dermatol. 2005;152:1059-61) which described a patient who was improving on infliximab but developed an anaphylactoid reaction and was then treated with adalimumab. The Committee noted that the patient's skin healed and after 3 weeks of treatment with improving inflammatory markers and neutrophil count. The Committee noted a study by Cariñanos et al (Inflamm Bowel Dis. 2011;17:153-4) where patients experienced clinical improvement after 11 days and complete healing of PG after a median of 34 days (range, 15-60). The Committee noted another case report where a patient with severe superficial PG responded to adalumimab therapy after failure of infliximab therapy (Reddick et al. Dermatol Online J. 2010;16:15). The Committee also noted a report of the use of adalimumab for treatment of PG in patients with Crohn's disease where patients responded with significant improvement after only 3 injections (Alkhouri et al Inflamm Bowel Dis. 2009;15:803-6).

9.12 The Committee noted some studies related to etanercept. The Committee noted a retrospective analysis by Charles et al. (Int J Dermatol. 2007;46:1095-9) involving seven patients. All seven patients with PG responded well to etanercept. The Committee also noted a report by Roy et al. (J Am Acad Dermatol. 2006;54) on the successful treatment of 3 patents using etanercept.

9.13 Committee noted a case where a patient was successfully treated with ustekinumab (Guenova E, H.N Engl J Med. 2012;366:1450).

9.14 Members noted the high costs of these treatments and considered there was likely to be a "class-effect" in this therapeutic group.

9.15 Members considered that as adalimumab was given subcutaneously and therefore it would be easier to use than infliximab. Members had no strong preference for any particular agent as all funded TNF Inhibitors have been used in this condition successfully, even though RCT data is only available for infliximab.

10 Ferric Carboxymaltose – Iron Deficiency Anaemia

Application

10.1 The Committee considered an application from Vifor Pharma to fund ferric carboxymaltose (Ferinject) for the treatment of iron deficiency anaemia.

Recommendation

Chair

10.2 The Committee **recommended** that ferric carboxymaltose be listed on the Pharmaceutical Schedule only if cost-neutral to iron polymaltose administered via the rapid protocol.

10.3 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 publicly funded health and disability support services.*

Discussion

10.4 The Committee noted that parenteral iron is usually used instead of oral iron when oral absorption is poor or due to gastrointestinal intolerance or during the third trimester of pregnancy, and prior to or following excessive blood loss in an iron-deficient patient (ferritin<100) with surgery planned in less than 60 days. The Committee noted that ferric carboxymaltose (FCM) is an intravenous iron preparation and 1000 mg can be administered as a single infusion over 15 minutes and considered that FCM has the same therapeutic effect to iron polymaltose and a similar effect to iron sucrose.

10.5 The Committee considered the evidence provided by the supplier in the form of six randomised controlled trials comparing the safety and efficacy of FCM with oral iron in patients with non-dialysis dependent chronic kidney disease (Quinbi et al. Nephrol Dial Transplant 2011;26:1599-1607), women with heavy uterine bleeding (Van Wyck et al. Transfusion 2009;49:2719-28), postpartum women (Seid et al. Am J Gynecol 2008;199:435.e1-435.e7, Breyman et al. Int J Gynecol Obstet 2008; doi:10.1016/j.ijgo.2007.10.009 and Van Wyck et al. Obstet Gynecol 2007;110:267-78) and patients with inflammatory bowel disease (Kulnigg et al. Am J Gastroenterol 2008;103:1182-1192).

10.6 The Committee considered that FCM was generally well tolerated in the studies with lower incidence of gastrointestinal side effects and in some cases more rapid normalisation of iron stores. The Committee considered that intravenous iron can cause hypophosphataemia which is not a risk with oral preparations. The Committee considered that the average dose used of FCM in the trials was 1410 mg. Several of the studies were non-inferiority studies which the Committee considered was proven.

10.7 The Committee noted that in practice, compliance with oral iron can be variable, can take two months to correct haemoglobin levels and in some conditions where malabsorption is likely, such as inflammatory bowel disease and chronic kidney disease, intravenous iron is preferred.

10.8 The Committee considered that the strength of the evidence was fair and the quality moderate however there were no trials provided which compared FCM with iron polymaltose.

10.9 The Committee considered that there are different protocols for parenteral iron administration being used in DHB hospitals with many DHBs adopting rapid iron polymaltose protocols for doses of up to 2500 mg iron.

Chair

10.10 The Committee considered the Auckland DHBs iron polymaltose rapid administration guideline which has been informed by a trial by Garg (Intern Med J 2011; 41: 548-54). The protocol allows a 1500 mg dose of iron polymaltose diluted in 250 ml saline to be administered, if tolerated over 73 minutes. The Committee noted that the datasheet for iron polymaltose does not specify instructions for administration, however it does specify as it does for FCM that resuscitation equipment should be on hand.

10.11 The Committee considered the Garg study, in which 100 patients were assigned to receive iron polymaltose infusion according to the rapid protocol. The authors reported that 92% of patients successfully completed the rapid protocol with the main side effects being nausea, lightheadedness, fever, rash, chest pain (non-ischaemic), cough, flushing. The Committee considered that the patient acceptance of the rapid protocol was high.

10.12 The Committee considered that if iron polymaltose can be given over 73 minutes according to the rapid protocol, there would be fewer advantages of FCM, noting that FCM administration is likely to take at least 30 mins from set up to finish.

10.13 The Committee noted that iron polymaltose and FCM are similar in that they are low molecular weight dextrins and have a lower incidence of anaphylactoid reactions compared with previously used dextrans. The Committee noted that although the application states that FCM can be given without first administering a test dose, it is possible that iron polymaltose does not require a test dose either. The Committee understood that at least one hospital in Australia is administering FCM without a test dose, but in 500ml normal saline (instead of 250ml).

10.14 The Committee considered that patients who required more than 1000 mg dose of FCM would require two visits to either the GP or the hospital over more than a week whereas higher doses of iron polymaltose could be given in one visit and this would need to be taken into consideration when estimating health sector costs and the costs to patients.

10.15 The Committee considered a review by Gozzard D (Drug Design, Development and Therapy 2011; 5: 51-60) which looked at when high dose intravenous iron replacement was required. The authors state that a dose of greater than 1000 mg is generally needed for patients with non-dialysis dependent chronic kidney disease to optimise iron status before starting erythropoietin therapy, in patients with inflammatory bowel disease and anaemia, in pregnancy, post-partum or in people with heavy uterine bleeding and in cancer associated anaemia.

10.16 The Committee considered a discussion paper provided with the application, which included the ADHB indications for intravenous iron to treat pre-operative anaemia to achieve a target of 150 g/L. The paper stated that 76% of patients presenting for Dukes D colon cancer surgery and 35% patients presenting for hip surgery are identified iron deficient. The Committee noted that the published doses based on body weight and current haemoglobin are almost all greater than 1000 mg.

10.17 The Committee noted that iron polymaltose or sucrose is likely to be given during dialysis for patients with kidney disease or during a hospital stay. In those instances, the Committee considered there to be little benefit of a rapid intravenous iron

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preparation. The Committee considered that in the out-patient setting iron polymaltose could be administered by infusion, often according to the rapid protocol.

10.18 The Committee considered that if funded, FCM could be administered in the community more easily than currently available parenteral preparations and that this would both free up hospital outpatient clinics and may be more convenient for patients, particularly those who are not required to attend hospital for other reasons. The Committee considered that practices may change to encourage more pre-operative iron infusions.

10.19 Overall, the Committee considered the benefits of FCM to be marginal and therefore considered that FCM should be funded only if the overall costs (including pharmaceutical, administration and patient costs) are comparable to iron polymaltose administered according to the rapid protocol.

11 Sildenafil – The use of Sildenafil in Cardiac Surgery

Application

11.1 The Committee reviewed the use of sildenafil in cardiac surgery following a PHARMAC staff request.

Recommendation

11.2 The Committee **recommended** that sildenafil be available in the hospital setting for use in perioperative cardiac surgery and in intensive care including as an alternative to nitric oxide.

11.3 The Committee **recommended** that PHARMAC staff investigate the possibility of obtaining a sildenafil intravenous injection.

11.4 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; (iv) The clinical benefits and risks of pharmaceuticals; and (v) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services.*

Discussion

11.5 The Committee noted that in the process of considering the cardiology pharmaceuticals for funding in DHB hospitals PHARMAC had received comments regarding the use of sildenafil in cardiac surgery from:

11.5.1 College of Anaesthetists – Sildenafil is used pre-operatively in severe PAH presenting for cardiac surgery.

11.5.2 College of Surgeons – Sildenafil has been used in cardiothoracic surgery in Auckland City Hospital since 2007 following a submission to the medicines committee and the development of a guideline. It noted that there is no data to support its use but strong theoretical reasons in some settings.

Chair

11.5.3 Cardiac Society – Sildenafil has an increasing use in the perioperative management of cardiac surgical patients and should be available for this purpose to cardiac surgeons, intensivists and anaesthetists.

11.6 The Committee noted information supplied by Dr Mark Edwards (Anaesthetist and Clinical Director of Cardiothoracic anaesthesia, Auckland City Hospital) on behalf of the Cardiac Society including:

11.6.1 Sildenafil is used pre-operatively in patients with high pulmonary vascular resistance who have or are at risk of developing right ventricular dysfunction in the perioperative period. These include heart transplant recipients, left ventricular assist device recipients, lung transplant recipients and some patients with significant valvular heart disease.

11.6.2 Some patients with unexpected RV dysfunction would have sildenafil started in the post-operative period.

11.6.3 Sildenafil would be weaned in ICU or prior to hospital discharge, and would not be anticipated to be used in the community for these patients.

11.6.4 There is little clinical evidence to support perioperative sildenafil use. What there is largely observational and based on haemodynamic outcomes rather than hard clinical endpoints.

11.6.5 The alternatives to sildenafil would be inhaled nitric oxide or iloprost.

11.6.6 Sildenafil is limited by it being only available in an oral form which is inconvenient intraoperatively, where sildenafil has to be given crushed via NG tube or sublingually, and as it is a three or four times a day medication in comparison to the once-daily tadalafil.

11.6.7 Estimated 40 patients per annum in Auckland hospital using a dose of 25-50mg three or four times a day.

11.7 The Committee noted articles including Shim et al (2006) and Palma et al (2011) for PAH patients undergoing valve or paediatric congenital cardiac surgery, and Boffini et al (2009) and De Santo (2008) for the treatment of right ventricular dysfunction post-heart transplantation.

11.8 The Committee concluded that there was no data to indicate the effect of sildenafil on the clinically significant end points of morbidity and mortality but that sildenafil appears to have a beneficial effect on peri-operative pulmonary haemodynamics and as a result may reduce cardio-pulmonary bypass and ventilation time and reduce stays in ICU resulting in earlier discharge.

11.9 The Committee noted that feedback from two DHB hospitals is that nitric oxide is no longer routinely used in ICU and sildenafil is being used in right heart failure and pulmonary hypertension without previous nitric oxide use. The Subcommittee considered that this would only occur for a short period as it would be confined to ICU.

Chair

11.10 The Committee noted that the cost of sildenafil had reduced considerably with the introduction of generics and that the daily cost was small compared to the daily cost associated with ICU and hospital stays.

11.11 The Committee noted that sildenafil was available as a tablet and could be compounded into an oral solution. The Committee also considered that an intravenous injection form would be useful in patients where oral sildenafil is unlikely to be absorbed or where oral administration is impractical such as in patients with end-stage heart failure who have poor gut absorption, emergency treatment or prolonged cardiac surgery. The Committee noted that an intravenous injection would be more expensive but would have low usage, as it would only be used when an oral form was unsuitable.

11.12 The Committee noted a 16 week double-blind, placebo-controlled RCT of 405 patients with PAH by Galie et al. (2009) which found that tadalafil improved exercise capacity (6MWT). However the Committee noted that only the 40mg dose reached statistical significance and that while tadalafil has some benefits over sildenafil in terms of once daily dosing the cost comparisons of both treatments are highly dependent upon the effective dose.

11.13 The Committee noted that Lepore et al. (2005) demonstrated favourable haemodynamic effects of sildenafil +/- inhaled nitric oxide in patients with PAH associated with CCF in the cath lab setting. The Committee noted that there were an increasing number of applications through the NPPA process for sildenafil for heart failure patients and left ventricular dysfunction.

11.14 The Committee considered that sildenafil should be available in the hospital setting for use in perioperative cardiac surgery and in intensive care including as an alternative to nitric oxide. The Committee considered its use would be limited to the hospital setting as patients would be weaned prior to discharge.

11.15 The Committee considered that sildenafil could be restricted to cardiac anaesthetists or intensivists.

12 Rivaroxaban for Stroke Prevention in Non-valvular Atrial Fibrillation

Application

12.1 The Committee reviewed an application from Bayer for the listing of rivaroxaban (Xarelto) on the Pharmaceutical Schedule for stroke prevention in non-valvular atrial fibrillation (AF).

Recommendation

12.2 The Committee deferred making a recommendation on rivaroxaban for stroke prevention in non-valvular atrial fibrillation (AF). The Committee **recommended** that the application be referred to the Haematology, Cardiology and Neurology Subcommittees for consideration, including for further advice on its potential reversibility and view on how it compares with the other novel anticoagulants including dabigatran and apixaban.

Chair

Discussion

12.3 The Committee noted that there are currently two anticoagulants funded for this indication; warfarin and the direct thrombin inhibitor, dabigatran. The Committee also noted that aspirin is currently being used for lower risk patients.

12.4 The Committee noted that the main evidence for the efficacy of rivaroxaban, a Factor Xa inhibitor in AF is the ROCKET AF trial (Patel et al. N Engl J Med. 2011;365:883-91). This was a double-blind trial, where 14,264 patients with non-valvular AF who were at increased risk for stroke were randomly assigned to receive either rivaroxaban (at a daily dose of 20 mg) or dose-adjusted warfarin. In the intention to treat (ITT) analysis, the rate of stroke and systemic embolism (primary end point) was 2.1% and 2.4% per year respectively (HR 0.99, 95% CI 0.74-1.03). There was no significant difference between rivaroxaban and warfarin in the primary safety end point of major and non-major clinically relevant bleeding (14.9% versus 14.5% per year, respectively (HR 1.03, 95% CI 0.96-1.11, p=0.44)). There was significant reductions in the rates of intracranial haemorrhage (0.5% vs. 0.7%, p=0.02, HR 0.67, 95% CI 0.47 to 0.93) and fatal bleeding (0.2% vs. 0.5%, p=0.003) in the rivaroxaban group. Major bleeding from a gastrointestinal site was more common in the rivaroxaban group, with 224 bleeding events (3.2%), as compared with 154 events in the warfarin group (2.2%, p<0.001) as was a haemoglobin drop of >2g/dl (2.8 vs. 2.3% p=0.02) and requirement for a blood transfusion (1.6 vs. 1.3% p=0.04). It was noted that the ITT results were not reported for all the pre-specified outcomes and there was no good reason provided for this. The Committee noted that 23.7% of patients in the rivaroxaban group and 22.2% of patients in the warfarin group stopped their assigned therapy before an end point event of the study termination date.

12.5 The Committee noted that the trial population included those at higher risk of stroke, as assessed by CHADS2 and may not be reflective of the treatment population here in New Zealand. The mean CHADS2 score was 3.48 (rivaroxaban) / 3.46 (warfarin) which is higher that the RELY study of dabigatran where the mean CHADS2 score was 2.1. Patients in the warfarin group had INR values in the target range a mean 55% of the time which is relatively low compared to other studies including RELY study where is was 64% (Connolly SJ, Circulation. 2008;118:2029-37). The Committee noted that it is unclear what effect this would have on efficacy and safety outcomes reported.

12.6 The Committee considered that rivaroxaban appears to be non-inferior to warfarin in terms of the primary efficacy endpoint, but that superiority has not been demonstrated. The Committee noted that there are currently no trials which directly compare rivaroxaban to dabigatran and an indirect comparison between the treatments is not reliable because the available clinical studies were done in different patient populations.

12.7 In regards to safety, the Committee noted that rivaroxaban was associated with fewer bleeding related deaths but with more cases of serious gastrointestinal bleeding. The Committee noted that there was no indication from the ROCKET AF study that rivaroxaban was associated with a higher risk of myocardial infarction when compared to warfarin. The Committee noted that at study end, 92% of patients were switched to standard medical therapy with a VKA and significantly more patients transitioning from rivaroxaban than from warfarin developed primary events during the first month after termination of randomised treatment (22 vs. 7; p=0.008) (Patel et al. N Engl J Med.

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2011;365 (10):883-91 online supplementary files) The Committee noted that there is no long term safety data related to this drug. The Committee noted the paucity of data on the reversibility of these new novel anticoagulants, including rivaroxaban. The Committee noted that some pre-clinical studies suggest that some agents may have the potential to reverse rivaroxaban, but noted that this has not been confirmed in any clinical studies.

12.8 The Committee noted that there was another Factor Xa inhibitor, apixaban which has been submitted for registration in New Zealand. The Committee noted the results from two studies related to apixaban in AF. The Committee noted the results from the ARISTOTLE trial (N Engl J Med 2011;365:981-992) which was a randomized, double-blind trial, comparing apixaban to warfarin in 18,201 patients with AF and at least one additional risk factor for stroke. The Committee noted that the rate of the primary outcome was 1.27% per year in the apixaban group, as compared with 1.60% per year in the warfarin group (HR 0.79; 95% CI, 0.66 to 0.95; p<0.001 for noninferiority; p=0.01 for superiority). The rate of major bleeding was 2.13% per year in the apixaban group, as compared with 3.09% per year in the warfarin group (HR 0.69; 95% CI, 0.60 to 0.80; p<0.001), and the rates of death from any cause were 3.52% and 3.94%, respectively (HR 0.89; 95% CI, 0.80 to 0.99; p=0.047). The Committee noted that the trial results indicate that apixaban is superior to warfarin in preventing stroke or systemic embolism, causes less bleeding, and results in lower all-cause mortality.

12.9 The Committee noted the results from the AVERROES study (Connolly et al N Engl J Med 2011;364:806-817) where 5599 patients with AF who were at increased risk of stroke and unsuitable for vitamin K antagonist therapy were randomly assigned to receive apixaban (5 mg twice daily) or aspirin (81-324 mg per day). The Committee noted in the intention to treat analysis the rate of occurrence of stoke or systemic embolism (primary end point was 1.6% vs. 3.7% per year, HR 0.45 95% CI 0.32-0.62 p<0.001). The Committee noted there were no significant differences in the rates of major bleeding or all-cause mortality.

12.10 The Committee noted that funding rivaroxaban in AF would result in additional cost to the Pharmaceutical Budget due to the terms of the supply agreement for dabigatran where additional rebates are applied after certain expenditure levels are reached.

12.11 The Committee considered that having multiple novel anticoagulants available and funded may pose safety issues from prescribing, dispensing and administration errors as well as due to the complexities around switching from one agent to another. For this reason, and given that dabigatran is already funded, the Committee considered that it would be appropriate for it to review the funding application for apixaban before it makes a recommendation on rivaroxaban in this indication. The Committee also considered that it would be appropriate to refer this application to the Haematology, Cardiology and Neurology Subcommittees for advice on whether rivaroxaban has advantage over dabigatran (including the possibility of a viable reversibility agent) and also as to whether apixaban might offer any further benefits in this therapeutic group.

13 Rivaroxaban for the treatment of deep vein thrombosis (DVT) and for the secondary prevention of DVT and pulmonary embolism (PE)

Chair

Application

13.1 The Committee reviewed an application from Bayer for the listing of rivaroxaban (Xarelto) on the Pharmaceutical Schedule for the treatment of deep vein thrombosis (DVT) and for the secondary prevention of DVT and pulmonary embolism (PE).

Recommendation

13.2 The Committee deferred making a recommendation on rivaroxaban for the treatment of deep vein thrombosis (DVT) and for the secondary prevention of DVT and pulmonary embolism (PE). The Committee **recommended** that the application for rivaroxaban in this indication be referred to the Haematology Subcommittee for consideration, including for further advice on its potential reversibility and opinion on how it compares to dabigatran and apixaban in this indication.

Discussion

13.3 The Committee noted that there was one key trial for rivaroxaban in the treatment of DVT, the EINSTEIN trial.

13.4 The Committee noted that the EINSTEIN-DVT (EINSTEIN Investigators N Engl J Med 2010;363:2499-251) was a randomised, open-label, non-inferiority trial, which enrolled 3,449 patients with acute, symptomatic, confirmed proximal DVT without PE. The Committee noted that the study participants were randomised to receive up to 12 months treatment with oral rivaroxaban (15mg twice daily for three weeks followed by 20mg once daily) or standard care (enoxaparin 1mg/kg twice daily for at least five days, and a VKA titrated to an INR of 2.0 to 3.0). However, the Committee noted that 0.3% of the rivaroxaban group and 0.5% of the enoxaparin/warfarin group had CrCl <30ml/min, and as enoxaparin requires dose adjustment in severe renal impairment, this would potentially bias the results of this trial.

13.5 The Committee noted that patients at high risk of bleeding, with any other indication for VKA therapy and with reduced hepatic or renal function were excluded from the trial, and the average age of participants was 56 years. The Committee noted that the primary endpoint was symptomatic, recurrent venous thromboembolism (VTE), defined as the composite of DVT and PE. The Committee noted that rivaroxaban had noninferior efficacy with respect to the primary outcome; 2.1% for rivaroxaban vs. 3.0% enoxaparin–warfarin (HR 0.68; 95% CI 0.44 to 1.04; p<0.001). The Committee noted that superiority was not demonstrated (p=0.08). The Committee noted that the principal safety outcome (major bleeding or clinically relevant non major bleeding) was not significantly different between groups, occurring in 8.1% of the patients in each group (HR 0.97, 95% CI 0.76-1.22, p=0.77).

13.6 The Committee noted that the same study also reported the results of EINSTEIN-extension, a superiority study which recruited 1,197 patients who had received 6 to 12 months of warfarin or rivaroxaban therapy for DVT or PE, and randomised them in a double-blind fashion to receive continuation treatment with rivaroxaban or placebo for a further 6 or 12 months. The Committee noted that rivaroxaban was found to be superior to placebo for prevention of recurrent VTE (events recorded in 1.3% vs. 7.1% of patients, HR 0.18, 95% CI 0.09-0.39, p<0.001).

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13.7 The Committee noted that rivaroxaban showed non-inferiority compared with the enoxaparin / warfarin comparator. The Committee noted that superiority was not demonstrated. The Committee noted that that the time in therapeutic range for the warfarin group varied between a low of 54.1% in the first month to 66.4% in the tenth month and that is was unclear what influence this may have had on the efficacy outcome in the first three weeks. The Committee also noted that there was no information in the study comparing the rates of post-thrombotic syndrome (PTS) between the two treatment arms although PTS is a significant clinical issue following a DVT/PE.

13.8 The Committee noted that the rates of adverse events (AEs) were similar in both arms of the EINSTEIN-DVT trial, occurring in 62.7% and 63.1% of patients in the rivaroxaban and control groups respectively. There were no significant differences in the rates of serious AEs (12.0% vs. 13.6%), AEs leading to discontinuation (4.9% vs. 4.7%), or AEs leading to or prolonging hospitalisation (11.2% vs. 12.3%). Likewise there were no significant differences between rivaroxaban and standard care in the reported rates of major bleeding (0.8% vs. 1.2%), first instance of major or clinically relevant non-major bleeding occurring during treatment (8.1% vs. 8.1%), or total deaths (2.2% vs. 2.9%).

13.9 The Committee also noted one key study of the use of rivaroxaban in treatment of PE - the EINSTEIN – PE study (N Engl J Med 2012;366:1287), an open label RCT in which 4832 patients were randomised 1:1 to treatment with rivaroxaban or a VKA after enoxaparin. The same dosage regime was used as for the EINSTEIN – DVT study. The Committee noted that the primary endpoint was symptomatic, recurrent venous thromboembolism (VTE).

13.10 The Committee noted that a quarter of the participants had concurrent DVT identified and the INR average TTR was 62% in this study. The Committee noted that no significant difference was found in the primary outcome (HR 1.12, 95% CI 0.75-1.68) and that the non-inferiority test was statistically significant (p=0.003). The Committee noted that here was no significant difference in the pre-specified primary safety outcome of first episode of major or clinically significant bleeding (HR for rivaroxaban 0.90, 95% CI 0.76-1.07) and that overall mortality was not significantly different.

13.11 The Committee noted the results of the Schulman et al Re-COVER study (N Engl J Med 2009;361:2342-52), a double blinded double dummy randomised controlled non-inferiority trial in which 2564 patients with DVT or PE were randomised 1:1 to initial enoxaparin plus warfarin or initial enoxaparin plus dabigatran 150mg bd with 5 days' overlap. The primary outcome was symptomatic, recurrent venous thromboembolism (VTE). The Committee noted that dabigatran had non-inferior efficacy with respect to the primary outcome. Of the 1274 patients randomly assigned to receive dabigatran, 2.4%, as compared with 2.1% of the 1265 patients randomly assigned to warfarin had recurrent venous thromboembolism (HR 1.10, 95% CI 0.65-1.84). The Committee noted that superiority was not demonstrated. The Committee noted that there was no significant difference in major bleeding episodes, which occurred in 1.6% patients assigned to dabigatran and in 1.9% patients assigned to warfarin (HR 0.82, 95% CI 0.45-1.48). Episodes of any bleeding were observed in 16.1% patients assigned to dabigatran and 21.9% patients assigned to warfarin (HR 0.71, 95% CI 0.59-0.85). The Committee noted that the numbers of deaths, acute coronary syndromes, and abnormal liver-function tests were similar in the two groups. The Committee noted that the extension study for this trial, Re-MEDY used warfarin as a comparator, unlike the

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EINSTEIN extension study (http://www.trialresultscenter.org/study12090-RE-MEDY.htm). The Committee noted that Medsafe-registration for dabigatran in this indication could be sought in the near future.

13.12 The Committee noted a study by Becattini et al (N Engl J Med 2012;366:1959-1967) which investigated the benefit of aspirin for the prevention of the recurrence of VTE. The Committee noted that this was a multicentre, double-blind study of patients with first-ever unprovoked venous thromboembolism who had completed 6 to 18 months of oral anticoagulant treatment. The Committee noted that patients were randomly assigned to aspirin, 100 mg daily, or placebo for 2 years, with the option of extending the study treatment. The primary efficacy outcome was the recurrence of venous thromboembolism, and major bleeding was the primary safety outcome. The Committee noted that during a median treatment period of 23.9 months, 5.9% patients taking aspirin and 11.0% taking placebo had a recurrence (HR 0.55, 95% CI 0.33-0.92). The Committee noted that one patient in each treatment group had a major bleeding episode and adverse events were similar in the two groups.

13.13 The Committee noted that overall there was a lack of long term outcome data for rivaroxaban in this indication and the issue of reversibility of the novel anticoagulants is still unknown. The Committee noted that there are small studies (including pre-clinical studies) showing that prothrombin complex concentrate may reverse the anticoagulant effect of rivaroxaban but this has yet to be confirmed in larger studies.

13.14 The Committee considered that treatment with rivaroxaban has its advantages as it is less complex, not requiring LMWH cover during initiation. Members noted that enoxaparin treatment during the transition onto warfarin is, however, often managed in the primary care setting. The Committee considered that many patients currently already receive a therapeutic dose of enoxaparin in the primary care setting before a DVT/PE is confirmed diagnostically, if there is a high degree of clinical suspicion. The Committee also noted that it is likely that dabigatran when used in this setting only requires treatment with enoxaparin as well during initiation because the study was designed in that way, rather than for any clinical reason.

13.15 The Committee noted that compliance with rivaroxaban would potentially be more crucial when compared to warfarin and that missing a dose could have a great impact due to its shorter half-life. The Committee considered that although rivaroxaban is only indicated for the treatment of acute DVT, it will likely also be used in the acute PE setting as they are considered to be the same disease. The Committee considered that it is difficult to estimate what proportion of patients with acute VTE would have a DVT and what proportion would have a PE.

13.16 The Committee noted that funding rivaroxaban for this indication would be associated with additional cost to the Pharmaceutical Schedule when compared with warfarin. Members noted that it would also be a cost when compared with dabigatran when rivaroxaban is registered for use in this indication, given the terms of the supply agreement for dabigatran where additional rebates are applied after certain expenditure levels are reached.

13.17 The Committee considered that having too many novel anticoagulants available and funded may pose safety issues from prescribing, dispensing and administration errors as well as the complexities around switching between agents. The Committee noted

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that it would be appropriate for it to consider all the new anticoagulants including dabigatran and apixaban before it makes a recommendation on rivaroxaban in this indication.

13.18 The Committee considered that the application should be referred to the Haematology Subcommittee for its view on the reversibility and clinical benefits of rivaroxaban as well as the place in therapy of other novel oral anticoagulants including apixaban.

14 Melatonin - for primary insomnia in patients aged 55 years or over, secondary insomnia in children/adolescents with neurodevelopmental/psychiatric comorbidities and secondary insomnia associated with dementia

Application

14.1 The Committee considered an application from Aspen Pharma for the funding of melatonin prolonged release in three indications; primary insomnia in patients aged ≥55 years, secondary insomnia in children/adolescents with neurodevelopmental/ psychiatric comorbidities, and secondary insomnia in patients with dementia.[1]

14.2 In addition, the Royal Australia New Zealand College of Psychiatrists (RANZCP) provided a submission for secondary insomnia in children and adolescents with neurodevelopmental or psychiatric comorbidities.

Recommendation

14.3 The Committee **recommended** that the funding application for melatonin should be declined for primary insomnia in patients aged ≥55 years and declined in secondary insomnia in patients with dementia.

14.4 The Committee **recommended** that melatonin should be funded, with a low priority, for secondary insomnia in children and adolescents with neurodevelopmental or psychiatric comorbidities. The Committee **recommended** that melatonin be funded for this patient group subject to the following draft special authority criteria:

> **Initial application** only from a psychiatrist or paediatrician or medical practitioner on the recommendation of a psychiatrist or paediatrician. Approvals valid for 12 months for applications meeting the following criteria:
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> 1. Patient has been diagnosed with persistent and distressing insomnia secondary to a Neurodevelopmental Disorder (such as Autism Spectrum Disorder or Attention Deficit Hyperactivity Disorder) and
> 2. Patient is aged ≤xx years.
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> **Renewal application** only from a psychiatrist or paediatrician or medical practitioner on the recommendation of a psychiatrist or paediatrician. Approvals valid for 12 months for applications meeting the following criteria:

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1. At its meeting on 9 & 10 May 2013, PTAC noted that PHARMAC had requested the information from Aspen in relation to melatonin for indications other than primary insomnia.

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1. Patient has been diagnosed with persistent and distressing insomnia secondary to a Neurodevelopmental Disorder (such as Autism Spectrum Disorder or Attention Deficit Hyperactivity Disorder) and
2. Patient is aged ≤ xx years, and
3. Patient is continuing to benefit from treatment.

14.5 The Committee **recommended** that advice should be sought from the Paediatric Society and the RANZCP regarding what the appropriate age cut-off for treatment should be and the appropriate treatment comparator.

14.6 *The Decision Criteria particularly relevant to this recommendation are:* (*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; (vii) the direct cost to health service users.*

Discussion

14.7 The Committee noted that primary insomnia in patients aged ≥55 years is the registered indication for melatonin. The two off-label indications in secondary insomnia were requested by the Mental Health Subcommittee of PTAC in June 2010 and 2012.

Primary insomnia in patients aged ≥55 years

14.8 The Committee noted the key evidence for the use of melatonin for primary insomnia comprised of two randomised placebo controlled trials of 3 week duration; Lemoine et al. (J. Sleep Res 2007;16:372-380) and Wade et al. (Curr Med Res Opin 2007;23(10):2597-2605).

14.9 The Committee noted that Lemoine et al. 2007 was a randomised controlled trial (RCT) in 170 patients aged ≥55 with primary insomnia. 96% of patients completed the study. A visual analogue scale was used to measure changes in sleep outcomes with a 10mm change considered clinically significant. Melatonin statistically significantly improved quality of sleep (-22.5 versus -16.5mm, p=0.047) and improved morning alertness (-15.7 vs. -6.8mm, p=0.002) compared with placebo. There were no withdrawal problems at week 3 and no safety concerns.

14.10 The Committee noted that Wade et al. 2007 was a RCT in 354 patients aged ≥55 with primary insomnia. The responder rate was 26% for melatonin compared with 15% for placebo (p=0.014), i.e. a combined improvement in sleep quality and morning alertness. 70% of the melatonin responders had a clinically relevant improvement in quality of life. Sleep latency on melatonin was shorter than placebo by 8.8 minutes (p=0.028) although there was no statistically significant difference in total sleep time. The study identified no safety concerns.

14.11 The Committee noted a randomised placebo controlled trial of 6 months (Wade et al. BMC Medicine 2010;8:51) which investigated the longer term efficacy and safety of melatonin and the differences in response depending on age and endogenous melatonin. The primary outcome was sleep latency. Patients with low endogenous melatonin did not differ from placebo, however in elderly patients (age 65-80) melatonin significantly reduced sleep latency compared to placebo regardless of melatonin levels (-19.1 vs. -1.7 min; p=0.002). The effects of melatonin were maintained or enhanced

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over 6 months with no tolerance. There was no withdrawal or rebound insomnia on discontinuation.

14.12 The Committee also reviewed evidence from a number of observational studies of melatonin and zolpidem. Members noted that melatonin can replace benzodiazepines and reduce withdrawal issues from benzodiazepines, but patients tended to stay on melatonin instead. Cost utility analysis provided by the supplier included non-direct costs and productivity calculations that would not be included in PHARMAC CUA and members considered the extrapolation of benefits to be speculative.

14.13 Overall, the Committee considered that the evidence for melatonin compared with placebo was strong and of good quality. However the evidence comparing melatonin with the comparator zopiclone was weak and of poor quality, and comprised of indirect comparisons.

14.14 The Committee considered that melatonin was similar in efficacy to zopiclone and other hypnotic pharmaceuticals. Members considered that there was insufficient evidence to quantify benefits for melatonin such as reduced cardiovascular events, accidents or falls and other side effects when compared with zopiclone.

14.15 The Committee noted that melatonin would be used at a dose of 2mg per day and could replace zopiclone and some other benzodiazepines. Members considered there could be significant long term use of melatonin by patients with primary insomnia and that usage may extend into secondary insomnia. The Committee considered that both these factors would increase the financial risk of funding melatonin. Members considered that the use of melatonin may reduce the use of zopiclone and benzodiazepines, but overall funding melatonin was likely to grow the market for sleep medication in terms of the number of patients and the length of treatment.

Secondary insomnia in children with neurodevelopmental and psychiatric comorbidities

14.16 The Committee noted the key evidence for the use of melatonin in secondary insomnia in children comprised of two randomised placebo controlled trials; Wasdell et al (J Pineal Res. 2008;44:57-64), and Cortesi et al. (J Sleep Res. 2012. doi: 10.1111/j.1365-2869.2012.01021.x. [Epub ahead of print]).

14.17 The Committee noted Wasdell et al. 2008 was a crossover RCT followed by a 3-month open-label study to determine the efficacy of controlled-release melatonin (5mg) in sleep delay and impaired sleep of children (aged 2–18 years) with neurodevelopmental disabilities including autistic spectrum disorders, who did not respond to sleep hygiene intervention (n=51). Fifty patients completed the crossover trial and 47 completed the open-label phase. Total sleep time improved by 30 minutes on melatonin compared to placebo ($p<0.01$) and significantly shorter sleep latency was observed ($p<0.01$). Members considered the 30 minute improvement in sleep time to be clinically significant. Statistically significant improvements with melatonin compared with placebo were reported in Clinical Global Impression of severity and improvement from baseline, Parents' Global Assessment Scale, and caregiver ratings of family stress. Members noted that improvement was maintained.

14.18 The Committee noted Cortesi et al. 2012 was an RCT investigating melatonin (3mg), singly and combined with cognitive behavioural therapy (CBT), for persistent insomnia

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in children with autism spectrum disorders aged 4-10 years (n=160). Patients were assigned randomly to either (1) combination of melatonin and CBT; (2) melatonin; (3) four sessions of CBT; or (4) placebo drug treatment condition for 12 weeks. Results from actigraph readings showed statistically significant improvements in all active treatments compared to placebo for the primary outcomes of total sleep time (change from baseline at 12 weeks: combination 22%, melatonin 17%, CBT 9% and placebo <1%, p<0.001), sleep onset latency (61%, 44%, 23%, <1%, p<0.001), wake after sleep onset (58%, 43%, 10%, <1%, p<0.001) and sleep efficiency. The study identified no safety concerns.

14.19 The Committee noted the longer-term open label study of melatonin (4-6 mg) in 88 children with neurodevelopmental disorders; De Leersnyder et al. (Pediatr Neurol. 2011 Jul;45(1):23-6). 70.5% of children still used melatonin daily at three months follow-up and treatment duration ranged from 6-72 months. Compared to baseline, parents reported statistically significant reductions in sleep latency (44%, p<0.001) increased total sleep time (10%, p<0.001) and reduced awakenings. There were no serious adverse events.

14.20 The Committee noted a number of meta-analyses including Rossignol et al. (Dev Med Child Neurol. 2011;53(9):783-92. doi: 10.1111/j.1469-8749.2011.03980.x. Epub 2011 Apr 19). This studied melatonin use in autism spectrum disorders and reviewed five double blind randomised placebo controlled trials and 13 uncontrolled studies. The review was limited by the relatively small sample sizes and by study methods, with parent reports having a greater effect size than actigraphic results. Statistically significant results were greater sleep time (44 minutes more than placebo) and shorter sleep latency (39 minutes less than placebo). Some studies reported improved daytime behaviour with melatonin. There were minimal to no side effects from melatonin use.

14.21 The Committee also reviewed evidence from a number of open label studies of melatonin which showed improved sleep measures, minimal adverse events, and a tendency to return to previous sleep patterns on discontinuation of melatonin.

14.22 The Committee noted there has been speculation that using exogenous melatonin could delay puberty, although there is minimal data to support this currently (van Geijlswijk et al. Psychopharmacology (2011) 216:111–120). This study also reported that treatment gains on melatonin were maintained out to three years with no tendency to increase the dose.

14.23 The Committee noted the RANZCP submission on patient numbers and dose (range 1-5mg, mainly 2-3mg per day). Members considered that melatonin appears to be the treatment of choice for many families who purchase it privately. According to IMS data and expert opinion current treatments used include promethazine (aged 0-4 years), privately funded melatonin (aged 5-11, and boys aged 12-19), privately funded melatonin or zopiclone/ benzodiazepines/ quetiapine (girls aged 12-19). The Committee considered that further advice should be sought from the Paediatric Society and the Mental Health Subcommittee about the appropriate treatment comparator.

14.24 The Committee noted that children with attention deficit hyperactivity disorder (ADHD) tended to have sleep onset problems and that stimulant treatment made the problem worse. Members considered that this is a major issue for parents/carers and can result

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in impaired concentration and learning for children. Children with other neurodevelopmental / behavioural problems have similar difficulty with sleep onset.

14.25 The Committee noted two double blind placebo controlled trials of melatonin in children with ADHD; Weiss et al. (J Am Acad Child Adolesc Psych. 2006;45(5):512-9), and Van der Heijden et al. (J Am Acad Child Adolesc Psych. 2007;46:233-241). Both trials reported that sleep latency and total sleep time were significantly improved compared with placebo, with no safety issues. Weiss et al. (n=27) reported continued improvement in the open label follow up. Van der Heijden et al. (n=105) reported no real change in behavioural or cognitive measures or quality of life.

14.26 Overall, the Committee considered that the evidence for melatonin compared with placebo for secondary insomnia in children with neurodevelopmental issues was weak with small numbers and of poor quality. However the evidence does show some consistent effect. The evidence for ADHD was weak but of moderate quality.

14.27 The Committee considered that melatonin was similar in efficacy to other hypnotic pharmaceuticals, although none were indicated for paediatric use (including melatonin). Melatonin may be used with stimulants and other medications for neurodevelopmental disorders in children e.g. anticonvulsants. Members noted that many of these children already take privately purchased melatonin, with others using zopiclone, benzodiazepines and quetiapine (mainly in older girls).

14.28 The Committee noted that the dose of melatonin was likely to be 2 mg per day, with long term use in childhood likely if efficacious. The evidence is strongest for ADHD and ASD although demand is likely to be wider and include intellectual disabilities. The Committee noted that sleep improves with age in ADHD and ASD. Members noted there were minimal to no side effects with melatonin in the studies, although long term safety risks are still unknown.

Secondary insomnia in patients with dementia

14.29 The Committee noted the key evidence for the use of melatonin in secondary insomnia in patients with dementia comprised of two randomised placebo controlled trials; Singer et al. (Sleep. 2003;26(7):893-901) and Asayama et al. (J Nippon Med Sch. 2003;70(4):334-41).

14.30 The Committee noted the largest trial Singer et al. was a RCT of melatonin 2.5mg or 10mg per night or placebo (n=157). There were no statistically significant differences between the treatment groups and placebo for total sleep time and sleep latency. Carer determined sleep quality was statistically significantly improved for melatonin 2.5mg dose only. There were no adverse events.

14.31 The Committee noted the small trial Asayama et al. was a RCT of melatonin 3mg or placebo (n=20). On melatonin, actigraph recorded sleep time improved by 33% compared to placebo (p=0.017) and sleep activity decreased by 45% (p=0.014). Daytime cognitive scores statistically significantly improved on melatonin, but there was no change in daytime sleep and activity.

14.32 The Committee also reviewed evidence from a number of reviews of melatonin including Deschenes et al. (Curr Psychiatry Rep. 2009 Feb.; 11(1): 20–26) and Jansen

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et al. (Cochrane Review, The Cochrane Library 2011, Issue 3). Deschenes et al. showed little positive evidence for efficacy. The Cochrane Review was of small studies with limited data and suggested there is no good evidence that melatonin improves cognition, some evidence of improved behaviour, and an association with longer term use and lowering of mood.

14.33 Overall, the Committee considered that the evidence for melatonin compared with placebo for secondary insomnia in patients with dementia was weak and of poor quality.

14.34 The Committee considered that melatonin was probably similar in efficacy to other hypnotic pharmaceuticals. Melatonin may be used with multiple other agents including donepezil and may be used instead of zopiclone, quetiapine or benzodiazepines, probably at a dose of 2mg per day. Members considered that melatonin would be used long term if efficacious and that estimated patient numbers could be higher if used for behavioural and psychological symptoms of dementia.

15 Bovine Lipid Extract Surfactant – Pulmonary Distress

Application

15.1 The Committee considered an application from Rex Medical Limited for the listing of bovine lipid extract surfactant (BLES) on the Pharmaceutical Schedule for the rescue treatment on neonatal respiratory distress syndrome.

Recommendation

15.2 The Committee **recommended** that the application be declined.

15.3 *The Decision Criteria* particularly relevant to this recommendation are*: The Decision Criteria particularly relevant to this recommendation are: (i) the health needs of all eligible people within New Zealand; (iv) the clinical benefits and risks of pharmaceutical.*

Discussion

15.4 The Committee noted that preterm births account for approximately 8 to 10% of all births in New Zealand and that the excess mortality in this group is mainly confined to those born at less than 32 weeks and weighing less than 1500 g. The Committee noted that preterm infants are both qualitatively and quantitatively deficient in pulmonary surfactant leading to respiratory distress syndrome (RDS). Members noted that intratracheal administration of surfactant reduces morbidity and mortality in preterm infants.

15.5 The Committee noted that there are two types of natural surfactants currently available in the New Zealand market, an older product extracted from minced bovine lungs which has very little use and a product derived from minced porcine lungs (Curosurf) that dominates the market. Members noted that BLES is collected by lavage of the intact bovine lungs and is closer to native surfactants than synthetic surfactants and similar to the currently used porcine product.

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15.6 The Committee considered the evidence provided by the supplier in the form of six published and unpublished clinical trials evaluating the efficacy and safety of BLES carried out in Canadian hospitals. The Committee noted that there were no trials comparing BLES with the porcine product currently used in New Zealand.

15.7 The Committee noted that Dunn et al studied differing dosage regimens. Study #3 (Dunn et al. Paeds 1990;86:564-71) was an unblinded RCT of single versus multiple doses (up to three further doses) of BLES at a concentration of 100 mg / kg versus placebo (air) in 75 infants for rescue treatment of respiratory distress syndrome (RDS). The mean gestational age was 32 weeks; the infants had an average weight of ~1900 g and were in good condition at birth. Primary endpoints were oxygen and ventilator requirements in the first week of life. The infants were stratified by gestational age (two groups – 30 to 33 weeks and 34 to 36 weeks), antenatal steroid exposure and sex. Fraction of inspired oxygen (FiO2), arterial/alveolar (a/A) ratio and ventilation index all improved in the first 24 hours in the surfactant groups compared to placebo. Members noted that there was no difference in duration of ventilation, oxygenation, intraventricular haemoglobin (IVH), patent ductus arteriosus (PDA), pneumothorax, chronic lung disease and death between groups, although the study was poorly powered for these endpoints. Of the 48 infants followed up to 24 months there were no differences in chronic lung disease or neurodevelopment, although those who received multiple doses of BLES were more likely to have chronic wheeze (p=0.04).

15.8 The Committee noted that Dunn's Study #4 (Dunn et al Paeds 1991;87:377-86) was an unblinded RCT of prophylactic BLES vs. BLES rescue treatment within the first 6 hours vs. placebo (air) for RDS in 182 infants born under 30 weeks gestational age. The mean gestational age was 27 weeks with a weight of ~1000 g at birth. The BLES dose was 75 mg for infants with a gestational age of 24-26 weeks and 100 mg for those 27-29 weeks. Only 31 of the 60 infants in the rescue treatment group required surfactant. FiO2, a/A ratio and ventilation index improved in both BLES groups compared with control and the BLES groups showed less pulmonary air leaks and chronic lung disease compared to controls. Rescue treatment resulted in less days incubated (p=0.008), less days in NICU (p=0.04) and less PDAs (p=0.05) compared with controls. There was no difference in necrotising enterocolitis (ENC), IVH and retinopathy of prematurity (ROP) and death between the groups. Of the 159 surviving infants, 72% were followed for up to 24 months and there was no difference in wheeze, death or neurodevelopment outcome between the groups.

15.9 The Committee noted that Peliowski et al conducted a double blinded randomised control trial of BLES 135 mg/kg (5ml/kg) versus Exosurf (a synthetic surfactant) 67.5 mg/kg (5ml/kg) for rescue treatment (Peliowski et al. Pediatr Res 1998;43:293A). The study enrolled 1,133 infants who were stratified into three groups by weight (≤ 750 g, 750 – 1250 g and > 1250 g) with a primary outcome of intact cardiopulmonary survival at 36 weeks gestation equivalent age. The Committee noted that there was no difference in outcome at 36 weeks, however, there were increased deaths in the Exosurf group post 28 days (BLES 84.5% vs. Exosurf 79.8% (p=0.04)). In the BLES groups there was an increase in sepsis (28% vs. 22.7% Exosurf, p=0.046), a decrease in pulmonary interstitial emphysema (8.6% vs. 17%, p=<0.0001) and a decrease in incidence of pneumothorax (8.5% vs. 12.2%, p=0.047) and less air leaks in the 750-1250 g subgroup (14.4% vs. 31.6%, p=<0.0001).

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15.10 [withheld under s 9(2)(b)(ii) of the OIA]

15.11 [withheld under s 9(2)(b)(ii) of the OIA]

15.12 The Committee noted an unblinded randomised controlled trial by Lam et al (Paed Pulm 2005;39:64-9) comparing BLES with Survanta for rescue treatment in 63 infants diagnosed with RDS, birth weights between 500 and 1800 g and a mean gestational age of 27 weeks. The primary outcome was the clinical response as indicated by the oxygen index which was lower in the BLES group (p=0.0009) and this was evident within 6 hours. Four infants died in the BLES group vs. 1 in the Survanta; mechanical ventilation was reduced in the BLES group (16.9 days vs. 19.8, p=0.02) and there was a trend towards less CLD (9/26 vs. 19/30, p=0.06).

15.13 The Committee considered that the evidence was of low/moderate quality and strength with no comparison against Curosurf, the product that is almost exclusively used in New Zealand. The Committee noted that twice the volume of BLES is used per kilogram compared to the volume of Curosurf (5 ml per kg vs. 2.5 ml per kg), and it also noted that a smaller volume is the preferred treatment. The Committee noted that desaturation can occur when treating infants with surfactants and ideally the required volume should be minimised.

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