

PTAC meeting held 6 & 7 May 2010

(minutes for web publishing)

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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 published.

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 the privacy of natural persons (section 9(2)(a));
 - (ii) protect information where the making available of the information would be likely to unreasonably prejudice the commercial position of the person who supplied or who is the subject of the information (section 9(2)(b)(ii));
 - (iii) protect information which is subject to an obligation of confidence or which any person has been or could be compelled to provide under the authority of any enactment, where the making available of the information would be likely to prejudice the supply of similar information, or information from the same source, and it is in the public interest that such information should continue to be supplied (section 9(2)(ba)(i)); and/or
 - (iv) enable PHARMAC to carry on, without prejudice or disadvantage, negotiations (including commercial and industrial negotiations (section 9(2)(j)).
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1 Minutes of PTAC Meeting Held February 2010

1.1 The Committee reviewed the minutes of the PTAC meeting held on 25 & 26 February 2010 and made the following minor amendment:

1.1.1 Prasugrel hydrochloride (Effient) – paragraph 6.5: The Committee considered that the comparator, clopidogrel, should be added to the paragraph. The existing paragraph:

“The Committee noted that over 15 months the absolute risk reduction for the primary endpoint (death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke) was 2.2% in the overall cohort, 2.4% in patients with ST-segment elevation myocardial infarction, 1.8% with stent insertion, and 4.8% in patients with diabetes. The Committee considered that overall prasugrel offered a modest benefit with an increased risk of haemorrhage.”

should be changed to read:

“The Committee noted that TRITON-TIMI-38 compared prasugrel (60-mg loading dose and 10-mg daily maintenance for 6-15 months) with clopidogrel (300-mg loading dose and 75-mg daily maintenance for 6-15 months). After 15 months the absolute risk reduction with prasugrel for the primary endpoint (death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke) was 2.2% in the overall cohort, 2.4% in patients with ST-segment elevation myocardial infarction, 1.8% with stent insertion, and 4.8% in patients with diabetes. The Committee considered that overall, prasugrel offered a modest benefit with an increased risk of haemorrhage.”

2 Matters Arising – Fenofibrate

2.1.1 Fenofibrate – paragraph 5.11: The Committee noted that the ACCORD trial referred to in its minute on 25 & 26 February was now published, and that the study had reported a negative outcome. The Committee **recommended** that, further to its minute of February 2010, paragraph 10.11, there was no need for it to review fenofibrate again at this time.

3 Levofloxacin – treatment for helicobacter infection

Application

- 3.1 The Committee noted an application from The New Zealand Society of Gastroenterology (NZSOG) for the funding of levofloxacin as a second line treatment of Helicobacter pylori infection.

Recommendation

- 3.2 The Committee **recommended** that PHARMAC staff respond to the NZSOG and request that it approach a company willing to register levofloxacin and then submit an application to PHARMAC for further consideration by PTAC.

Discussion

- 3.3 The Committee noted that levofloxacin has not been registered by Medsafe. Members considered that to formally review a product usually there should be a registered formulation available and a potential supplier.
- 3.4 Members noted that there were no funded second line therapies for *H. pylori* eradication due to the discontinuation of tripotassium dicitratobismuthate and tetracycline in the New Zealand setting.

4 Cholecalciferol (OsteVit-D)/ cholecalciferol and calcium carbonate (OsteVit D and Calcium) prevention and treatment of vitamin D deficiency

Application

- 4.1 The Committee reviewed an application from Wilson Consumer Product and Key Pharmaceuticals for the funding of cholecalciferol and cholecalciferol with calcium carbonate for the prevention and treatment of vitamin D deficiency.

Recommendation

- 4.2 The Committee **recommended** that OsteVit-D and OsteVit-D and Calcium be listed in the Pharmaceutical Schedule only if cost neutral to the health sector.
- 4.3 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; and (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

- 4.4 The Committee reviewed the Tang et al study (Lancet 2007; 370:657-66), which it considered a high quality systematic review and meta-analysis of randomised controlled trials of calcium, vitamin D and the combination for the prevention of fracture. Members noted that the 17 trials which reported fracture as an outcome gave a combined estimate for risk of fracture for calcium alone or in combination with vitamin D of 0.88 (95 % confidence interval (CI) 0.83 - 0.95).
- 4.5 The Committee reviewed the study by Bischoff-Ferrari et al (JAMA 2005; 293:2257-2264), a meta-analysis of randomised controlled trials. Members noted that the risk of hip fracture was not reduced in the analysis of all vitamin D studies together, pooled relative risk was 0.88 (CI 0.69-1.13), but when the trials with a dose of greater than 700 IU (17.5 micrograms) were examined the risk was lower at 0.74 (CI 0.61-0.88)
- 4.6 The Committee reviewed the DIPART study (BMJ 2010; 340: b5463), an individual patient meta-analysis of trials of calcium and vitamin D in fracture prevention. Calcium and vitamin D gave a hazard ratio for any fracture of 0.92 (CI 0.86 to 0.99) but no effect of vitamin D alone. Members noted that the doses of vitamin D were between 10-20 micrograms (400-800 IU) a day and calcium of 1,000mg a day. The absolute risk reduction for any fracture for the combination of calcium and vitamin D was 0.5% for three years, number needed to treat for three years of 200 and for one year of 600.
- 4.7 The Committee considered that vitamin D alone was less likely to have an effect but vitamin D 400 – 800 IU daily in combination with calcium > 1,200 mg may be beneficial. Members considered that there would be no difference in outcome between the individual and combination products, but acknowledged there may be some compliance benefits but these were not proven. Members noted that there was a potential risk of hypercalcaemia.
- 4.8 The Committee considered that there was unlikely to be any therapeutic difference between the daily dosing of vitamin D and monthly dosing. Members noted that the 1,000 IU a day for vitamin D individually was higher than that in therapeutic trials, but that the monthly dose was also higher than that in trials.
- 4.9 The Committee considered that it was unlikely that an individual with severe vitamin D deficiency would become hypercalcaemic due to a loading dose of 500,000 IU over 10 days. Members noted a citation in the Working group of the Australian and New Zealand Bone and Mineral Society (MJA 2005; 182:281-285) that used 10,000 IU daily for 90 days (900,000 IU) without evidence of harm.
- 4.10 The Committee considered there was no unmet clinical need in this therapeutic group, but that the proposed formulation may be beneficial for some patients due to palatability.

5 Osteoporosis Treatments

- 5.1 The Committee noted that PHARMAC staff were seeking advice from PTAC in relation to several currently unfunded treatments for osteoporosis: risedronate, zoledronic acid and raloxifene as first-line or second-line treatments and teriparatide and strontium ranelate as second-line treatments only. The Committee noted that its advice would concentrate on the use of these treatments in postmenopausal osteoporosis (i.e., not glucocorticosteroid-induced osteoporosis or Paget's disease).
- 5.2 The Committee considered that of the funded treatments, alendronate was currently the first-line treatment of choice for osteoporosis. The Committee noted that usage of etidronate had declined over the past few years and considered that the available evidence suggested that it has only limited efficacy in osteoporosis.
- 5.3 The Committee considered that there was currently an unmet clinical need for a treatment for osteoporosis in patients who could not tolerate alendronate. The Committee considered that it would be useful to have a funded treatment with a different mechanism of action to bisphosphonates for patients who could not take bisphosphonates.
- 5.4 The Committee noted that all patients eligible for treatment with any of the five agents would require supplementation with calcium and vitamin D, and that funding a second-line treatment could increase prescribing of vitamin D, as patients would no longer be receiving vitamin D supplementation in the combination alendronate with cholecalciferol product.
- 5.5 The Committee noted that there did not appear to be any clinical trials comparing the treatments under discussion with each other, and indirect comparisons were difficult because of the different patient populations and treatment regimens used in the published trials of these treatments. In general, however, of the five unfunded treatments the Committee placed the greatest priority on funding zoledronic acid as a second-line treatment for osteoporosis in patients intolerant to alendronate, taking into account its efficacy, cost and tolerability profile. The recommendations for all other treatments were largely based on their cost relative to their benefits compared with currently funded treatments and alternative proposals for unfunded treatments. Members expressed a preference for strontium ranelate over raloxifene as a second-line treatment in patients intolerant to bisphosphonates, and considered that the superior efficacy of teriparatide for the same indication did not justify its cost (which is currently more than [withheld under s9(2)(b)(ii), s9(2)(ba)(i) and/or s9(2)(j) of the OIA] the cost of alendronate).

Zoledronic Acid

Application

- 5.6 The Committee noted that it had previously reviewed an Application from Novartis for zoledronic acid (Aclasta) in 2008, and had recommended it be funded for Paget's disease with a high priority and as a second-line treatment for osteoporosis in patients intolerant to oral bisphosphonate therapy with a medium-high priority.

- 5.7 The Committee noted that in 2009 PHARMAC staff had received a commercial proposal from Novartis for funding of zoledronic acid as a first-line treatment for osteoporosis, subject to the same Special Authority criteria that apply to alendronate. The Committee noted that the funding of zoledronic acid was considered by the Osteoporosis Subcommittee in March 2009, and that the Subcommittee recommended that zoledronic acid be funded as a first-line treatment for osteoporosis only if it was cost-neutral versus alendronate. The Subcommittee considered that it would not be unreasonable to limit funding of zoledronic acid to patients who were intolerant to oral bisphosphonate therapy if there was a substantial price differential, and agreed with PTAC's recommendation to list zoledronic acid as a second-line treatment with a medium-high priority.

Recommendation

- 5.8 The Committee **recommended** that zoledronic acid be funded as a second-line treatment for osteoporosis subject to Special Authority criteria restricting its use to patients intolerant to alendronate with a medium-high priority.
- 5.9 The Committee **recommended** that zoledronic acid be funded as a first-line treatment for osteoporosis subject to the same Special Authority criteria that apply to alendronate (underlying cause osteoporosis only) only if it was cost-neutral versus alendronate.
- 5.10 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

- 5.11 The Committee noted that there appeared to be no new clinical evidence of relevance since it had last considered the funding of zoledronic acid in 2008.
- 5.12 The Committee considered that the available evidence supported the efficacy of zoledronic acid compared with placebo in reducing vertebral and non-vertebral fractures, including hip fractures, in patients with osteoporosis (Black et al, N Engl J Med 2007; 356:1809-22).
- 5.13 The Committee considered that the results of clinical trials suggest that zoledronic acid 5 mg annual infusion provides similar efficacy to alendronate 70 mg weekly dosing in postmenopausal osteoporosis (McClung et al, Bone 2007;41:122-8; Saag et al, Bone 2007;40:1238-43).
- 5.14 The Committee considered that the available evidence does not support the use of zoledronic acid in patients with osteopenia only, or in patients with glucocorticosteroid-induced osteoporosis.
- 5.15 The Committee considered that intravenous (IV) zoledronic acid is associated with fewer gastrointestinal side effects than alendronate. The Committee noted that zoledronic acid was associated with post-injection side effects such as flu-like symptoms, which were generally transient and manageable. The Committee noted that there was a lack of

longer-term safety data for zoledronic acid and that for this reason it was only subsidised for three years in Australia.

- 5.16 The Committee considered that the patient population that would most benefit from zoledronic acid would be men and postmenopausal women with osteoporosis who are intolerant to alendronate, and that there was an unmet need for a second-line treatment for these patients. It was noted that another potential second-line treatment option, raloxifene, was not indicated for the treatment of osteoporosis in males.
- 5.17 The Committee considered that zoledronic acid would be associated with improved compliance compared with alendronate; however, the Committee considered that it may not be more convenient for patients, given that most patients would still need to take vitamin D and calcium supplementation. The Committee noted that zoledronic acid is marketed as a once-yearly intravenous infusion, but considered that there is no good data on the optimum interval between infusions or the optimum treatment duration.
- 5.18 The Committee noted that zoledronic acid had gained less than 10% of the osteoporosis treatment market share after two years in international markets, even in markets with no funding restrictions. The Committee considered that the low uptake internationally may be due to patients still needing to take vitamin D and calcium supplementation (therefore reducing the convenience advantage of zoledronic acid) and also the aversion many people have to needles/injections (especially in the elderly population). The Committee considered that it would be reasonable to assume that zoledronic acid would gain a similar market share in New Zealand, largely at the expense of alendronate prescribing. The Committee noted that zoledronic acid was currently funded within some hospitals.
- 5.19 The Committee noted that use of zoledronic acid in general practice was generally associated with approximately 30–45 minutes of clinic time (involving both the GP and a nurse), including checking the patients' renal function, insertion of an IV cannula, the minimum 15-minute infusion time and monitoring the patient during the infusion. The Committee considered that administering zoledronic acid was likely to be reasonably straight-forward, however it is likely that there would be varied uptake in GP clinics and there would be a direct cost to the patient.
- 5.20 The Committee considered that there was no clinical reason why any restrictions should be placed on the use of zoledronic acid; however, it would be reasonable to apply Special Authority criteria similar to alendronate for first-line use in osteoporosis or for second-line use in patients intolerant to alendronate, depending on price.

Risedronate

Application

- 5.21 The Committee noted that it had previously reviewed an Application from Sanofi-Aventis for risedronate (Actonel) in 2001 and had recommended that risedronate be funded subject to the same criteria as alendronate with a low to moderate priority for osteoporosis and a moderate priority for Paget's disease.

- 5.22 The Committee noted that in 2009 the Osteoporosis Subcommittee suggested that PHARMAC staff investigate pricing of risedronate, as it could be less expensive than alendronate and was generally considered to provide similar efficacy.

Recommendation

- 5.23 The Committee considered that there was no clinical reason not to fund risedronate, and **recommended** that it be funded for first-line use in osteoporosis – either subject to Special Authority restrictions similar to alendronate or as an open listing as an alternative to etidronate, depending on price – only if it was cost-neutral or a saving to the Pharmaceutical Schedule.
- 5.24 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

- 5.25 The Committee considered that the available evidence supported the efficacy of risedronate compared with placebo in reducing vertebral fractures and hip fractures in patients with osteoporosis (Harris et al, JAMA 1999;282:1344-1352; Reginster et al, Osteoporos Int 2000;11:83-91; McClung et al, N Engl J Med 2001;344:333-40). The Committee noted that the efficacy of risedronate versus placebo appeared to be greater in older patients ≥ 80 years of age (McClung et al, N Engl J Med 2001;344:333-40).
- 5.26 The Committee considered that current evidence indicates that risedronate 5 mg daily or 35 mg weekly and alendronate 70 mg weekly have similar efficacy (with some evidence indicating alendronate may be more effective in terms of improvements in bone mineral density and other biochemical markers) and a similar side-effect profile (Hosking et al, Curr Med Res Opin 2003;19:383-94; Bonnicksen et al, J Clin Endocrinol Metab 2006;91:2631-7; Cadarette et al, Osteoporos Int 2009;20:1735-47).
- 5.27 The Committee considered that risedronate would not provide any particular clinical or compliance advantage over alendronate; therefore, there would be no justification for funding risedronate if it was more expensive than alendronate.
- 5.28 The Committee considered that there was no clinical reason why any restrictions should be placed on the use of risedronate and any such restrictions would be on the basis of price.
- 5.29 The Committee considered that if risedronate was listed without restrictions it would replace the use of etidronate and would reduce the use of alendronate, although it was difficult to estimate the likely extent of reduction in alendronate use.

Raloxifene

Application

- 5.30 The Committee noted that it had previously reviewed an Application from Eli Lilly for raloxifene (Evista) on several occasions between 2000 and 2006 and had recommended that raloxifene be funded as a second-line treatment for osteoporosis in patients intolerant to bisphosphonates with a high priority.
- 5.31 The Committee noted that in 2009 PHARMAC staff had sought the Osteoporosis Subcommittee's view on the need for funding of raloxifene in the context of other osteoporosis treatments (both funded treatments and those under consideration for funding). In general the Subcommittee favoured the use of raloxifene as a second-line treatment following oral bisphosphonate therapy. The Subcommittee considered that zoledronic acid provided better efficacy than raloxifene in this setting and would be the preferred option if both were available.

Recommendation

- 5.32 The Committee **recommended** that raloxifene be funded as a second-line treatment for osteoporosis subject to Special Authority criteria restricting its use to patients intolerant to alendronate with a low priority.
- 5.33 The Committee **recommended** that raloxifene be funded as a first-line treatment for osteoporosis subject to the same Special Authority criteria that apply to alendronate (underlying cause osteoporosis only) only if it was cost-neutral or cost-savings versus alendronate.
- 5.34 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

- 5.35 The Committee considered that the results of clinical trials supported the efficacy of raloxifene 60 mg per day compared with placebo in reducing vertebral fractures in patients with osteoporosis (Ettinger et al, JAMA 1999;282:637-45; Delmas et al, J Clin Endocrinol Metab 2002;87:3609-17; Siris et al, J Bone Miner Res 2005;20:1514-24); however, the Committee considered that the available evidence suggested that raloxifene has very little effect on non-vertebral fractures including hip fractures. The Committee noted that there did not appear to be any evidence supporting the use of raloxifene in glucocorticosteroid-induced osteoporosis.
- 5.36 The Committee noted that the side effect profile of raloxifene differed from that of bisphosphonates: the most serious adverse effect associated with raloxifene is an approximate three-fold increase in risk of venous thromboembolism (VTE); other side effects include hormonal effects such as hot flushes. The Committee considered that the cost of diagnosing and treating VTE should be taken into account in any cost-utility analysis for raloxifene.
- 5.37 The Committee noted that raloxifene is associated with a reduction in the risk of invasive breast cancer in postmenopausal women with osteoporosis (Cauley et al, Breast Cancer

Res Treat 2001;65:125-34) and in postmenopausal women at increased risk of invasive breast cancer (Vogel et al, JAMA 2006;295:2727-41). The Committee considered that inclusion of reduction in invasive breast cancer risk in any cost-utility analysis of raloxifene for osteoporosis would require consideration of alternative treatments for reduction of invasive breast cancer risk such as tamoxifen and prophylactic mastectomy. The Committee also considered that any benefit in the reduction in risk of invasive breast cancer needs to be balanced against the increase in risk of VTE.

- 5.38 The Committee considered that there was no clear evidence for improved compliance with raloxifene compared with alendronate, although in practice it might be associated with improved compliance, because unlike alendronate, it can be taken at any time of day without regard to meals and does not require patients to stand up for 30 minutes after ingestion.
- 5.39 The Committee noted that raloxifene was more expensive than alendronate and appeared to provide less benefit in terms of reduction of non-vertebral fractures.
- 5.40 The Committee considered that the groups of patients who would most benefit from raloxifene would be patients with osteoporosis intolerant to bisphosphonates and patients with osteoporosis at high risk of invasive breast cancer for whom other standard treatments for prevention of invasive breast cancer were not an option.
- 5.41 The Committee considered that there was no clinical reason why any restrictions should be placed on the use of raloxifene and any such restrictions would be on the basis of price.
- 5.42 The Committee considered that, if funded, raloxifene was unlikely to replace bisphosphonate use to any great extent.

Strontium Ranelate

Application

- 5.43 The Committee noted that Servier, the supplier of strontium ranelate (Protos), did not intend to make a funding Application and that PHARMAC staff had sourced information for the Committee's review following a recommendation from the Osteoporosis Subcommittee to investigate this agent. The Committee noted that Servier had provided the Australian Pharmaceutical Benefits Advisory Committee (PBAC) public summary documents relating to its application for Australian funding to assist the Committee's review.

Recommendation

- 5.44 The Committee **recommended** that strontium ranelate be funded as a second-line treatment for osteoporosis subject to Special Authority criteria restricting its use to patients intolerant to all funded bisphosphonates with a low priority.
- 5.45 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

- 5.46 The Committee noted that strontium ranelate is made up of two atoms of stable strontium and one molecule of ranelic acid. It is registered for the treatment of postmenopausal osteoporosis; the recommended dose is one 2 g sachet once daily, taken at night before bed with a minimum of 30 ml water. The Committee noted that the bioavailability of strontium is reduced if it is taken with food or calcium.
- 5.47 The Committee reviewed two key clinical trials investigating the efficacy and safety of strontium ranelate. The first (SOTI: Meunier et al, N Engl J Med 2004;350:459-68) was a randomised clinical trial of 1,649 postmenopausal women with documented osteoporosis and at least one vertebral fracture who were assigned to receive either strontium ranelate or placebo for three years. The endpoints were new vertebral fractures and bone mineral density (BMD). A number of patients did not receive the randomised treatment and a number were excluded from the analysis because they did not have baseline x-rays; the final intention-to-treat population was 719 patients in the strontium ranelate group and 723 in the placebo group. A total of 628 patients in the strontium ranelate group and 632 patients in the placebo group completed the study. Patients were well matched for age (mean age in both groups was 69 years) and T-Scores (-2.4 in both groups). At three years, new vertebral fractures had occurred in 20.9% of patients taking strontium ranelate and 32.8% in the placebo group. In patients taking strontium ranelate, BMD increased at the lumbar spine, the femoral neck and at the hip, compared with a reduction in BMD in the placebo group. Compliance was estimated at 85% in the placebo group and 83% in the strontium ranelate group. Adverse events associated with strontium ranelate included diarrhoea and minor changes in serum calcium, phosphorous, parathyroid hormone and creatine kinase. Changes in biochemical markers tended to occur early and usually self-corrected.
- 5.48 The second study (TROPOS: Reginster et al, J Clin Endocrinol Metab 2005;90:2816-22) involving 5,091 randomised patients was similar to the SOTI study but with the intention of investigating the effect of strontium ranelate on reducing the risk of non-vertebral fractures in postmenopausal women. Subjects were those with a T-score <-2.5 (femoral neck) and older than 74 years or 70-74 years of age with one additional risk factor. Patients received strontium ranelate or placebo for three years. A total of 159 patients were excluded from the study prior to starting treatment so that the final intention-to-treat population was 2,749 patients in the strontium ranelate group and 2,453 in the placebo group. A total of 1,687 patients in the strontium ranelate group and 1,633 patients in the placebo group completed the study. The mean age of patients in both groups was 77 years. Overall, the incidence of >1 osteoporosis-related fracture was 11.2% in the strontium ranelate group and 12.9% in the placebo group (absolute risk reduction, ARR, 1.7%). The relative risk (RR) was reduced by 16% for all non-vertebral fractures (P = 0.04) in strontium ranelate-treated patients in comparison with the placebo group. In patients with a high risk of hip fracture (age ≥ 74 yr and femoral neck BMD T-score ≤ -3) (1,977 patients), the RR reduction for hip fracture was 36% (P = 0.046). BMD increased in the strontium ranelate group at the femoral neck and at the hip, compared with a reduction in BMD in the placebo group. Adverse events associated with strontium

ranelate were nausea, diarrhoea, headache and dermatitis and eczema. There was also a trend towards an increased risk of VTE.

- 5.49 The Committee considered that the results of these studies supported a benefit of strontium ranelate over placebo in reducing the risk of vertebral fractures, but noted the small ARR with non-vertebral fractures.
- 5.50 The Committee noted that although there were no studies directly comparing strontium with raloxifene or alendronate, results from the clinical trials of each agent suggested that strontium may be more effective than raloxifene, but less effective than alendronate.
- 5.51 The Committee noted results of a recent study (Middleton et al, J Bone Miner Res 2010;25:455-62) showed that when strontium ranelate is given after bisphosphonates its effects on BMD were almost nullified, except for effects on the spine (although the improvements in spine BMD were lower than in patients not previously treated with bisphosphonates), and that this effect lasted for six months. The Committee considered that this was of concern as it implied that patients would need to take strontium ranelate for at least a year following cessation of bisphosphonates (possibly longer in the case of prior zoledronic acid treatment) before effects would be seen.
- 5.52 The Committee considered that the longer-term effects of strontium ranelate were unknown, noting that there was a lack of long-term safety data.
- 5.53 The Committee considered that the patients who would most benefit from strontium ranelate would be patients with osteoporosis who were intolerant to bisphosphonates.

Teriparatide

Application

- 5.54 The Committee noted that PHARMAC staff had sourced information on teriparatide (Forteo) for the Committee's review following a recommendation from the Osteoporosis Subcommittee to investigate this agent, and that Eli Lilly had provided an amended version of its Australian PBAC funding application to assist the Committee's review.

Recommendation

- 5.55 The Committee **recommended** that teriparatide be funded as a last-line treatment for osteoporosis subject to Special Authority criteria restricting its use to patients with evidence of ongoing fractures and/or T-scores < -3 after trying all funded osteoporosis treatments with a low priority and only if a significant price reduction could be achieved.
- 5.56 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

- 5.57 The Committee noted that teriparatide is a recombinant fragment of human parathyroid hormone and is an anabolic agent that stimulates new bone formation. It is indicated in New Zealand for use in the treatment of postmenopausal osteoporosis and in glucocorticosteroid-induced osteoporosis. It is administered as a 20 µg once-daily subcutaneous injection.
- 5.58 The Committee reviewed the key randomised controlled trial (Neer et al, N Engl J Med 2001;344:1434-41) in which 1,326 postmenopausal women with osteoporosis were assigned to receive teriparatide 20 µg daily, teriparatide 40 µg daily or placebo. Patients were intended to receive treatment for two years but the study was stopped early by the supplier because of findings that teriparatide increased the incidence of osteosarcoma in rats; as a result, the median duration of observation in the trial was 21 months. New vertebral fractures occurred in 14% of patients in the placebo group and in 5% and 4% of patients taking 20 µg and 40 µg teriparatide respectively; new non-vertebral fractures were seen in 6% of the placebo group and in 3% of patients in both teriparatide groups. Compared with placebo, teriparatide 20 µg increased overall BMD at most sites and both doses increased overall total-body BMD. Teriparatide was also found to reduce back pain and was associated with less height loss than placebo. Adverse events included nausea, dizziness and leg cramps.
- 5.59 The Committee noted that there was a lack of long-term safety data for teriparatide, which was reflected in the recommendation that patients receive a maximum of 18 months' treatment, although members noted that the supplier intended to apply for an extension of the maximum treatment time.
- 5.60 The Committee noted that the effectiveness of teriparatide is not reduced following bisphosphonate treatment. The Committee noted that the supplier had told PHARMAC staff that the benefits of teriparatide are only maintained if patients went on to bisphosphonate treatment after completion of teriparatide treatment.
- 5.61 The Committee considered that patients most likely to benefit from teriparatide would be patients with osteoporosis who do not respond adequately to bisphosphonate treatment. The Committee considered that it would be difficult to identify, and target treatment to these patients, but that an approximate measure would be evidence of ongoing fractures and those with T-scores < -3 despite ongoing treatment with bisphosphonates.
- 5.62 The Committee noted that teriparatide was significantly more expensive than all the other treatments under consideration and would, therefore, likely be dominated by the other options in any cost-utility analysis of teriparatide as a second-line treatment for osteoporosis.
- 5.63 The Committee considered that even if teriparatide was restricted to last-line use following failure of all other funded treatments there would be an unacceptably high financial risk at the current proposed price, because of the risk of extensive use in rest homes where patients would likely have tried all other options.

6 Golimumab (Simponi) for second-line TNF-inhibitor treatment of rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis

Application

- 6.1 The Committee reviewed an Application from Merck Sharp & Dohme for the listing of golimumab (Simponi) on the Pharmaceutical Schedule as a second-line tumour necrosis factor (TNF) inhibitor treatment for rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis following adalimumab failure.

Recommendation

- 6.2 The Committee **recommended** that golimumab be listed in the Pharmaceutical Schedule subject to Special Authority criteria restricting its use to patients with severe rheumatoid arthritis following failure of adalimumab treatment with a low priority.
- 6.3 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, (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.*
- 6.4 The Committee also **recommended** that the Application for the listing of golimumab on the Pharmaceutical Schedule as a second-line TNF-inhibitor treatment for psoriatic arthritis and ankylosing spondylitis following adalimumab failure be declined, on the basis of lack of evidence of its use as a second-line TNF-inhibitor treatment in these indications.

Discussion

General discussion

- 6.5 The Committee noted that the TNF inhibitor adalimumab was currently the only community funded biologic treatment, subject to Special Authority criteria restricting its use to "last-line" treatment of patients with severe rheumatoid arthritis, psoriatic arthritis, chronic plaque psoriasis, Crohn's disease and ankylosing spondylitis.
- 6.6 The Committee noted there were no biologic treatments currently funded in the community for patients who did not receive benefit from adalimumab, although some hospital-administered biologic treatments could be used following adalimumab failure, such as infliximab (for all indications) and rituximab (for rheumatoid arthritis only). The Committee considered that currently the community treatments most likely used by patients who did not receive adequate benefit from adalimumab would be disease-modifying antirheumatic drugs (DMARDs) and non-steroidal anti-inflammatory drugs (NSAIDs), and sometimes patients would continue on adalimumab despite not receiving a good response – with specific treatments depending on the indication.

- 6.7 The Committee noted that golimumab, like adalimumab, is a human monoclonal antibody to TNF alpha.
- 6.8 The Committee noted that golimumab, in combination with methotrexate, is indicated for the treatment of active rheumatoid arthritis in adult patients when the response to DMARDs therapy has been inadequate and in the treatment of active rheumatoid arthritis in adult patients not previously treated with methotrexate. Golimumab, alone or in combination with methotrexate, is also indicated for the treatment of active psoriatic arthritis in adult patients when the response to previous DMARD therapy has been inadequate, and golimumab monotherapy is indicated for the treatment of active ankylosing spondylitis in adult patients. The recommended dose of golimumab in all registered indications is 50 mg given as a subcutaneous injection every four weeks. The Committee noted that adalimumab needs to be administered fortnightly, and considered that the monthly treatment regimen with golimumab would likely result in fewer injection-site reactions.

Rheumatoid arthritis

- 6.9 The Committee noted that clinical studies suggest that 35%–50% of patients do not achieve an adequate response to treatment with a first TNF inhibitor (defined as at achieving at least an American College of Rheumatology (ACR) 20 response at week 12). The Committee considered that the literature supported an approximate 61% response rate for patients taking adalimumab as their first TNF inhibitor.
- 6.10 The Committee noted the results of two randomised, placebo-controlled trials of golimumab as a first-line TNF inhibitor in patients with rheumatoid arthritis who were methotrexate-naïve (“Go-Before”; Emery et al, *Arthritis Rheum* 2009;60:2272-83) or who had active arthritis despite ongoing treatment with methotrexate (“Go-Forward”; Keystone et al, *Annal Rheum Dis* 2009;68:789-796) which showed that golimumab 50 mg or 100 mg every four weeks, in combination with methotrexate, was more effective than methotrexate alone for improving signs and symptoms of arthritis. The studies found little difference in outcome between patients taking golimumab 50 mg and patients taking golimumab 100 mg, and patients taking golimumab in combination with methotrexate had better outcomes than patients taking golimumab alone. In Go-After there was no significant difference in response between the golimumab and placebo arms in patients not taking concomitant methotrexate. These results suggest that golimumab should be given in combination with methotrexate in patients with rheumatoid arthritis to achieve the greatest efficacy.
- 6.11 The Committee noted that the Application included indirect comparisons between placebo-controlled studies of golimumab and placebo-controlled studies of adalimumab and etanercept in rheumatoid arthritis. The Committee noted that these studies were not conducted in patients who had received prior TNF-inhibitor treatment and patients enrolled in the studies were not entirely reflective of patients who would meet the adalimumab Special Authority criteria in New Zealand. The Committee noted that the supplier’s indirect comparison analysis concludes that golimumab is non-inferior to etanercept and adalimumab. The Committee considered that there were aspects of the analysis which suggested that this conclusion should be treated with caution, for example the endpoints in the golimumab studies were measured at 14 weeks, compared with 12 weeks in the comparator studies, which may have advantaged the golimumab outcomes, and selection of some of the outcome measures appeared somewhat

arbitrary. Overall, however, the Committee considered that there was no particular reason to suggest that there would be any great difference in outcomes between these three TNF inhibitors (adalimumab, etanercept and golimumab) as a first-line TNF inhibitor treatment, although the evidence for non-inferiority was poor.

- 6.12 The Committee reviewed a randomised controlled trial (“Go-After”; Smolen et al, Lancet 2009;374:210-221) in which patients with active rheumatoid arthritis who had received previous treatment with TNF inhibitor(s) were assigned to golimumab 50 mg (n=153), golimumab 100 mg (n=153) or placebo (n=155) every four weeks for 24 weeks. More than 95% of patients had been treated for four weeks or more with at least one TNF-inhibitor; 34% of patients had been treated with more than one TNF-inhibitor. The main reasons for stopping previous TNF-inhibitor treatments were lack of efficacy and intolerance. At week 14, 35% of golimumab 50 mg patients and 38% of golimumab 100 mg patients achieved the primary endpoint of ACR20, compared with 18% of patients in the placebo group ($p < 0.001$). At week 16, patients who had not achieved a minimum of ACR20 were given rescue therapy and changed treatment from placebo to golimumab 50 mg or from golimumab 50 mg to golimumab 100 mg. At week 24, more patients in the golimumab groups achieved ACR20 than in the placebo groups. Responses in patients taking golimumab 50 mg were not statistically significantly different from those in patients taking golimumab 100 mg at both 14 weeks and 24 weeks. Patients receiving golimumab (50 mg or 100 mg) and concomitant methotrexate had an ACR20 response rate of 47%, compared with an 18% ACR20 response rate in patients taking placebo plus methotrexate and a 29% ACR20 response rate in patients taking golimumab alone at week 16. Response to golimumab was greater in patients who had taken one or two previous TNF inhibitors compared to the small subgroup of patients who had taken three previous TNF inhibitors (in which there was no statistically significant difference in response between golimumab and placebo). Golimumab was generally well tolerated in this study with no unexpected adverse events reported.
- 6.13 The Committee considered that, based on the results of the Go-After study, there was good evidence to suggest that golimumab 50 mg every four weeks would produce a response in approximately 35% of patients (approximately 17% more patients than placebo) in patients with rheumatoid arthritis who had received prior treatment with adalimumab or etanercept, and that this benefit could be greater if golimumab is taken with methotrexate (as per its registered indication).
- 6.14 The Committee noted that there were no studies comparing golimumab with any other potential second-line biologic treatment (eg other TNF inhibitors or rituximab) in patients with rheumatoid arthritis who have received inadequate benefit from adalimumab or any other first-line biologic treatment.
- 6.15 The Committee considered that, if funded as a second-line TNF inhibitor, golimumab would be unlikely to reduce much of the use of adalimumab, except for a small proportion of patients who may be continuing to take adalimumab despite significant side effects or inadequate response. However, the Committee considered that funding golimumab as a second-line TNF inhibitor in the community could reduce the use of rituximab and infliximab within hospitals.
- 6.16 The Committee considered that any restrictions placed on the use of golimumab would be to contain cost (as with adalimumab).

- 6.17 The Committee considered that, taking into account the proposed pricing and the relatively low response rate from second-line TNF-inhibitor treatment, golimumab is unlikely to be cost-effective and agreed with PHARMAC staff's estimate that the cost per quality adjusted life year (QALY) gained would likely be greater than \$100,000.
- 6.18 The Committee noted that it had considered information on last-line treatment for rheumatoid arthritis (post adalimumab) at the February PTAC meeting. The Committee noted that rituximab is likely to be more cost-effective compared with TNF inhibitors because of its lower price and similar efficacy and, therefore, considered that it was the preferred option for last-line treatment of rheumatoid arthritis.

Psoriatic arthritis and ankylosing spondylitis

- 6.19 The Committee noted that clinical trial results suggest that approximately 30%–50% of patients with psoriatic arthritis and 40%–50% of patients with ankylosing spondylitis do not respond adequately to first-line treatment with a TNF inhibitor.
- 6.20 The Committee noted that the results of placebo-controlled studies in psoriatic arthritis ("Go-Reveal"; Kavanaugh et al, *Arthritis Rheum* 2009;60:976-986) and ankylosing spondylitis ("Go-Raise"; for which the supplier provided the study report but no publication) supported the efficacy of golimumab compared with placebo as a first-line TNF inhibitor in these indications. The Committee noted that response rates did not appear to be significantly affected by concomitant methotrexate. The Committee also noted that golimumab was well tolerated, with few patients in the trials discontinuing treatment due to toxicity.
- 6.21 The Committee noted that the supplier had provided indirect comparisons of golimumab and other TNF inhibitors as first-line treatments for these indications which conclude that golimumab is non-inferior to etanercept and adalimumab for psoriatic arthritis and that golimumab is non-inferior to etanercept, infliximab and adalimumab for ankylosing spondylitis. Members raised similar concerns with these analyses as for the supplier's indirect comparison analysis in rheumatoid arthritis. The Committee considered that, overall, there was no evidence indicating a significant difference in efficacy between the TNF inhibitors as first-line treatments in these indications, although there was also no good evidence that golimumab is non-inferior.
- 6.22 The Committee noted that the supplier had not provided any evidence in support of golimumab as a second-line TNF-inhibitor treatment for psoriatic arthritis or ankylosing spondylitis (ie, in the indications for which funding was being sought).

7 Darunavir 400 mg tablets for treatment-naïve and early treatment experienced HIV

Application

- 7.1 The Committee reviewed an application from Janssen-Cilag for the funding of darunavir 400 mg (Prezista) for the treatment of HIV in the treatment naïve and early treatment experienced patients.

Recommendation

- 7.2 The Committee **recommended** that darunavir 400 mg be listed in the Pharmaceutical Schedule under the same restriction that currently applies to all oral antiretrovirals for treatment naïve and early treatment experienced patients if cost neutral to atazanavir.
- 7.3 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; and (vii) The direct cost to health service users*

Discussion

- 7.4 The Committee reviewed the ARTEMIS study at 48 weeks (Ortiz et al, AIDS, 2008; 22:1389-1397) and 96 weeks (Mills et al, AIDS, 2009; 23:1679-1688). Members noted that this was a randomised, controlled non-inferiority study that compared darunavir/ritonavir 800/100 mg once daily to lopinavir/ritonavir 800/200 mg once daily in combinations with fixed dose tenofovir and emtricitabine. Members noted that the treatment group was naïve with a HIV-1 RNA of at least 5,000 copies/ml. Members noted that 689 treatment naïve patients were randomised 343 in the darunavir arm and 346 in the lopinavir arm. Members noted that at 96 weeks 79% of the darunavir arm had an undetectable viral load versus 71% in the lopinavir arm.
- 7.5 The Committee noted that darunavir had an established safety profile due to the use of the 300mg strength in the resistance setting (usual dosage 600 mg twice a day). Members noted that the unpublished ODIN study suggested no difference in the side-effect profile between the 1200 mg and 800 mg dosing regimens.
- 7.6 Members noted that darunavir was a second generation protease inhibitor (PI) which had a different resistance profile than older PIs. Members noted that darunavir in the resistance setting (300 mg strength) had greater activity than currently funded PIs with a greater threshold for resistance. Members noted that the 400 mg tablet had the same activity as other PIs in the naïve patient group.
- 7.7 The Committee considered that darunavir 400 mg would be used in combination with Nucleosides Reverse Transcriptase Inhibitors (NRTIs) for naïve patients, and in other combinations in the multiclass resistance setting.

- 7.8 The Committee noted that the DHHS guidelines December 2009 recommended darunavir/ritonavir as one of four preferred first line antiretroviral regimens alongside efavirenz, raltegravir and atazanavir/ritonavir. Members considered that PI based regimens are generally associated with more gastro-intestinal symptoms and lipid abnormalities compared with Non-Nucleosides Reverse Transcriptase Inhibitors (NNRTI) based regimens. Members also noted that the British HIV guidelines currently recommend NNRTI based regimens, with boosted PI based regimens only recommended as first-line therapy in naïve patients when patients were deemed unsuitable for NNRTIs. The Committee considered that darunavir 400 mg would replace atazanavir in the treatment naïve group but would not have a major impact on the Non-Nucleoside Reverse Transcriptase Inhibitors at this time.
- 7.9 Members considered that the 800 mg dosing regimen may be used in the treatment experienced patient group in the future but there was no data to currently support this indication.

8 Metronidazole vaginal gel 0.75% w/w

Application

- 8.1 The Committee reviewed an application from Douglas Pharmaceuticals for metronidazole (Zidoval) vaginal gel 0.75% w/w for the treatment of bacterial vaginosis.

Recommendation

- 8.2 The Committee **recommended** that Zidoval be listed in the Pharmaceutical Schedule only if cost neutral to the health sector.
- 8.3 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; and (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 reviewed Hansen et al study (J. Reproductive Medicine, 2000; 45:889-896) a small non-powered study comparing 500 mg oral metronidazole twice daily with vaginal metronidazole gel twice daily. Members noted that each treatment had similar effectiveness in terms of clinical cure outcomes (71% at five weeks).
- 8.5 The Committee reviewed the Ferris et al study (J. Family Practise, 1995; 41:443-449), a small randomised trial with patients receiving either 500 mg oral metronidazole twice daily for seven days, 5g vaginal metronidazole twice daily for seven days or 5g clindamycin vaginal cream once daily for seven days. There was no statistical difference between the cure rates.

- 8.6 The Committee noted that bacterial vaginosis (BV) is a common condition of the female genital tract with 29% of women of child bearing age having evidence of BV. Members noted that the incidence rate may be higher than suggested by the supplier. Members noted that there were several funded treatment options for BV, namely oral metronidazole or ornidazole and further noted that oral clindamycin was indicated for BV but not funded without Specialist recommendation. Members noted that recurrence of BV following treatment was common, and further noted that BV spontaneously resolved in approximately one third to one half of all cases.
- 8.7 The Committee considered that metronidazole vaginal gel may be beneficial to those who require oral metronidazole in repeated courses but are significantly troubled by adverse gastrointestinal side-effects and require a different therapy. Members also noted that patients with peripheral neuropathy or those using warfarin may benefit from Zidoval. Members considered that metronidazole was no more effective than oral metronidazole but had a different side effect profile.
- 8.8 The Committee noted that a different therapy would also be beneficial such as clindamycin vaginal cream. Members considered there was no clinical reason not to list Zidoval.

9 Rituxumab (Mabthera) for chronic lymphocytic leukaemia

Application

- 9.1 The Committee considered an application from Roche for the funding of rituximab (Mabthera) for chronic lymphocytic leukaemia (CLL).

Recommendation

- 9.2 The Committee **recommended** that rituximab be funded for first-line treatment of CLL with a medium priority.
- 9.3 The Committee **recommended** that rituximab be funded for the treatment of rituximab-naïve patients who have relapsed CLL disease with a low priority.
- 9.4 The Committee **recommended** that the application to fund rituximab in patients who have relapsed CLL disease following previous treatment with rituximab be declined.
- 9.5 The Committee **recommended** that the application be referred to the Cancer Treatments Subcommittee for consideration, and to draft appropriate Special Authority criteria.
- 9.6 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,* (vi) *The budgetary impact (in terms of the*

pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule and (viii) The Government's priorities for health funding, as set out in any objectives notified by the Crown to PHARMAC, or in PHARMAC's Funding Agreement, or elsewhere.

Discussion

- 9.7 The Committee noted that while the application was for treatment of CLL, this also included small lymphocytic lymphoma (SLL), as these are considered the same disease but for location of cancer cells.
- 9.8 The Committee considered that the strength and quality of the evidence in support of this application to be of moderate quality, with the major trials being open-label.
- 9.9 Members noted that CLL / SLL is an incurable illness, although in a minority of cases there is potential for durable remission with bone marrow transplantation.
- 9.10 The Committee noted that currently first-line treatment of CLL in New Zealand consists of fludarabine and cyclophosphamide (FC) chemotherapy, but that most patients will relapse after primary treatment and then go on to other second-line regimens such as cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP). Members noted that fludarabine chemotherapy is highly myelotoxic.
- 9.11 Members noted that the application was for funding of rituximab for first line treatment of patients with CLL, as well patients with relapsed disease, both for rituximab-naïve patients and in rituximab-experienced patients.
- 9.12 The Committee reviewed evidence from the CLL-8 study, a Phase 3 randomised, open-label study comparing six courses of either FC or rituximab plus FC (R-FC) as first-line treatment in patients with treatment-naïve CD20-positive CLL. Members noted that this was available in abstract form only (*Hallek Blood (ASH Annual Meeting Abstracts) 2008 2008 112: Abstract 325 and Hallek Blood (ASH Annual Meeting Abstracts) 2009 114: Abstract 535*). Members noted at median 37.7 months follow-up patients in the R-FC arm had a median 19 month progression-free survival advantage over patients in the FC arm (51.8 versus 32.8 months, HR 0.563, $p < 0.001$). Members further noted, that most patients in CLL-8 ($n=513$) were Binet B stage, and the treatment effect was best described in this group.
- 9.13 The Committee also reviewed evidence from the REACH study (*Robak et al. J Clin Oncol. 2010 Apr 1;28(10):1756-65*). This was an international, multicentre, randomised trial compared six cycles of rituximab plus FC (R-FC) with six cycles of FC alone in 552 patients with previously treated CLL. Members noted that this study indicated a median increase in progression-free survival of 10 months in the R-FC arm (30.6 versus 20.6 months, HR 0.65, $p < 0.001$) after a median follow-up time of 25 months. Members noted that the REACH study excluded (1) patients refractory to fludarabine, (2) patients who had previously received rituximab, and (3) patients who had received the combination FC. Members considered that the data for these groups were of poor strength and quality.
- 9.14 The Committee reviewed evidence from Wierda study (*J Clin Oncol. 2005 Jun 20;23(18):4070-8.*) which was an open-label prospective trial involving 177 previously

treated patients with CLL. All patients received R-FC as per trial protocol. The trial results indicated that the overall response rate to R-FC in patients who were previously considered to be refractory to fludarabine was around 20% lower than for other patients (58% versus 74-77%).

- 9.15 The Committee considered that the CLL-8 study indicated that treatment-naïve patients with Binet stage B CLL would benefit most from rituximab treatment but that treatment-naïve patients with Binet stages A and C would also benefit highly. The Committee considered that treatment of relapsed disease would provide a lesser benefit than first-line use.
- 9.16 Members considered that data from the CLL-8 study demonstrated that patients with chromosome 17p deletion CLL experienced no benefit from the addition of rituximab to FC, and funding of rituximab for CLL should exclude such patients.
- 9.17 The Committee considered that there was no evidence provided to support the use of rituximab in rituximab-experienced patients with relapsed CLL disease.

10 Sildenafil for pulmonary arterial hypertension, paediatric indications

Application

- 10.1 The Committee reviewed an application from [withheld under s9(2)(a) of the OIA] for access widening to sildenafil on the Pharmaceutical Schedule for the treatment of pulmonary arterial hypertension of the newborn.

Recommendation

- 10.2 The Committee recommended that sildenafil access be widened, following confirmation by the Pulmonary Arterial Hypertension Subcommittee, to include:

PAH secondary to chronic diaphragmatic hernia with a high priority;

PAH secondary to chronic lung disease with a high priority; and

PAH secondary to other lung disease with a high priority.

- 10.3 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;* (v) *The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services, and* (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

- 10.4 The Committee considered an application from [withheld under s9(2)(a) of the OIA] for sildenafil treatment in infants with pulmonary arterial hypertension (PAH) associated with chronic diaphragmatic hernia (CDH), chronic lung disease (CLD), and PAH associated with other lung disease.
- 10.5 Members noted that the eligibility criteria set out for PAH therapies excludes patients with PAH secondary to left heart disease or respiratory disease (groups two and three of the Venice Classification) but includes persistent pulmonary arterial hypertension of the newborn (PPHN) (part of group one of the Venice Classification; idiopathic PAH). Members noted that the Pulmonary Arterial Hypertension Panel (the Panel) had sought an application from [withheld under s9(2)(a) of the OIA] following a number of applications for the above indications which the Panel considered were secondary to respiratory disease rather than PPHN. Members noted that Panel members had sourced several papers in addition to those provided by the applicant.
- 10.6 The Committee noted that the Panel had received 11 applications for sildenafil for patients with the above indications in the past year.
- 10.7 The Committee noted that infants in the above categories are often sick, unstable from a cardiovascular perspective and require prolonged hospitalisation dependant upon respiratory support and monitoring. Hence, sildenafil is often initiated in the acute or semi-acute setting. Members noted that the applicant had suggested that the use of sildenafil in these patients reduces the duration of admissions and enables earlier discharge from hospital.
- 10.8 The Committee considered that the strength and quality of the evidence for the relevant patient groups was weak, comprising small mainly uncontrolled trials, case reports, reviews and expert opinions. The Committee also considered that the data is difficult to interpret. However, members considered that future randomised controlled trials would be unlikely due to unethical considerations and that while this is an evolving area there may never be strong data supporting treatment in these populations.
- 10.9 The Committee considered the evidence for the use of sildenafil in infants with PPHN. Members noted the papers included various aetiologies, including PPHN secondary to meconium aspiration syndrome (MAS), pneumonia, respiratory distress syndrome and sepsis (all PAH secondary to other lung diseases), as well as idiopathic PPHN. Members considered that the studies suggested benefit in oxygenation indices and mortality (Vargas-Origel et al, *Am J Perinatol*, 2010 Mar; 27(3):225-30; Steinhorn et al, *Journal of Pediatrics*, 2009; 155:841-7; Baquero et al, *Pediatrics*, 2006; 117:1077-83).
- 10.10 The Committee considered there was limited evidence for the use of sildenafil in patients with PAH secondary to CDH. Members noted that one study had shown significant clinical improvements but persistent abnormal pulmonary vascular resistance (PVR) +/- vascular reactivity (Keller et al, *Pediatr Crit Care Med*, 2006; 7(6):589-94) and another study, which had monitored echocardiography indices, blood pressure, and ventilation parameters over two weeks, had shown acute benefit (Noori et al, *Neonatology*, 2007; 91:92-100) . Members noted that one letter had shown an increase in mortality in the sildenafil group, although the author noted that those receiving sildenafil were more severely affected (Hunter et al, *Arch Dis Child Fetal Neonatal Ed*, 2009; 94:F467).

- 10.11 The Committee considered one paper looking at sildenafil in patients less than two years old with PAH secondary to CLD. Members noted that subjects in this study had a mix of aetiologies including bronchopulmonary dysplasia, CDH, PPHN and pulmonary hypoplasia. Members noted that this study showed haemodynamic improvements and weaning of inhaled nitric oxide and ventilation (Mourani et al, *J Pediatr*, 2009; 154:379-384).
- 10.12 Members noted that several papers had identified a risk of retinopathy in premature infants treated with sildenafil (Vargas-Origel et al, *Am J Perinatol*, 2010 Mar; 27(3):225-30 and Huddleston et al, *Pediatric Cardiol*, 2009 30:871-882).
- 10.13 The Committee considered that, due to the small doses required in infants, sildenafil treatment may be less expensive to the health sector overall than the high cost of additional inpatient treatment when sildenafil was not available.
- 10.14 The Committee noted that [withheld under s9(2)(a) of the OIA] had estimated that 20-30 patients per year in the above groups may require treatment, but that this estimate excluded patients with PAH secondary to other lung disorders such as MAS. Members noted, however, that PAH secondary to MAS was often an acute episode treated in hospital. Members considered that, if patients with PAH secondary to MAS were included, the number of patients that could require treatment may be up to 30-40/year. The Committee noted that the PAH Panel had seen 11 applications for these patients in the past year, so 30-40/year may prove to be an overestimate.
- 10.15 The Committee considered that expenditure would depend on patient numbers, dose and duration of treatment. Members noted that the doses used in trials were around 1.5 – 8 mg/kg/day. Members considered that the likely duration of treatment would be variable, with some neonates being successfully treated and weaned off sildenafil over three to six months and some requiring longer term treatment, potentially out to two years or more. Members considered that more information needed to be sought from hospital pharmacies on how sildenafil suspensions were made up, in particular what strength of tablets were used, to gain an accurate estimate of costs.
- 10.16 The Committee considered that cost offsets may be obtained through earlier discharge from hospital and potentially a reduction in the use of inhaled nitric oxide or extracorporeal membrane oxygenation.

11 Losartan for the treatment of patients with hypertension and gout

Application

- 11.1 The Committee reviewed an application from [withheld under s9(2)(a) of the OIA] ([withheld under s9(2)(a) of the OIA] Nga Kaitiaki o Te Puna Rongoa o Aotearoa) for the widening of access of losartan on the Pharmaceutical Schedule for the treatment of hypertension in patients with chronic hyperuricaemia and gout.

Recommendation

- 11.2 The Committee **recommended** that the Application for widening access to losartan for the treatment of hypertension in patients with chronic hyperuricaemia and gout be declined.

The Decision Criteria particularly relevant to this recommendation are: (iv) *The clinical benefits and risks of pharmaceuticals.*

Discussion

- 11.3 The Committee considered the application for access widening to losartan for hypertension in patients with chronic hyperuricaemia and gout.
- 11.4 The Committee noted that currently losartan is restricted to patients who are intolerant to ACE inhibitors or where the patient's blood pressure is not adequately controlled on maximum tolerated doses of an ACE inhibitor. The Committee noted that losartan is described in the European League Against Rheumatism, EULAR, guidelines (Zhang et al, *Ann Rheum Dis*, 2006; 65:1312-1324) as an appropriate antihypertensive agent to use in patients with gout and hypertension.
- 11.5 The Committee noted that gout is a significant public health problem in New Zealand especially in Maori and Pacific men, where incidence is much higher than Europeans, and that it is of greater concern than diseases such as rheumatoid arthritis.
- 11.6 The Committee noted that losartan reduces hypertension and that there was moderate evidence in the application that losartan reduces, or slows the rate of rise of uric acid levels. However, the Committee considered that the amount of the uric acid reduction was low at about 10% to 15%. The Committee considered that uric acid is a surrogate marker and that there is no evidence to indicate that losartan-induced uric acid lowering results in clinically significant reductions in cardiovascular risk, gout attacks, or the long-term clinical effects of gout. In addition, during the LIFE study (Høiegggen et al, *Kidney International*, 2004; 65:1041-1049) uric acid levels increased in patients on losartan but to a lesser degree.
- 11.7 The Committee considered that the argument for using losartan was a well constructed hypothesis and that a trial to determine if a losartan-induced reduction in uric acid results in reduced gout attacks would be desirable.
- 11.8 The Committee considered that recent evidence (Dalbeth and Gow, *NZMJ*, 2007; 120(1252) suggests that gout is poorly managed in New Zealand and that international guidelines seem to underestimate the appropriate dose of allopurinol and its adjustment according to renal function. The Committee considered that PHARMAC should consider revising any education materials, perhaps in association with the Rheumatology Association of New Zealand, and that consideration should also be given to a potential listing of benzbromarone as it has a different mechanism of action to allopurinol and may be a safer option in patients with renal failure.
- 11.9 The Committee noted that benzbromarone is not registered for use in New Zealand. The Committee considered that if it was not possible to source a supply of registered

benzbromarone, PHARMAC staff should investigate the new xanthine oxidase inhibitor febuxostat, which could be used in patients with mild-moderate renal impairment.

- 11.10 Kua whakamihi te Komiti ki a [withheld under s9(2)(a) of the OIA], mō tana whakamōhio i te take nei ki tā rātou whakaaro. Kua tūtohu te Komiti, hei maiohatia ētahi pānui anō nō Ngā Kaitiaki o Te Puna Rongoā o Aotearoa e pā ana ki te take nei. The Committee wanted to formally thank [withheld under s9(2)(a) of the OIA] for bringing this issue to the attention of PTAC, and noted that it would welcome further correspondence on the points raised above.