Cancer Treatments Subcommittee of PTAC (CaTSoP) meeting held 25 June 2009

(minutes for web publishing)

CaTSoP 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 CaTSoP meeting; under the Terms of Reference, only the relevant portions of minutes relating to CaTSoP discussions about applications that contain a recommendation are generally published.

CaTSoP 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.

The CaTSoP minute concerning trastuzumab has been included despite the fact that it does not contain a specific recommendation by CaTSoP, as it contains information that renders it desirable in the public interest to make the information available.

These Subcommittee minutes were reviewed by PTAC at its meeting on 12 &13 November 2009, the record of which is available on the PHARMAC website.

Contents

1 Deferasirox and deferiprone for chronic iron overload

1.1 The Subcommittee noted that PTAC (February 2009) had requested review by haematologists of the oral iron overload treatments deferiprone and deferasirox. The Subcommittee noted the relevant PTAC minutes (including those from April 2008 and February 2009); the potential treatment algorithm and Special Authority recommended by PTAC (February 2009); and the applications provided for deferasirox and deferiprone supplied by Novartis and Orphan Australia respectively.

1.2 The Subcommittee noted that deferiprone has been available for longer than deferasirox and as such there are more long-term data. The Subcommittee noted that there have been no head-to-head studies comparing deferasirox to deferiprone.

1.3 The Subcommittee noted that there had been some controversy in the development of deferiprone with respect to the actions of the supplier and the lead investigator, and that this had negatively impacted on its use. The Subcommittee noted that deferiprone required the patient to take a tablet or oral liquid three times per day; that there have been concerns regarding its side-effect profile including agranulocytosis and liver toxicity; and that it required weekly blood tests. The Subcommittee considered deferiprone to be effective in reducing iron overload and that the side-effect profile had proven to be acceptable.

1.4 The Subcommittee noted that deferasirox was a once daily tablet and considered it to be effective in reducing iron overload and have an acceptable side-effect profile.

1.5 The Subcommittee considered that deferasirox is preferable to deferiprone as it requires less monitoring, there are fewer concerns over its side-effect profile, and it has a compliance advantage as it is a once daily treatment.

1.6 The Subcommittee considered that if an oral treatment became available then it would be preferred to the currently funded desferioxamine injection as patients could expect to receive tens of thousands of injections or infusions in their lifetime. The Subcommittee considered that all patients who could tolerate an oral treatment would switch to it very quickly and that it would result in increased compliance.

1.7 The Subcommittee noted the patient groups that funding had been requested for including:

- patients with congenital inherited anaemias;
- younger patients with acquired anaemias who develop iron overload from long term blood transfusions; and,
- other patients with acquired anaemias who develop iron overload blood transfusions and who are eligible for chelation therapy under the current registered indications.

1.8 The Subcommittee noted that PTAC had recommended that an oral agent should be funded for patients with chronic transfusional iron overload due to congenital inherited anaemias and considered that this was appropriate. However, the Subcommittee also considered that there were several smaller niche patient groups with acquired anaemia and transfusion dependence, but otherwise with good health, where long term survival could be predicted, and treatment with an oral agent may be appropriate including:

- Paroxysmal nocturnal hemoglobinuria (PNH)
- Acquired Pure Red cell Aplasia (PRCA)
- Some low risk myelodysplastic syndromes

1.9 The Subcommittee **recommended** that an oral iron overload treatment should be listed on the Pharmaceutical Schedule with a high priority.

2 Gemcitabine and vinorelbine for relapsed Hodgkin's disease and T-cell lymphoma

2.1 The Subcommittee considered an application from PHARMAC staff for the widening of access to combined gemcitabine and vinorelbine for patients with relapsed Hodgkin's disease or T-cell lymphoma. Members noted that the application had been generated following CaTSoP's advice from February 2009 where it noted there had been a significant number of Cancer Exceptional Circumstances (CaEC) applications for these treatments. The applications for Hodgkin's disease and T-cell lymphoma are discussed separately.

Hodgkin's Disease

2.2 The Subcommittee considered that Hodgkin's disease (HD) was a relatively rare cancer type. Members considered that the treatment path for HD was well established with the majority of patients being cured with first-line treatment, usually with standard chemotherapy regimens such as ABVD (adriamycin, bleomycin, vinblastine, and dacarbazine). Members considered that patients who relapse would usually be treated with second-line salvage chemotherapy, such as ICE (ifosfamide, carboplatin and etoposide) followed by high-dose chemotherapy and a bone marrow or peripheral blood stem cell transplant in patients who responded.

2.3 The Subcommittee considered that because of the high cure rates with early treatment and first salvage very few patients, 5-15 per year, would require third-line treatment for relapsed or non-responding HD. Members noted that currently such patients would likely receive palliative chemotherapy or occasionally reinduction salvage chemotherapy and a second transplant if they responded.

2.4 The Subcommittee reviewed evidence from a pilot study in which 40 relapsed HD or non-Hodgkin's lymphoma (including T-cell lymphoma) patients received vinorelbine 25 mg/m^2 and gemcitabine 1000 mg/m^2 on days 1 and 8 every 21 days with GCSF support in an outpatient setting (Spencer et al 2007, Internal Medicine Journal 37; 760–766). Members noted that response rates were 75% for the HD patients; and after 34 months follow-up

overall survival was 50%. Members noted that haematological toxicity was approximately one third of that seen with conventional salvage chemotherapy regimens.

2.5 The Subcommittee noted that although evidence for gemcitabine in combination with vinorelbine in relapsed HD was limited, it did demonstrate similar efficacy to other salvage regimens. Members further noted that most currently used salvage regimens have significant toxicity and are complex to administer, requiring significant inpatient resource, whereas combination gemcitabine and vinorelbine is relatively simple to administer and has fewer toxicity issues. Members considered that if patients responded well to gemcitabine and vinorelbine they may then be offered a transplant.

2.6 The Subcommittee considered that if funded gemcitabine in combination with vinorelbine might displace currently used complex salvage chemotherapy regimens such as ICE and would reduce costs associated with inpatient administration of these chemotherapies and associated adverse event management. However, members considered that if a patient continued to relapse, they may eventually receive complex salvage regimens anyway.

2.7 The Subcommittee **recommended** that combination treatment with gemcitabine and vinorelbine be funded for up to 6 cycles for patients who fail to respond to second-line salvage chemotherapy or who relapse after transplantation (ie in the third-line setting). Members gave this recommendation a medium priority.

2.8 The relevant decision criteria for this recommendation are: 1: *the health needs of all eligible people within New Zealand; 3: the availability and suitability of existing medicines, therapeutic medical devices and related products and related things; 4: the clinical benefits and risks of pharmaceuticals; 5: the cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services; and 6: the budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule;*

T-cell Lymphoma

2.9 The Subcommittee considered that "T-cell lymphoma" described a heterogeneous group of numerous different diseases, some of which are very rare. Members considered that in New Zealand approximately 20–30 patients per year would be diagnosed with T-cell lymphoma.

2.10 The Subcommittee noted that different T-cell lymphomas have different prognoses and treatment options; however, members considered that treatment pathways for T-cell lymphomas were poorly defined, principally due to the rarity of different types of T-cell lymphoma and lack of randomised clinical trials to inform treatment choices. The Subcommittee considered that evidence for effective treatments in the T-cell lymphomas was limited and of poor quality. Members considered that current treatment options were inadequate, with many patients either not responding to treatment or only having a transient response. Members therefore considered that alternative funded treatment options were needed.

2.11 The Subcommittee considered that treatment options for patients with T-cell lymphoma would include CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone), DHAP (dexamethasone, cytarabine and cisplatin), ICE (ifosfamide, carboplatin and

etoposide) followed by a bone marrow transplant or peripheral blood stem cell transplant in patients who responded to the first-line treatment. Members considered that in New Zealand many patients would currently receive CHOP but noted that most patients only had a transient response to this treatment.

2.12 The Subcommittee reviewed evidence from a pilot study in which 40 relapsed HD or non-Hodgkin's lymphoma (including T-cell lymphoma) patients received vinorelbine 25 mg/m^2 and gemcitabine 1000 mg/m^2 on days 1 and 8 every 21 days with GCSF support in an outpatient setting (Spencer et al Internal Medicine Journal 37 (2007) 760–766). Members noted that response rates were 70% for the T-cell lymphoma patients; and after 34 months follow-up overall survival was 50%. Members noted that haematological toxicity was approximately one third of that seen with conventional salvage chemotherapy regimens.

2.13 The Subcommittee considered that, given the lack of defined treatment pathways for T-cell lymphomas, combination treatment with gemcitabine and vinorelbine would likely be used in the first-line setting because it was easier to administer and less toxic than current treatment options (including reduced rates of neutropenia). The Subcommittee noted that the clinical evidence on gemcitabine and vinorelbine for T-cell lymphomas was limited to its use as salvage treatment. However, the Subcommittee considered that it was unlikely that trials would be undertaken for first-line treatment. Members considered that if gemcitabine and vinorelbine were funded current treatments may still be used later in the treatment paradigm as patients would likely relapse.

2.14 The Subcommittee **recommended** that combination treatment with gemcitabine and vinorelbine be funded for up to 6 cycles for patients with T-cell lymphoma. Members gave this recommendation a medium priority. Members considered that in the first-line setting combination gemcitabine and vinorelbine would likely be used in combination with doxorubicin or ifosfamide.

2.15 The relevant decision criteria for this recommendation are: 1: *the health needs of all eligible people within New Zealand; 3: the availability and suitability of existing medicines, therapeutic medical devices and related products and related things; 4: the clinical benefits and risks of pharmaceuticals; 5: the cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services; and 6: the budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule;*

3 Trastuzumab (Herceptin) new data and other issues

3.1 The Subcommittee considered a paper from PHARMAC staff advising of new data for trastuzumab (Herceptin) in HER2-positive early breast cancer presented at the St. Gallen Primary Therapy of Early Breast Cancer International Conference (SGBCC) held on 11-14 March 2009. Members noted that the new data comprised slide presentations and abstracts of 4-year follow-up data from the HERA study and 5-year follow-up data from the FinHer study. Members noted that none of the new data had yet been published in a peer-reviewed journal.

3.2 The Subcommittee also reviewed correspondence from the principal investigator of FinHer, Prof Heikki Joensuu, and a letter from the supplier of trastuzumab (Roche Products (NZ) Limited) discussing the new data and providing some additional material for consideration.

HERA 4-year follow-up data

3.3 The Subcommittee noted that the data from the HERA study demonstrated that, after 4 years median follow-up, disease free survival (DFS) improvements in the trastuzumab treatment arm were still statistically significant; however, members noted that the Hazard Ratio for DFS benefit has reduced compared with 1-year and 2-year follow-up data although the absolute difference in the proportion of patients with disease events has remained stable. Members further noted that the statistically significant improvement in overall survival apparent at 2 years' follow-up was lost at 4 years' follow-up.

3.4 The Subcommittee considered that the study design of HERA, which allowed cross over of observation patients to trastuzumab treatment, prevented any definitive conclusions being drawn from the 4-year follow-up data. Members considered that the so called 'landmark' analysis of the HERA data, which attempted to examine the effect of Herceptin treatment in observation patients who did, or did not, cross over, was exploratory in nature and no conclusions can be drawn.

FinHer 5-year follow-up data

3.5 The Subcommittee noted that the primary endpoint presented for the 5-year median follow-up of FinHer differed from the pre-planned study endpoint. Members considered that a change in primary endpoint was not ideal but considered that it did not appreciably alter the conclusions that could be drawn. Members considered that distant disease free survival (DDFS), the new primary endpoint, could be an informative endpoint, in terms of prognosis, given the limited number of HER 2 positive patients in the study. The Subcommittee noted that at 5 years' median follow-up (the longest of any study to date), 9 weeks' trastuzumab, when administered concurrently with docetaxel, was associated with statistically significant improvement in DDFS. Members also noted a trend towards improvement in overall survival, but noted that this was not statistically significant.

3.6 The Subcommittee considered that some of the information provided by Roche regarding the FinHer study was misleading: in particular, members noted that in the set of slides provided by Roche (which comprised photographs of Prof Joensuu's presentation at St Gallen) some slides were missing and the conclusion slide, written and inserted by Roche, differed from that presented by Prof Joensuu.

Cardiac safety of trastuzumab

3.7 The Subcommittee noted data from a number of retrospective audit studies presented at the American Society of Clinical Oncology conference 2009 examining the cardiac safety of trastuzumab in clinical practice. Members noted that, in general, the rates of cardiac toxicity in these studies was much higher than had previously been seen in the various trastuzumab clinical trials. For example, in one study of UK patients who received 12 months' trastuzumab as per the HERA study protocol, 12% discontinued treatment due to cardiac toxicity – more than twice the rate seen in the HERA trial (Canney et al J Clin Oncol 27:15s, 2009 (abstract 582)).

3.8 The Subcommittee noted that the clinical trials had strict cardiac entry criteria; thus, it would be expected that cardiac complications would be higher in the real life setting. However, the high rates seen in the various audits presented at ASCO were of concern. Members considered that the risk to patients was increased where cardiac monitoring was inadequate and expressed concern that in their clinical experience only around 20% of patients are actually receiving the cardiac monitoring tests prescribed. Members considered that the cardiac toxicity of 12 months' trastuzumab treatment remained a concern, in that although it appeared that cardiac toxicity of trastuzumab could be managed in most patients by stopping trastuzumab treatment and ongoing treatment with cardiac medications, the long-term cardiac effects were unknown. Members noted that 9 weeks' treatment did not appear to be associated with the same degree of cardiac toxicity issues as many of the 12 month regimens.

General discussion

3.9 The Subcommittee noted that trastuzumab was currently funded on the Pharmaceutical Schedule for the treatment of metastatic breast cancer and for a 9-week course for HER2-positive early breast cancer. Members further noted that funding for a 12 month treatment course for patients with HER2-positive early breast cancer was available through a separate scheme managed by the Ministry of Health (MoH).

3.10 The Subcommittee considered that the new HERA and FinHer data did not substantially change the evidence base for trastuzumab in HER2-positive early breast cancer. Members considered that the optimal duration of treatment remains unknown and only more research, such as the SOLD study, would answer this question. Members noted that during a SGBCC panel discussion at the St. Gallen Primary Therapy of Early Breast Cancer International Conference (SGBCC) held on 11-14 March 2009, Prof Ian Smith, lead author of the 2 year median follow-up HERA data published in the Lancet in 2007, remarked that "SOLD was the most important Herceptin trial currently running". Members further noted that a synopsis of the SOLD trial had been circulated to Breast International Group members for their consideration to participate. Members also noted that there were other short versus long duration trastuzumab trials running internationally and results were awaited.

3.11 The Subcommittee considered that 12 months' treatment was the recognised international standard regimen but noted that 9 weeks' treatment remained an appropriate treatment option for patients. Members considered that treatment duration for an individual patient could be determined only through discussion with the treating clinician. Members noted that since 12 months trastuzumab was funded in their experience a significant number of patients continue to opt for the short course, 9 weeks', treatment regimen.

3.12 The Subcommittee welcomed the MoH funding of trastuzumab for up to 12 months, but considered that it would be preferable to have 12 months' trastuzumab listed in the Pharmaceutical Schedule instead, to reduce the administrative burden for hospital staff.

4 Capecitabine for high risk stage II colorectal cancer

4.1 The Subcommittee considered an application from clinicians, including the Chairman of the Gastrointestinal Cancer Special Interest Group of the New Zealand Association of Cancer Specialists (GISIG-NZACS), for the widening of access to capecitabine for patients with high-risk stage II colorectal cancer. The Subcommittee noted that at its March 2008 meeting it had deferred making a recommendation for access to capecitabine to be widened to include high-risk stage II colorectal cancer pending PHARMAC staff seeking a consensus definition of 'high-risk stage II colorectal cancer' from NZACS and evidence for the safety and efficacy of adjuvant fluoropyrimidines in this patient population.

4.2 The Subcommittee noted that capecitabine was not indicated for stage II colorectal cancer.

4.3 The Subcommittee reviewed evidence from a number of studies that identified high-risk prognostic factors for patients with Stage II colon cancer in patients treated with surgery alone. Members considered that the presence of stage T4 disease, low numbers of lymph nodes examined and vascular invasion identified poor prognosis (high risk) Stage II disease. Members considered that some patients with high-risk stage II disease had relapse rates approaching that of stage III colon cancer patients.

4.4 The Subcommittee noted a Cochrane systematic review (Figueredo et al 2008. published in the Cochrane Database of Systematic Reviews 2008, Issue 3.) of randomised clinical trials evaluating adjuvant chemotherapy versus surgery alone in stage II colon cancer patients. Members noted that results from this review found no statistically significant improvement in overall survival; however, disease recurrence was significantly reduced in the patients receiving systemic adjuvant chemotherapy with an absolute difference of 3.6% (Hazard Ratio 0.83 (95% CI 0.75, 0.91) p= 0.00018).

4.5 The Subcommittee also reviewed evidence from a large trail (QUASAR, Lancet 2007; 370: 2020–29), not included in the Cochrane review, in which patients with colorectal cancer were randomised to receive adjuvant 5-fluorouracil (5-FU) and folinic acid (leucovorin, LV) (n=1622) or to observation (n=1617). Members noted that 91% of patients enrolled had stage II (node negative) disease. Members noted that after a median follow-up of 5.5 years the data demonstrated a statistically significant improvement in overall survival (HR 0·84 (95% CI 0·68–1·00); p=0·046, , absolute difference of 2.8%) and disease recurrence (HR 0·78 (95% CI 0·66–0·93); p=0·004, absolute difference of 3.7%) in the stage II cancer patients receiving chemotherapy compared with observation alone.

4.6 The Subcommittee noted that the applicants had provided prognostic data derived from the online decision-making tool "Adjuvant! Online". Members noted that this tool was commonly used by oncologists but considered that, in general, it provided optimistic estimates of treatment benefits and, therefore, its estimates should be treated with caution.

4.7 The Subcommittee considered that, overall, adjuvant chemotherapy improves disease free survival in high risk stage II colorectal cancer patients. Members considered that it was likely that there was also some survival benefit but that this benefit was likely to be small.

4.8 The Subcommittee considered that, currently, high-risk stage II colorectal cancer patients would be treated with infusional adjuvant 5FU and LV. Members noted that, although it had not specifically been tested in patients with stage II colorectal cancer, oral capecitabine had been studied as a replacement to 5FU injections (with or without LV) in various settings, including stage III colorectal cancer. Members noted that in this setting capecitabine had shown equivalent efficacy to 5FU, but had a different toxicity profile. Members considered that, although the toxicity issues with capecitabine can be significant, they were manageable.

4.9 The Subcommittee considered that since capecitabine is an oral product it could be taken at home by the patient, thus reducing need for hospital resources. Members considered that although the drug acquisition cost of capecitabine is higher than that of 5FU/LV, when taking into account hospital cost savings, and that high-risk stage II disease has relapse rates similar to stage III disease, capecitabine may be reasonably cost-effective compared with infusional 5FU in this setting.

4.10 The Subcommittee considered that, if funded, approximately 250 patients per year would be eligible for capecitabine treatment in the first year. Members considered that since it was an oral treatment more patients would receive treatment than those currently being treated with infusional 5FU/LV.

4.11 The Subcommittee **recommended** that access to capecitabine be widened to include high-risk stage II colorectal cancer. The Subcommittee gave this recommendation a high priority.

4.12 The Subcommittee **recommended** amending the Special Authority criteria applying to capecitabine as follows (additions in bold, deletions in strikethrough):

> Initial application only from a relevant specialist. Approvals valid for 12 months for applications meeting the following criteria:
> Any of the following:
> 1 The patient has advanced gastrointestinal malignancy; or
> 2 The patient has metastatic breast cancer*; or
> 3 The patient has stage III (Dukes' stage C) colorectal*# cancer and has undergone surgery; or
> **4 All of the following:**
> **4.1 The patient has stage II (Dukes' stage B) colorectal* cancer and has undergone surgery; and**
> **The patient has high risk disease defined as**
> **4.2 Any of the following:**
> **4.2.1 Stage T4 disease; or**
> **4.2.2 Vascular invasion (including serosal cancer deposits); or**
> **4.2.3 Fewer than 10 lymphnodes examined at resection; or**
> 4**5** Both:
> 4**5**.1 The patient has poor venous access or needle phobia*; and
> 4**5**.2 The patient requires a substitute for single agent fluoropyrimidine*.
> Renewal only from a relevant specialist. Approvals valid for 12 months for applications meeting the following criteria:
> Either:
> ~~5~~**1** The patient requires continued therapy; or
> ~~6~~**2** The tumour has relapsed and requires re-treatment.
> Note indications marked with * are Unapproved Indications, #capecitabine is approved for stage III (Dukes' stage C) colon cancer.

4.13 The relevant decision criteria for these recommendations are: 1: *the health needs of all eligible people within New Zealand; 3: the availability and suitability of existing medicines, therapeutic medical devices and related products and related things; 4: the clinical benefits and risks of pharmaceuticals; 5: the cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services; and 6: the budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule;*

5 Review of rituximab special authority criteria

5.1 The Subcommittee noted that PHARMAC staff had requested the Subcommittee's views in relation to the possibility of widening funded access to rituximab (MabThera). Members noted that this request related to responses received by PHARMAC during consultation on its recent decision to widen funded access to rituximab from 1 July 2009 for the first-line treatment of patients with indolent, low-grade Non Hodgkin's Lymphoma (NHL). Members reviewed relevant consultation responses as well as additional information provided by some respondents and the supplier of rituximab (Roche products (NZ) limited).

5.2 The Subcommittee noted that respondents had requested further changes to the rituximab Special Authority and/or access to other patient groups as follows:

- treatment of chronic lymphocytic leukaemia/small lymphocytic lymphoma
- re-treatment of large cell lymphoma for up to 4 cycles
- reducing the renewal treatment-free period to 6 months
- increasing the number of cycles funded from 6 to 8 for initial treatment and from 4 to 6/8 for re-treatment of indolent NHL
- increasing the number of cycles funded from 6 to 8 cycles for retreatment of post transplant lymphoproliferative disorder (PTLD).

5.3 The Subcommittee considered these requests separately.

Chronic lymphocytic leukaemia/small lymphocytic lymphoma

5.4 The Subcommittee noted that rituximab was not currently indicated for the treatment of patients with chronic lymphocytic leukaemia or small lymphocytic lymphoma (CLL/SLL) but noted that the supplier intends to submit an application to Medsafe for this indication.

5.5 The Subcommittee considered that CLL and SLL could, essentially, be considered to be the same disease. Members considered that historically there was inequity of access with some, but not all, patients with CLL/SLL accessing rituximab funding as "low-grade lymphoma".

5.6 Members considered that, in relation to CLL/SLL, the current Special Authority criteria for rituximab which includes the Note: *"Indolent, low-grade lymphomas' includes follicular,*

mantle, marginal zone and lymphoplasmacytic/Waldenstrom macroglobulinaemia. Rituximab is not funded for Chronic lymphocytic leukaemia/small lymphocytic lymphoma." remained appropriate. Members considered that the addition of this Note did not constitute a narrowing of access as asserted by the supplier. The Subcommittee considered that although some SLL patients were included in early rituximab studies, the evidence supporting use in these early studies was poor.

5.7 The Subcommittee deferred making a recommendation for the funding of rituximab for CLL/SLL pending Medsafe approval of this indication and receipt of a funding application from the supplier.

Re-treatment of large cell lymphoma

5.8 The Subcommittee noted that rituximab, when given in combination with a multi-agent chemotherapy regimen with curative intent, was currently funded for up to 8 cycles for patients with treatment-naive aggressive CD20-positive NHL.

5.9 The Subcommittee considered that there were 2 distinct populations of patients with large cell lymphoma not funded under the current Special Authority criteria that may benefit from rituximab treatment, as follows:

(a) Rituximab treatment-naïve patients whose disease has relapsed following prior non-rituximab chemotherapy; and

(b) Rituximab re-treatment in patients whose disease has relapsed following prior rituximab containing treatment.

5.10 The Subcommittee noted evidence from the HOVON trial (Vellenga et al. Blood. 2008 Jan 15;111(2):537-43) which demonstrated that the addition of rituximab to salvage DHAP (cisplatin, cytarabine and dexamethasone) improved progression-free survival in patients with aggressive CD20+ B-cell NHL who were refractory to prior anthracycline-based chemotherapy.

5.11 The Subcommittee **recommended** that access to rituximab be widened to include funding for up to 6 cycles for patients with relapsed/refractory rituximab-naïve aggressive CD20-positive B-cell NHL. Members considered that the number of patients in this population was currently very small and would be getting smaller over time, since most new patients would now receive rituximab as part of their first-line treatment. The Subcommittee gave this recommendation a High priority.

5.12 The Subcommittee noted evidence from the CORAL study presented at the American Society Haematology meeting in 2008. Members noted that in this study patients with relapsed/refractory diffuse large B-cell lymphoma (with or without prior rituximab exposure) were randomised to receive salvage chemotherapy consisting of R-ICE (rituximab, ifosfamide, carboplatin, etoposide) or R-DHAP; after three cycles, responders received stem cell transplant followed by a second randomisation to rituximab maintenance treatment (375 mg/m^2, one injection every 2 months six times) or observation. Members noted that in patients not previously treated with rituximab, rituximab-containing salvage chemotherapy provided a high response rate (overall response rate (ORR) 82%, 2 yr event free survival (EFS) 66%); however, in patients who had previously received rituximab and relapsed within 12 months of diagnosis response

was less (ORR 54%, 2 yr EFS approximately 20%). The Subcommittee noted however that although patients who relapse following treatment with rituximab have a poorer prognosis, nonetheless such patients may yet benefit from further treatment with rituximab.

5.13 The Subcommittee **recommended** that rituximab re-treatment be funded for up to 4 cycles in patients with relapsed/refractory aggressive CD20 positive NHL disease following prior rituximab treatment. Members **recommended** that patients should have had a rituximab treatment-free interval of 6 months or more and that rituximab retreatment be funded as part of a chemotherapy regimen given with curative intent including a planned stem cell or bone marrow transplant. Members considered that the number of patients in this population would be small, approximately 30 per year. The Subcommittee gave this recommendation a Medium priority.

Reducing the renewal treatment-free period

5.14 The Subcommittee reiterated its view that treatment free period should remain at 12 months; members considered a 6 month interval was too short to determine true disease relapse rather than non-response to treatment. The Subcommittee noted that no data had been presented in support of a change to this requirement.

Increasing the number of cycles funded for indolent NHL

5.15 The Subcommittee noted that currently up to 6 cycles of rituximab were funded for initial treatment and 4 cycles for re-treatment for patients with indolent, low grade NHL.

5.16 The Subcommittee noted a Phase II study in which rituximab was administered in combination CVP chemotherapy (cyclophosphamide, vincristine and prednisone) for 8 cycles in patients with treatment naïve follicular lymphoma (Marcus et al 2008, J Clin Oncol 26:4579-4586), which showed that the addition of rituximab to CVP chemotherapy significantly improved time to treatment failure, overall and complete response rates, time to progression and overall survival. However, members noted that not all patients in the clinical trial received the full 8 cycles of treatment planned. In addition, members considered that this regimen was not frequently used, or was not as effective, as the more commonly used R-CHOP regimen (rituximab plus cyclophosphamide, doxorubicin and vincristine) which is usually administered for 6 cycles. The Subcommittee **recommended** that rituximab funding for the initial treatment of patients with indolent, low grade NHL remain at 6 cycles.

5.17 The Subcommittee considered that the current funding of 4 cycles for re-treatment of patients with relapsed/refractory indolent, low grade NHL was historical, resulting from when the cancer basket was developed, at which time rituximab monotherapy was used for up to 4 cycles in these patients. Members considered that currently rituximab retreatment in combination with other chemotherapy drugs for up to 6 cycles was standard in most studies in patients with relapsed/refractory indolent, low grade NHL; for example Van Oers et al (Blood, 15 November 2006, Vol. 108, No. 10, pp. 3295-3301) demonstrated that in patients with relapsed/resistant follicular lymphoma 6 cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) increased overall response rate and complete response compared with CHOP.

5.18 The Subcommittee **recommended** that the number of cycles of rituximab funded for the re-treatment of patients with relapsed/refractory indolent, low grade NHL be increased from 4 to 6 cycles.

Increasing the number of cycles funded for retreatment of post transplant lymphoproliferative disorder

5.19 The Subcommittee noted that under the current Special Authority criteria up to 8 cycles of rituximab were funded for initial treatment and up to 6 cycles for retreatment for patients with post transplant lymphoproliferative disorder (PTLD), giving a total of 14 funded cycles. Members considered that in PTLD rituximab is usually given as monotherapy in the first line setting, with rituximab in combination with other chemotherapy, usually CHOP, given to patients with refractory/relapsed disease.

5.20 The Subcommittee **recommended** that the number of cycles of rituximab funded for the retreatment of patients with relapsed/refractory remain at 6 cycles.

5.21 The relevant decision criteria for these recommendations are: *1: the health needs of all eligible people within New Zealand; 3: the availability and suitability of existing medicines, therapeutic medical devices and related products and related things; 4: the clinical benefits and risks of pharmaceuticals; 5: the cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services; and 6: the budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.*

6 Nilotinib for imatinib-refractory chronic myeloid leukaemia (CML)

6.1 The Subcommittee reviewed a resubmission from Novartis New Zealand for the listing of nilotinib (Tasigna) on the Pharmaceutical Schedule for the treatment of patients with imatinib-resistant or imatinib-intolerant, chronic or accelerated phase, chronic myeloid leukaemia (CML).

6.2 The Subcommittee noted that at its June 2008 meeting it had recommended that both dasatinib (Sprycel, Bristol-Myers Squibb (NZ) Ltd) and nilotinib be funded with a medium priority; however, PTAC, at its February 2009 meeting, reviewed the June 2008 CaTSoP minutes and recommended that the application for nilotinib be declined because the data supporting nilotinib was, in its opinion, very weak.

6.3 The Subcommittee noted, and welcomed, PHARMAC's recent decision to fund dasatinib for patients with CML.

6.4 The Subcommittee reviewed longer-term data from study 2101, a single open-label non-randomised phase II study of nilotinib in patients with imatinib-resistant/intolerant CML. Members noted that data now comprised median duration of nilotinib therapy of 19 months for chronic phase patients and 9 months for accelerated phase patients. Members considered that the data demonstrated durable responses to nilotinib treatment.

6.5 The Subcommittee considered that even though nilotinib and dasatinib belong to the same therapeutic class they had clinically relevant differences, including different activity in CML with different BCR-ABL kinase mutations and different safety profiles. For example, dasatinib (but not nilotinib) is associated with fluid retention and, therefore, would not be recommended in patients with cardiac co-morbidity, while nilotinib (but not dasatinib) is associated with increased serum lipase and, therefore, would not be recommended in patients with previous history of pancreatitis or diabetes.

6.6 The Subcommittee considered that, ideally, both nilotinib and dasatinib would be funded, which would allow treatment choice to be tailored to a patient's individual clinical profile and co-morbidities.

6.7 The Subcommittee **recommended** that nilotinib be funded under the same Special Authority criteria as dasatinib only if cost neutral to the Pharmaceutical Budget. The Subcommittee gave this recommendation a medium priority.

6.8 The Subcommittee further **recommended** that if it was not possible to achieve a cost-neutral listing, nilotinib be funded only for patients with CML resistant to, or patients intolerant of/contraindicated to, both imatinib and dasatinib treatment i.e. third-line treatment. The Subcommittee gave this recommendation a high priority.

6.9 The relevant decision criteria for these recommendations are: 1: *the health needs of all eligible people within New Zealand; 3: the availability and suitability of existing medicines, therapeutic medical devices and related products and related things; 4: the clinical benefits and risks of pharmaceuticals; 5: the cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services; and 6: the budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.*