

30 July 2010

## Proposal to fund erlotinib and to widen funded access to rituximab, capecitabine and mycophenolate mofetil

PHARMAC is seeking feedback on a proposal to:

1. fund erlotinib (Tarceva) from 1 October 2010 for second line treatment of patients with advanced, unresectable, Non Small Cell Lung Cancer; and
2. widen funded access to rituximab (Mabthera) from 1 October 2010 to include:
  - (a) funding for up to 6 cycles for patients with relapsed/refractory rituximab-naïve aggressive CD20-positive B-cell Non Hodgkin's Lymphoma (NHL); and
  - (b) funding for up to 4 cycles of ritixumab retreatment in patients with relapsed/refractory aggressive CD20-positive B-cell NHL; and
  - (c) increasing the number of funded cycles from 4 to 6 for ritixumab retreatment in patients with relapsed indolent NHL; and
3. widen funded access to capecitabine (Xeloda) from 1 October 2010 to include:
  - (a) funding for adjuvant treatment of patients with high risk stage II colorectal cancer; and
  - (b) neoadjuvant treatment of patients with locally advanced rectal cancer; and
4. widen funded access to mycophenolate mofetil (Cellcept) from 1 October 2010 to include patients with diseases that have not responded to other standard immunosuppressant treatments,

through a provisional agreement with Roche Products (NZ) Ltd.

Further details of the proposal can be found on the following pages.

### Feedback sought

PHARMAC welcomes feedback on this proposal. To provide feedback, please submit it in writing by **4 pm, Friday 13 August 2010** to:

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All feedback received before the closing date will be considered by PHARMAC's Board (or Chief Executive acting under delegated authority) prior to making a decision on this proposal.

## Details of the proposal

PHARMAC has reached a provisional agreement with Roche Products (NZ) Limited for supply of erlotinib (Tarceva) and widening of funded access to capecitabine (Xeloda), rituximab (Mabthera) and mycophenolate mofetil (Cellcept). We are now seeking feedback on this proposal. Details of the proposal are as follows:

### *Tarceva (erlotinib)*

- From 1 October 2010 Tarceva would be listed in Section B and in Part II of Section H of the Pharmaceutical Schedule at the following prices and subsidies (ex-manufacturer, excluding GST):

Pharmaceutical	Brand	Form and Strength	Pack Size	Proposed price and subsidy
Erlotinib hydrochloride	Tarceva	Tab 100 mg	30	\$3,100.00
Erlotinib hydrochloride	Tarceva	Tab 150 mg	30	\$3,950.00

- The listing of Tarceva in Section B of the Pharmaceutical Schedule would be subject to the following Special Authority restriction:

#### **Erlotinib - Retail Pharmacy – Specialist - Special Authority for Subsidy**

**Initial application** only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 3 months for applications meeting the following criteria:

All of the following:

1. Patient has advanced, unresectable, Non Small Cell Lung Cancer (NSCLC); and
2. Patient has documented disease progression following treatment with first line platinum based chemotherapy; and
3. Erlotinib is to be given for a maximum of 2 months.

**Renewal application** only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months where radiological assessment indicates NSCLC has not progressed.

- Tarceva would be subject to a confidential rebate which would reduce the net price and subsidy paid by the Funder.
- Tarceva would have protection from subsidy reduction and delisting until 31 December 2013.

### *Mabthera (rituximab)*

- From 1 October 2010 the Special Authority criteria applying to the listing of rituximab in Section B of the Pharmaceutical Schedule would be amended to read as follows:

#### **Rituximab – PCT only – Specialist - Special Authority for Subsidy**

**Initial application — (Post-transplant)** only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 12 months for applications meeting the following criteria:

Both:

- 1 The patient has B-cell post-transplant lymphoproliferative disorder\*; and
- 2 To be used for a maximum of 8 treatment cycles.

**Initial application — (Indolent, Low-grade lymphomas)** only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 9 months for applications meeting the following criteria:

Either:

- 1 Both:
  - 1.1 The patient has indolent low grade NHL with relapsed disease following prior chemotherapy; and
  - 1.2 To be used for a maximum of 4 treatment cycles; or
- 2 Both:
  - 2.1 The patient has indolent, low grade lymphoma requiring first-line systemic chemotherapy; and
  - 2.2 To be used for a maximum of 6 treatment cycles.

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.

**Initial application — (Aggressive CD20 positive NHL)** only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 12 months for applications meeting the following criteria:

Either

- 1 All of the following:
  - 1.1 The patient has treatment-naive aggressive CD20 positive NHL; and
  - 1.2 To be used with a multi-agent chemotherapy regimen given with curative intent; and
  - 1.3 To be used for a maximum of 8 treatment cycles; or
- 2 Both:
  - 2.1 The patient has aggressive CD20 positive NHL with relapsed disease following prior chemotherapy; and
  - 2.2 To be used for a maximum of 6 treatment cycles.

Note: 'Aggressive CD20 positive NHL' includes large B-cell lymphoma and Burkitt's lymphoma/leukaemia

**Renewal — (Post-transplant)** only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist.

Approvals valid for 9 months for applications meeting the following criteria:

All of the following:

- 1 The patient has had a rituximab treatment-free interval of 12 months or more; and
- 2 The patient has B-cell post-transplant lymphoproliferative disorder\*; and
- 3 To be used for no more than 6 treatment cycles.

**Renewal — (Indolent, Low-grade lymphomas)** only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 9 months for applications meeting the following criteria:

All of the following:

- 1 The patient has had a rituximab treatment-free interval of 12 months or more; and
- 2 The patient has indolent, low-grade NHL with relapsed disease following prior chemotherapy; and
- 3 To be used for no more than 6 treatment cycles.

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.

**Renewal — (Aggressive CD20 positive NHL)** only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 12 months for applications meeting the following criteria:

All of the following:

- 1 The patient has had a rituximab treatment-free interval of 12 months or more; and
- 2 The patient has relapsed refractory/aggressive CD20 positive NHL; and
- 3 To be used with a multi-agent chemotherapy regimen given with curative intent; and
- 4 To be used for a maximum of 4 treatment cycles.

Note: 'Aggressive CD20 positive NHL' includes large B-cell lymphoma and Burkitt's lymphoma/leukaemia

Note: Indications marked with \* are Unapproved Indications.

- The confidential rebate currently applying to Mabthera would be increased which would reduce the net price and subsidy paid by the Funder.
- Mabthera would have protection from subsidy reduction and delisting until 31 December 2013.

#### *Xeloda (capecitabine)*

- From 1 October 2010 the Special Authority criteria applying to the listing of Xeloda in Section B of the Pharmaceutical Schedule would be amended to read as follows:

#### **Capecitabine - Retail Pharmacy – Specialist - Special Authority for Subsidy**

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

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
  - 4.2 Any of the following:
    - 4.2.1 the patient has stage T4 disease; or
    - 4.2.2 the patient has vascular invasion (including serosal cancer deposits); or
    - 4.2.3 Fewer than 10 lymph nodes were examined at resection; or
- 5 All of the following:
  - 5.1 The patient has locally advanced (clinically or radiologically staged T3/T4: N0,1,2) rectal cancer; and
  - 5.2 Surgery is planned; and
  - 5.3 Capecitabine to be given prior to surgery (neoadjuvant); and
  - 5.4 Capecitabine to be given at a maximum dose of 825 mg/m<sup>2</sup> twice daily in combination with radiation therapy for a maximum of 6 weeks; or
- 6 Both:
  - 6.1 The patient has poor venous access or needle phobia\*; and
  - 6.2 The patient requires a substitute for single agent fluoropyrimidine\*.

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

Either:

- 1 The patient requires continued therapy; or
- 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.

- The confidential rebate currently applying to Xeloda would be increased which would reduce the net price and subsidy paid by the Funder.
- Xeloda would have protection from subsidy reduction and delisting until 31 December 2013.

*Cellcept (mycophenolate mofetil)*

- From 1 October 2010 the prices and subsidies applying to the listing of Cellcept tablets and capsules in Section B and part II of Section H of the Pharmaceutical Schedule would be reduced as follows (ex-manufacturer, excluding GST):

Pharmaceutical	Brand	Form and Strength	Pack Size	Current price and subsidy	Proposed price and subsidy
Mycophenolate Mofetil	Cellcept	Tab 500 mg	50	\$206.66	\$70.00
Mycophenolate Mofetil	Cellcept	Cap 250 mg	100	\$206.66	\$70.00

- From 1 October 2010 the Special Authority criteria applying to the listing of Cellcept tab 500 mg and cap 250 mg in Section B of the Pharmaceutical Schedule would be amended to read as follows:

**Mycophenolate mofetil - Special Authority for Subsidy**

Initial application only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid without further renewal unless notified for applications meeting the following criteria:

Either:

1 Organ transplant recipient; or

2 Both:

2.1 Steroids and azathioprine have been trialled and discontinued because of unacceptable side effects or inadequate clinical response; and

2.2 Either:

2.2.1 Cyclophosphamide has been trialled and discontinued because of unacceptable side effects or inadequate clinical response; or

2.2.2 Cyclophosphamide treatment is contraindicated.

- Cellcept would have protection from subsidy reduction and delisting until 30 June 2012.

## Background

### *Tarceva (erlotinib)*

Erlotinib is an oral, small molecule inhibitor of the epidermal growth factor receptor (EGFR) tyrosine kinase. Mutations in EGFR leading to their overexpression or overactivity are associated with a number of cancers, including lung cancer.

PHARMAC received an application from Roche Products (NZ) limited for the funding of erlotinib (Tarceva) as second-line treatment of locally-advanced or metastatic non-small cell lung cancer (NSCLC). The application was considered by the Cancer Treatments Subcommittee of the Pharmacology and Therapeutic Advisory Committee (CaTSoP) and the Pharmacology and Therapeutic Advisory Committee (PTAC). Relevant minutes are as follows:

### **CaTSoP February 2009**

#### **Erlotinib**

The Subcommittee considered an application from Roche Products for the listing of erlotinib for the second-line treatment of locally-advanced or metastatic non-small cell lung cancer (NSCLC). Members noted that this application had previously been reviewed by PTAC in 2006, at which time it was recommended for decline.

The Subcommittee noted that platinum doublets are considered the best first-line treatment option for advanced NSCLC, and that docetaxel is commonly used as a second-line agent.

Members reviewed the results of a clinical study authored by Shepherd et al (N Engl J Med. 2005 Jul 14;353(2):123-32.), which indicated a survival advantage of erlotinib over best supportive care in this patient group. However, the Subcommittee noted that there are no clinical trials that directly compare erlotinib with docetaxel in this patient group.

The Subcommittee considered that while there is insufficient evidence to indicate that erlotinib is more, or even similarly, effective than docetaxel, it appears that erlotinib may be better tolerated than docetaxel, in particular with regards to development of neutropenia and febrile neutropenia.

Members noted that not all patients currently receive docetaxel due to its toxicity, and that some patients who do receive it are given fewer than six cycles. Members considered that it was unlikely that the use of erlotinib would significantly reduce expenditure on docetaxel because many patients who received erlotinib as a second-line agent would likely end up taking docetaxel as a third-line agent upon disease progression.

Members noted that shifting docetaxel to third-line use may result in an increased number of patients being unable to tolerate docetaxel and, as such, some clinicians may prefer to use erlotinib only after failure of docetaxel.

The Subcommittee noted that only a small number of patients appear to respond to erlotinib, but that response in those patients, when it occurred, was significant. Members considered that early response is likely to be a good indicator of success.

The Subcommittee noted that it would be very difficult to target patients that are most likely to benefit from treatment with erlotinib based on the current evidence; however members considered that it would be reasonable to require a renewal application after 3 months with the requirement to demonstrate a lack of disease progression.

The Subcommittee **recommended** that erlotinib be listed as a second-line treatment for advanced or metastatic NSCLC subject to the above restriction. The Subcommittee considered that, within the context of cancer treatments, this recommendation should be considered a high priority.

The relevant decision criteria are: 1: *the health needs of all eligible people within New Zealand*; 2: *the particular health needs of Maori and Pacific peoples*; 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*; and 8: *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*).

## **PTAC May 2009**

### **Erlotinib (Tarceva) for Non Small-Cell Lung Cancer**

#### **Application**

The Committee reviewed a re-application from Roche Products for the listing of erlotinib on the Pharmaceutical Schedule for the second-line treatment of patients with locally-advanced or metastatic non-small cell lung cancer (NSCLC).

#### **Recommendation**

The Committee **recommended** that erlotinib be listed in the Pharmaceutical Schedule for the second-line treatment of patients with advanced or metastatic NSCLC. The Committee gave this recommendation a low priority.

The Decision Criteria relevant to this recommendation are: *(i) The health needs of all eligible people within New Zealand*; *(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*, *(vii) The direct cost to health service users*.

#### **Discussion**

The Committee noted that it had previously considered an application for erlotinib in May 2006 and concluded that the cost was high relative to modest clinical benefit, and recommended the application be declined. Members noted that in this re-application, although no new clinical trials have been published, Roche provided further discussion on the evidence in support of erlotinib, further analysis of the pivotal phase III study, BR.21, data from a large phase IV, open label, non-randomised cohort study (TRUST), and data from an open label phase IIIb study that was stopped early due to FDA approval (Spigel et al *Cancer*. 2008 Jun 15;112(12):2749-55).

The Committee noted that the re-application had been reviewed by CaTSoP at its February 2009 meeting and noted its recommendations.

The Committee reiterated its view that there was an unmet clinical need in patients with advanced NSCLC, for whom the prognosis is poor, but considered that erlotinib provided only a modest benefit compared with best supportive care.

The Committee considered that although it seemed that some patients responded well to erlotinib, for example non-smokers, patients with EGFR mutations or patients who develop a skin rash on treatment, it would be difficult to target those patients prospectively.

The Committee noted that there were no studies directly comparing erlotinib with other second line treatments, in particular docetaxel. Members considered that indirect comparison of data from a representative docetaxel study (Shepherd et al *J Clin Oncol* 2000;18:2095-2103) showed that erlotinib was likely to have similar efficacy but may be better tolerated than docetaxel and was certainly more convenient for patients to take. However, members noted that comparisons were confounded since the populations studied were not directly comparable (in terms of performance status) and the docetaxel studies had been performed some years earlier.

The Committee noted that NICE in the UK considered that “erlotinib could not reasonably be considered to have an overall survival benefit when compared with docetaxel, and that a progression-free survival benefit with docetaxel was more probable” (NICE, Final Appraisal Determination – Erlotinib for the treatment of non-small cell lung cancer, September 2008, paragraph 4.11).

The Committee considered that if funded, erlotinib would increase the overall number of patients accessing treatment for advanced NSCLC, principally because these patients would not need to access constrained DHB infusion services, unlike docetaxel treatment. Members further considered that funding erlotinib in the second line setting would shift docetaxel to third-line use.

The Committee noted that Maori have worse outcome with NSCLC compared with NZ Europeans. Members considered this was likely due to under-servicing at earlier stages of disease (screening, diagnostic, radiotherapy and first-line chemotherapy treatment). Members considered that funding erlotinib would not address the disparity and addressing under-servicing at earlier stages of disease should be a higher priority for investment by the health sector.

The Committee considered that the cost of erlotinib was high relative to its modest benefit. In particular members did not agree with the supplier’s view that it would be cost saving compared with docetaxel, when taking into account the increased numbers of patients likely to access treatment and the price reduction on docetaxel expected shortly as a result of patent expiry.

The proposal would result in approximately 100 patients with NSCLC accessing funded erlotinib each year. Erlotinib is an oral therapy, whereas the current treatments used in some of these patients must be administered by infusion in hospital, therefore, the funding of erlotinib would be likely to free up some hospital cancer infusion services and associated nursing resource.

### ***MabThera (rituximab)***

MabThera (rituximab), a monoclonal antibody, is a Pharmaceutical Cancer Treatment (PCT), meaning that only DHB hospitals can claim subsidies for its use. Rituximab is administered by infusion in hospital. Rituximab is currently funded, under Special Authority, for patients with Indolent Low grade Non Hodgkin’s lymphoma (NHL), aggressive CD20 positive NHL or B-cell post transplant lymphoproliferative disorder.

In 2009 PHARMAC consulted on a proposal to widen access to rituximab for the treatment of patients with indolent NHL, PHARMAC received a number of requests for access to widened further. PHARMAC staff sought advice on these matters from CaTSoP. The relevant minute is as follows:

#### **CaTSoP June 2009**

##### **Review of rituximab Special Authority criteria**

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).

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).

The Subcommittee considered these requests separately.

#### *Chronic lymphocytic leukaemia/small lymphocytic lymphoma*

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.

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”.

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.

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*

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-naïve aggressive CD20-positive NHL.

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.

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 salvag 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.

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.

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<sup>2</sup>, 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.

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*

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*

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.

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.

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.

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*

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.

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

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;

The proposal would result in up to 100 additional patients accessing funded rituximab each year.

### ***Xeloda (Capecitabine)***

Xeloda (capecitabine) is an orally administered form of the chemotherapeutic agent fluorouracil (5FU). Capecitabine is currently funded on the Pharmaceutical Schedule, under Special Authority, for the treatment of a variety of cancers.

PHARMAC received applications from clinicians for the widening of access to capecitabine for the pre-operative (neoadjuvant) treatment of locally advanced rectal cancer and the adjuvant treatment of patients with high-risk stage II colorectal cancer. The applications were reviewed by the PTAC and CaTSoP. Relevant minutes are as follows:

#### **CaTSoP March 2008**

##### **Capecitabine for neoadjuvant rectal cancer & high risk stage II colorectal cancer**

The Subcommittee reviewed an application from [ withheld under section 9(2)(a) of the OIA ], requesting that access to capecitabine (Xeloda) be widened to include pre-operative (neoadjuvant) treatment of locally advanced (node positive, stage III) rectal cancer and post-operative (adjuvant) treatment of high risk stage II colorectal cancer. The Subcommittee noted that neither population was covered by the current Medsafe-approved indication for capecitabine.

The Subcommittee noted that capecitabine is an oral fluoropyrimidine which has been studied as a replacement to 5-fluorouracil (5FU) (with/without calcium folinate, leucovorin, LV) injections in various settings. Members noted that as it is an oral product it is taken at home by the patient, thus reducing the need for patients to visit the hospital to receive treatment and avoiding complications of parenteral chemotherapy. Although the drug acquisition cost of capecitabine is higher than that of 5FU, members considered that when taking into account hospital cost savings, it is likely to be cost-effective compared with infusional 5FU treatment.

The Subcommittee noted that in a number of settings capecitabine has shown equivalent efficacy to 5FU, with a toxicity profile that is distinct from 5FU.

The Subcommittee discussed the two proposed patient populations separately:

#### *Neoadjuvant treatment of locally advanced (T3/T4: N0,1,2) rectal cancer*

The Subcommittee noted that chemoradiation (continuous infusion 5FU and radiation), is the standard of care for locally advanced rectal cancer. Members noted that the addition of 5FU-based chemotherapy to radiation therapy is used to radiosensitise the primary tumour and to eliminate systemic micrometastases.

The Subcommittee noted that there were some preclinical data suggesting that capecitabine may be a better radiosensitiser than infusional 5FU (Sawada N, Ishikawa T, Sekigushi F et al: X-ray irradiation induces thymidine phosphorylase and enhances the efficacy of capecitabine in human tumour xenografts. Clin Cancer Res 5:2948 – 2953); however, members considered this ideally needed to be confirmed in clinical trials. Members noted that currently there were no data demonstrating therapeutic equivalence of capecitabine with infusional 5FU in this setting; however, data will be forthcoming from study NSABP R-04, which is ongoing.

The Subcommittee considered that despite the lack of evidence for capecitabine in this setting, it was clear that chemoradiation with 5FU was efficacious in locally advanced rectal cancer and that capecitabine had shown equivalent efficacy to 5FU in other settings. Therefore, members considered that it made logical sense that in this setting that capecitabine should be used and it would likely be cost effective given the high resources and peripherally inserted central catheter (PICC line) complications associated with administration of continuous infusion 5FU.

The Subcommittee **recommended** that access to capecitabine be widened to include pre-operative (neoadjuvant) treatment of locally advanced (clinically or radiologically staged T3/T4: N0,1,2) rectal cancer, and gave this recommendation a high priority

The Subcommittee considered the decision criteria 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;* (v) *The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services;* and (viii) *The Government's priorities for health funding.*

#### *High risk stage II colorectal cancer patients*

The Subcommittee noted that the applicant had not provided evidence in support of the safety and efficacy of adjuvant fluoropyrimidines, either 5FU or capecitabine, in high risk stage II colorectal cancer patients, and members also considered that the definition of high risk stage II colorectal cancer was unclear.

The Subcommittee deferred making a recommendation for access to capecitabine being widened to include high risk stage II colorectal cancer. The Subcommittee considered that prior to it making a recommendation, PHARMAC staff should seek a consensus definition of 'high risk stage II colorectal cancer' from the New Zealand Association of Cancer Specialists (NZACS) and evidence for the safety and efficacy of adjuvant fluoropyrimidines in this patient population should be provided.

## **CaTSoP June 2009**

### **Capecitabine for High Risk Stage II Colorectal Cancer**

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.

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

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.

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)  $p=0.00018$ ).

The Subcommittee also reviewed evidence from a large trial (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.

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.

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.

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.

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.

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.

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.

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\*<sup>#</sup> 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**

**45 Both:**

**45.1 The patient has poor venous access or needle phobia\*; and**

**45.2 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:

**51 The patient requires continued therapy; or**

**62 The tumour has relapsed and requires re-treatment.**

Note indications marked with \* are Unapproved Indications, <sup>#</sup>capecitabine is approved for stage III (Dukes' stage C) colon cancer.

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.*

The proposal would result in up to 600 additional patients accessing funded capecitabine each year. Given that capecitabine is an oral therapy, compared with the currently used treatment in these patients, 5FU, which is administered by infusion in hospital, widening access to capecitabine would be likely to free up hospital cancer infusion services and associated nursing resources.

### **Cellcept (mycophenolate Mofetil)**

Cellcept (mycophenolate mofetil) is currently funded on the Pharmaceutical Schedule, under Special Authority, for renal, liver and heart transplant recipients, or for other organ transplant recipients with severe tophaceous gout making azathioprine unsuitable.

At its March 2010 meeting the Transplant Immunosuppressant Subcommittee of PTAC reviewed Exceptional Circumstances applications for transplant and immunosuppressant treatments, including mycophenolate, and a proposal for the listing of generic mycophenolate mofetil. Relevant excerpts from the minute of that meeting are as follows:

### *Exceptional Circumstances review*

The Subcommittee reviewed data provided by PHARMAC staff regarding Hospital, community and Cancer EC funding applications for various transplant and immunosuppressant treatments. Members considered that in general, from the information provided, the EC panel had approved relevant applications and declined applications where appropriate.

The Subcommittee noted that cyclosporin was now funded on the pharmaceutical Schedule without restriction; therefore further EC applications for this pharmaceutical are not expected.

The Subcommittee noted that the EC panel considers a large number of Hospital EC (HEC) applications for mycophenolate mofetil. Members noted that the panel needed to review most applications in some detail. Members noted that virtually all transplant applications (liver and lung) were automatically approved but that in most non-transplant indications the panel required that other treatment options had been trialled before HEC funding of mycophenolate was approved. Members considered that this approach was appropriate. Members considered that patients with lupus nephritis, autoimmune hepatitis, uveitis and vasculitis should have tried and failed steroids, cyclophosphamide and azathioprine prior to mycophenolate approval. However, members noted that because it causes infertility the use of cyclophosphamide was contraindicated in some patients, particularly young women of child bearing potential, therefore in such patients the use of mycophenolate earlier may be appropriate.

The Subcommittee considered that Pharmaceutical Schedule funding of mycophenolate for some regularly approved HEC indications would be helpful and recommended that mycophenolate be funded on the DCS list for patients with lupus nephritis, autoimmune hepatitis and vascular diseases. Members considered that if explicitly funded for these patients usage would likely increase, perhaps up to 3 fold, compared with current HEC applications.

### *Generic mycophenolate Mofetil*

The Subcommittee noted that a generic brand of mycophenolate mofetil had recently gained Medsafe approval. Members considered that generic mycophenolate should be funded, and if the cost was lower than the currently funded mycophenolate brand (Cellcept, Roche Products NZ Ltd) wider access should be considered in line with the recommendations made above in relation to EC applications for mycophenolate. Members considered that access could be widened further depending on its price relative to other treatment options. Members considered that if listed without restriction mycophenolate would be the preferred first line agent, replacing cyclosporin and cyclophosphamide in many indications.

PHARMAC recently consulted on a proposal to list Douglas Pharmaceuticals' brand of mycophenolate mofetil (Myaccord) 250 mg capsule and 500 mg tablet from 1 October 2010 under the same criteria as is now being proposed for Cellcept. No decision regarding the Douglas proposal has yet been made.