Cancer Treatments Subcommittee meeting held 15 April 2011

(minutes for web publishing)

Cancer Treatments Subcommittee minutes are published in accordance with the *Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) and PTAC Subcommittees 2008*.

Note that this document is not necessarily a complete record of the Cancer Treatments Subcommittee meeting; only the relevant portions of the minutes relating to Cancer Treatments Subcommittee discussions about an Application or PHARMAC staff proposal that contain a recommendation are published.

The Cancer Treatments Subcommittee may:

(a) recommend that a pharmaceutical be listed by PHARMAC on the Pharmaceutical Schedule and the priority it gives to such a listing;
(b) defer a final recommendation, and give reasons for the deferral (such as the supply of further information) and what is required before further review; or
(c) recommend that PHARMAC decline to list a pharmaceutical on the Pharmaceutical Schedule.

These Subcommittee minutes were reviewed by PTAC at its meeting on 11 & 12 August 2011, the record of which is available on the PHARMAC website.

Contents

1 Topotecan

1.1 The Subcommittee noted that in June 2008 when reviewing the funding of pegylated liposomal doxorubicin (PLDH, Caelyx) for treatment of patients with advanced ovarian cancer it noted that key evidence came from a study comparing PLDH with topotecan which was not available in New Zealand at that time. Members noted that PHARMAC staff had identified a source of generic topotecan for NZ and asked if there was any interest in it being funded.

1.2 The Subcommittee considered that there remained an unmet medical need for effective third line treatment options for patients with ovarian cancer. Members considered that various treatments in this setting appeared to be similarly efficacious, these included etoposide, weekly paclitaxel or gemcitabine, topotecan or PLDH.

1.3 The Subcommittee considered that funded topotecan would provide another treatment option, which would be useful, but it was quite toxic therefore it would not be suitable for all patients.

1.4 The Subcommittee **recommended** that PHARMAC staff seek a funding application for topotecan from the Gynaecology Special Interest Group of the Association of New Zealand Cancer Specialists.

2 Rituximab *for CLL*

2.1 The Subcommittee noted that during recent negotiations on a proposal to fund rituximab for patients with CLL Roche had raised an issue with the Special Authority criteria recommended by CaTSoP at its 20 August 2010 meeting.

2.2 Members noted that the recommended criteria were based on the entry criteria for the populations enrolled in the key clinical trials for relevant populations, namely CLL-8 for treatment naïve patients and REACH for relapsed refractory, rituximab naïve patients.

2.3 The Subcommittee noted that the proposed Special Authority criteria for relapsed refractory patients excluded patients who had previously received fludarabine and cyclophosphamide (FC) chemotherapy. Members noted that currently most patients with CLL, in the absence of rituximab funding, would be receiving FC chemotherapy, therefore, in practice the proposed criteria would exclude most patients from receiving funded rituximab in the relapsed refractory setting.

2.4 The Subcommittee reviewed evidence provided by Roche from an open label Phase II trial (Xavier et al Blood March 17, 2011 vol. 117 no. 11 3016-3024) in patients with relapsed CLL, with up to 3 prior treatments, to support the use of rituximab (in combination with FC) in patients who have previously been treated with FC. Members considered that this provided evidence that FC relapsed patients were responsive to treatment with R-FC, albeit to a lesser extent than treatment naïve or single agent relapsed/refractory patients.

2.5 The Subcommittee considered that it was reasonable to change its proposed Special Authority criteria to permit funding for patients who had previously received FC chemotherapy, however, members considered that funding should exclude patients with disease that had relapsed within 12 months of receiving FC chemotherapy. Members considered that this would result in a significantly larger number of patients accessing rituximab treatment over the first 2-3 years, however, the exact numbers of patients were difficult to determine.

2.6 The Subcommittee considered that funding for rituximab should be limited to treatment naïve or 1st relapse only since evidence from Xavier et al demonstrated that treatment response diminished with subsequent lines of therapy, with a marked drop off in response in patients who received 2 or more prior lines of treatment.

2.7 The Subcommittee **recommended** that rituximab should be funded under Special Authority criteria as follows:

> **Rituximab – PCT only – Specialist - Special Authority for Subsidy**
> **Initial application — (CLL)** 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 progressive Binet stage A, B or C chronic lymphocytic leukaemia requiring treatment; and
> 2. The patient is rituximab treatment naïve; and
> 3. Either
> 3.1. The patient is chemotherapy treatment naïve; or
> 3.2. Both:
> 3.2.1. The patient's disease has relapsed following no more than one prior line of chemotherapy treatment; and
> 3.2.2. The patient has had a treatment-free interval of 12 months or more if previously treated with FC chemotherapy; and
> 4. The patient has good performance status (WHO/ECOG grade 0-1); and
> 5. The patient has good renal function (creatinine clearance ≥ 60 ml/min); and
> 6. The patient does not have chromosome 17p deletion CLL; and
> 7. Rituximab to be administered in combination with fludarabine and cyclophosphamide for a maximum of 6 treatment cycles;
> 8. It is planned that the patient receives full dose intravenous fludarabine (25 mg/m2 IV for 3 days) and cyclophosphamide (250 mg/m2 IV for 3 days) or dose equivalent oral fludarabine.

2.8 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.*

3 Therapeutic Group Review

3.1. The Subcommittee reviewed data on the expenditure and usage of cancer pharmaceuticals including funding applications considered under the Cancer Exceptional Circumstances (CaEC) scheme.

3.2. *Gemcitabine*

3.2.1. The Subcommittee noted the recent price decrease for gemcitabine hydrochloride and **recommended** that the Special Authority be removed. Members considered that the majority of uses for gemcitabine were already covered by the Special Authority, therefore, the risk of a significant increase in expenditure from removing the Special Authority was limited.

3.3. *Peg-asparaginase*

3.3.1. The Subcommittee noted that PHARMAC had received a number of Cancer Exceptional Circumstances applications for peg-asparaginase for the treatment of patients with Acute Lymphoblastic Leukaemia (ALL). Members noted that peg-asparaginase was part of standard treatment protocols for paediatrics with ALL, and that this was influencing adolescent and adult treatment. Members considered that peg-asparaginase may have advantages over standard L-asparaginase (Leunase) in some patients due to decreased immunogenicity and prolonged half-life.

3.3.2. The Subcommittee **recommended** that peg-asparaginase should be listed on the Pharmaceutical Schedule subject to Special Authority criteria as follows:

> **PEG -L-asparaginase – PCT only – Specialist - Special Authority for Subsidy**
> **Initial application — (ALL)** 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 newly diagnosed acute lymphoblastic leukaemia; and
> 2 PEG -L-asparaginase to be used with a contemporary intensive multi-agent chemotherapy treatment protocol specifically for treatment of paediatric, adolescent and young adult patients.
>
> **Renewal — (ALL)** 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 relapsed acute lymphoblastic leukaemia; and
> 2 PEG -L-asparaginase to be used with a contemporary intensive multi-agent chemotherapy treatment protocol specifically for treatment of paediatric, adolescent and young adult patients; and
> 3 Treatment is with curative intent

3.4. *Ursodeoxycholic acid*

3.4.1. The Subcommittee noted that PHARMAC had received a number of Hospital Exceptional Circumstances applications for ursodeoxycholic acid for the prevention of hepatic complications and veno-occlusive disease in patients receiving high dose conditioning therapy prior to bone marrow or stem cell transplantation. Members noted that defibrotide used to be used for this

indication but its price had recently increased significantly and therefore hospitals were switching to ursodeoxycholic acid as a partial alternative as it was cost saving.

3.4.2. The Subcommittee **recommended** that the Special Authority criteria applying to the funding of ursodeoxycholic acid in Section B of the Pharmaceutical Schedule be amended to include funding for up to 13 weeks for patients at risk of veno-occlusive disease, or those with hepatic impairment, undergoing intensive conditioning treatment prior to allogeneic stem cell or bone marrow transplant.

3.4.3. The Subcommittee **recommended** that the Special Authority not be removed from ursodeoxycholic acid until consideration were given to the fiscal risk from its increased use as chemoprevention for colorectal cancer in patients with ulcerative colitis.

4 Lapatinib for Her 2 positive metastatic breast cancer

4.1. The Subcommittee considered an application from GlaxoSmithKline (GSK) for the funding of lapatinib ditosylate (Tykerb) on the Pharmaceutical Schedule as an alternative to trastuzumab for the first line treatment of patients with HER2 positive metastatic breast cancer (mBC).

4.2. The Subcommittee noted that the application had been reviewed by PTAC at its February 2011 meeting. Members also reviewed correspondence from GSK provided in response to PTAC's February 2011 minute.

4.3. The Subcommittee noted that the majority of evidence provided had already been reviewed by it on prior occasions. Members considered that there was little new evidence provided in the application.

4.4. The Subcommittee noted randomised evidence for the use of lapatinib as first line treatment for HER2 positive mBC was limited to 3 studies; EGF30001 (Di Leo et al J Clin Oncol 2008, Sherril et al Curr Med Res Opin. 2010), EGF30008 (Johnston et al J Clin Oncol 2009 and Schwartzberg et al J Clin Oncol 2010). and EGF104535 (study ongoing, abstract published Guan et al 2008 ASCO Breast cancer symposium). Members considered that overall the quality of evidence was poor noting that one of the studies retrospectively extracted data for HER2 positive patients from a mixed mBC population of unknown status (EGF 30001) and one study (EGF104535) enrolled trastuzumab treatment naïve mBC patients which is not very representative of that seen in New Zealand, or the majority of the western world.

4.5. The Subcommittee considered that overall the evidence demonstrated that the addition of lapatinib to standard first line mBC treatments (letrozole or paclitaxel) resulted in statistically significant improvements in progression free survival with numerical improvement in overall survival.

4.6. The Subcommittee reviewed an indirect meta-analysis comparing trastuzumab with lapatinib conducted by the supplier. However, members considered it was not possible to draw meaningful conclusions regarding the relative efficacy of lapatinib and trastuzumab from this meta-analysis because of study heterogeneity across the two treatment groups.

4.7. The Subcommittee considered that there were some features of lapatinib which should, in theory, make it a better drug than trastuzumab, namely: oral administration, its ability to cross the blood brain barrier and intracellular HER1 and HER2 targeting, however members noted that evidence from the only available head to head study (Neo-ALLTO presented at the San Antonio Breast Cancer Symposium in December 2010), albeit in a different breast cancer population, did not support this. Members noted that Neo-ALLTO was a three-arm study comparing the efficacy and tolerability of neo-adjuvant lapatinib plus paclitaxel, versus trastuzumab plus paclitaxel, versus the combination of lapatinib plus trastuzumab plus paclitaxel given as neo-adjuvant treatment in HER2 primary breast cancer. Members noted that lapatinib treated patients faired no better than trastuzumab treated patients while the best responses were seen in the combination arm. Pathological complete response (pCR) was significantly higher in the combination arm (lapatinib plus trastuzumab) compared with either trastuzumab or lapatinib alone (51.3% vs. 29.5% vs. 24.7%, respectively; $p < 0.01$ for both).

4.8. The Subcommittee considered that the side effect profile of lapatinib was quite different to trastuzumab, in particular members noted that lapatinib related diarrhoea can be a significant problem in a number of patients.

4.9. The Subcommittee considered that in the first line mBC setting lapatinib would most likely be used in combination with capecitabine, which is also associated with diarrhoea. Members considered that few patients would be administered lapatinib in combination with paclitaxel as most patients would have already received a taxane in the adjuvant setting, similarly, few patients would receive lapatinib in combination with letrozole, perhaps with the exception of elderly patients.

4.10. The Subcommittee considered that there was no clinical reason not to fund lapatinib as an alternative to trastuzumab for the first line treatment of patients with HER2 positive mBC. Members considered that if funded there would be limited uptake of lapatinib, with perhaps only 10% of patients being treated with lapatinib rather than trastuzumab at least initially, because clinicians are familiar with trastuzumab, it is better tolerated than lapatinib and infusion capacity for its administration is not an issue in most centres. However, members considered that lapatinib may be particularly useful for patients presenting with mBC whose disease has progressed during or shortly following adjuvant trastuzumab treatment, those living in rural areas or those with needle phobia.

4.11. The Subcommittee noted and agreed with PTAC's recommendation to decline funding of lapatinib as a second line treatment in patients with HER 2 positive mBC patients following disease progression on trastuzumab. However, members considered that lapatinib may be a useful alternative treatment option for HER2 positive mBC patients who are genuinely intolerant of trastuzumab (usually apparent within the first 1 or 2 doses), and vice versa.

4.12. The Subcommittee **recommended** that lapatinib should be funded as an alternative to trastuzumab for the first line treatment of patients presenting with HER 2 positive metastatic breast cancer only if cost neutral to the health sector. The Subcommittee **recommended** that in the event that lapatinib were funded, funding should be structured such that patients with HER2 positive mBC receive only one funded HER2

targetted treatment course, either trastuzumab or lapatinib, unless toxicity issues prevented first choice treatment being completed.

4.13. The Subcommittee further **recommended** that lapatinib should be funded as an alternative treatment option in patients with mBC, who show early intolerance to trastuzumab and whose disease has not progressed.

4.14. The Subcommittee further **recommended** that trastuzumab should be funded as an alternative treatment option in patients with mBC, who show early intolerance to lapatinib started for first-line metastatic disease and whose disease has not progressed.

4.15. The Decision Criteria particularly relevant to these recommendations are: *(i) The health needs of all eligible people within New Zealand; (ii) The particular health needs of Māori and Pacific peoples; (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.*

5 Trastuzumab for HER2 positive locally advanced or metastatic gastric cancer

5.1. The Subcommittee considered an application from Roche Products (NZ) Ltd for trastuzumab (Herceptin) to be funded for the treatment of patients with locally advanced or metastatic gastric cancer or gastro-oesophageal junction (GEJ) tumours exhibiting high levels of HER 2 positivity (IHC 2+/ISH+ or IHC 3+), in combination with capecitabine or 5FU and platinum based chemotherapy. The Subcommittee noted that the application had been reviewed by PTAC at its February 2011 meeting.

5.2. The Subcommittee considered that currently the majority of New Zealand patients with advanced gastric cancer would be treated with triplet chemotherapy comprising epirubicin, cisplatin and capecitabine (ECX) or epirubicin, cisplatin and fluorouracil (ECF).

5.3. The Subcommittee noted relevant evidence comprised a single open label, phase III study comparing trastuzumab plus chemotherapy or chemotherapy alone in 594 adult patients with FISH or IHC 3+ HER2 positive inoperable locally advanced or metastatic gastric or GEJ cancer (Trastuzumab for Gastric Cancer (ToGA) study, Bang et al. Lancet 2010;376:687-97). Members noted that the majority of patients enrolled had good performance status (ECOG of 0-1). Members noted that the addition of trastuzumab to chemotherapy led to a statistically significant improvement of 2.7 months in median overall survival (OS), the primary endpoint of the study, and a 1.2 month gain in progression free survival. Members noted that there was no difference in quality of life between the two treatment groups.

5.4. The Subcommittee noted a pre-planned subgroup analysis showing variable survival in patients with different levels of HER2 expression but considered that is was hard to discern any strong relationship between survival and HER2 expression levels.

Members further noted a dichotomy analysis of survival in patients with 'high' HER2 expression (defined as IHC 2+/FISH positive or IHC 3+) or 'low' HER2 expression (defined as IHC 0 or 1+/FISH positive) which showed that trastuzumab improved overall survival by 4.2 months in patients with 'high' HER2 expression. However, members noted that this was an unplanned post-hoc analysis therefore considered the validity of the result was questionable. Overall members considered that the evidence provided was of moderate strength and quality.

5.5. The Subcommittee considered that the role of HER 2 testing and concordance between FISH positivity, IHC positivity, and response to trastuzumab was not as clear as in breast cancer. Members considered that HER 2 expression appeared to be different in gastric cancers compared with breast cancer, for example some patients demonstrate FISH positivity without detectable protein expression and considered that HER 2 testing for gastric cancers should only be undertaken by specialist central laboratories.

5.6. The Subcommittee considered that the benefits of trastuzumab treatment for gastric cancer patients were modest and questioned whether the improvements were clinically relevant. Members noted that in the metastatic breast cancer setting trastuzumab provided considerably larger benefits.

5.7. The Subcommittee considered that the significance of the results from the ToGA had been overplayed and researchers appeared to have focussed on finding positive results through post-hoc analyses, and discounting everything else. Members considered that a second randomised controlled study was required in order to verify the results from ToGA and determine the true benefit of trastuzumab in this setting.

5.8. The Subcommittee noted that the suppliers own cost utility analysis had estimated a cost per QALY for trastuzumab greater that $100,000. Members considered that this analysis was conservative (i.e. the cost per QALY was likely to be higher) since it assumed equal efficacy between the doublet regimen (CF/X) used in ToGA trial and currently used triplet regimens (ECF/X), whereas, members considered that epirubicin would likely confer some additional efficacy benefit, for little cost, over CF/X.

5.9. The Subcommittee **recommended** that the application be declined.

5.10. The Decision Criteria particularly relevant to this recommendation are: (*i) The health needs of all eligible people within New Zealand; (ii) The particular health needs of Māori and Pacific peoples; (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 Pazopanib for advanced/metastatic renal cell carcinoma

6.1. The Subcommittee considered an application from GlaxoSmithKline (NZ) Ltd for the listing of pazopanib (Votrient) on the Pharmaceutical Schedule for the treatment of

patients with advanced or metastatic renal cell carcinoma (RCC). The Subcommittee noted that the application had been reviewed by PTAC at its February 2011 meeting.

6.2. The Subcommittee noted that pazopanib hydrochloride is an oral tyrosine kinase inhibitor (TKI). The committee noted that another TKI, sunitinib (Sutent, Pfizer inc), was recently funded for patients with poor and intermediate prognosis advanced or metastatic RCC. Members noted that the supplier had requested funding for pazopanib as an alternative first line treatment to sunitinib, or as a second line treatment for patients who were intolerant of sunitinib.

6.3. The Committee noted that key evidence comprised a single randomised, double blind, phase III study comparing pazopanib (800 mg daily) with placebo (study VEG105192, Sternberg et al Journal of Clinical Oncology, 2010 Feb 20;28(6):1061-8.) in treatment-naive and cytokine-pretreated patients with advanced RCC. Members considered that evidence to be of average quality but that the choice of placebo as the control arm was questionable given that at the time of starting the study interim results of studies comparing sunitinib or sorafenib with interferon had been published.

6.4. The Subcommittee noted that treatment with pazopanib significantly improved median progression free survival (PFS) by 5 months compared with placebo. However, members noted that although median overall survival was prolonged by 2.4 months this result did not meet the pre-specified significance level for this interim analysis and was likely confounded by permitted cross-over in the study.

6.5. The Subcommittee noted that despite improved PFS there was no apparent difference in quality of life for the two treatment groups. Members were disappointed by this result but considered that it pointed to the fact that TKIs in general had significant toxicity issues which impacted patients quality of life significantly. Members noted that pazopanib was associated with increased liver toxicity, fatigue and anorexia, all of which would negatively impact quality of life.

6.6. The Subcommittee noted that there was currently no direct evidence comparing pazopanib with other TKIs or interferon. Members considered that because sunitinib was already funded there was no evidence that pazopanib would address any unmet medical need in the treatment of patients with advanced RCC. However, members considered that competition in the TKI market through the introduction of a second molecule may be useful given the high cost of these treatments and would give clinicians and patients more choice.

6.7. The Subcommittee considered that there was no evidence to support the use of pazopanib after sunitinib treatment failure, or vice versa, but considered that because the two treatments had different side effect profiles pazopanib may be useful in patients who experienced treatment limiting sunitinib toxicity such as Palmar Plantar Erythrodysesthesia (PPE).

6.8. The Subcommittee **recommended** that pazopanib should be listed on the Pharmaceutical Schedule as an alternative to sunitinib under the same Special Authority criteria as sunitinib only if cost neutral to the Health Sector. The

Subcommittee further **recommended** that pazopanib should not be funded for second line use after failure of sunitinib treatment and vice versa.

6.9. The Subcommittee further **recommended** that if a cost neutral listing were not possible pazopanib should be listed on the Pharmaceutical Schedule for patients who experience treatment limiting PPE on sunitinib and whose disease had not progressed whilst on sunitinib, members gave this recommendation a low priority.

6.10. The Decision Criteria particularly relevant to this recommendation are: *(i) The health needs of all eligible people within New Zealand; (ii) The particular health needs of Māori and Pacific peoples; (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*

7 Deferasirox in congenital inherited anaemias

7.1. The Subcommittee considered a submission from Orphan Australia in response to the Subcommittee's minutes from its November 2010 meeting. The Subcommittee also noted that PTAC had recommended that the Subcommittee review its proposed Special Authority criteria for deferasirox as they were too wide and could possibly result in a large proportion of patients with congenital inherited anaemias accessing deferasirox, hence posing a fiscal risk.

7.2. The Subcommittee noted that there were currently three treatment options for iron chelation; desferrioxamine which is an injection, deferiprone and deferasirox which are both oral treatments. The Subcommittee noted that deferasirox potentially has a compliance advantage as it is a once-daily treatment versus deferiprone which requires administration three times a day. The Subcommittee noted that the first two treatment options are currently fully funded on the Pharmaceutical Schedule with deferiprone being restricted by Special Authority to patients with chronic transfusional iron overload due to congenital inherited anaemia.

7.3. The Subcommittee considered that desferrioxamine is an effective iron chelator and is considered the standard of care for children <6 years of age although there is a lack of evidence in this age group for all three iron chelators. The Subcommittee considered also that iron chelation is not started in children unless it is absolutely necessary to reduce rising iron levels as treatment with desferrioxamine has been associated with bone exostosis, ototoxicity and Yersinia infections.

7.4. The Subcommittee noted a recent study by El Alfy et al (J Pediatr Hematol Oncol. 2010 Nov; 32(8): 601-5) which evaluated the safety and efficacy of deferiprone in 100 children aged between 1 and 10 years of age. Although the trial was for a short duration of 6 months, the Committee noted that no unexpected adverse reactions were observed with deferiprone and treatment resulted in a significant decline in mean serum ferritin levels. The Subcommittee noted that deferiprone is not contraindicated in children < 6 years of age and although limited, there is adequate evidence to support it as a treatment option in children < 6 years of age. The

7.5. The Subcommittee also noted that heart disease (71%) was the leading cause of death in patients with thalassaemia major, followed by infections (13%) and liver disease (6%) according to Borgna-Pignatti C et al (Ann NY Acad Sci 1998; 16-17), and current evidence supports that deferiprone is the most effective iron chelator for cardiac protection.

7.6. The Subcommittee considered that although heart disease was the leading cause of mortality, it was still important to monitor iron in all three storage compartments; serum ferritin, cardiac iron (MRI T2*) and liver iron (MRI T2*). The Subcommittee considered that there is currently limited evidence to support deferasirox use in patients who have been ineffectively treated with deferiprone. There is however evidence that combination therapy with deferiprone and desferrioxamine would be effective in this patient group, especially in patients with rising cardiac iron levels. Although effective, the Subcommittee noted that combination therapy would however be associated with higher drug and administration costs, possibly higher than that for deferasirox. The need for subcutaneous infusions on top of oral treatment would also be unfavourable to patients and possibly result in reduced compliance leading to reduced efficacy. The Subcommittee considered that current evidence supports the use of combination therapy with deferiprone and desferrioxamine as the next treatment option following ineffective treatment with deferiprone but deferasirox could be an appropriate option in patients who would be unlikely to be compliant with combination therapy. The Subcommittee considered that clinicians would need to weigh up the possible treatment options for individual patients based on current evidence, treatment efficacy and patient compliance.

7.7. The Subcommittee considered that it would be appropriate to allow patients who have had intolerable gastrointestinal and joint symptoms from deferiprone to access deferasirox. The Subcommittee considered that although this would involve very subjective measures, it would be appropriate to allow clinicians to exercise their clinical judgements to weigh up drug tolerability and treatment efficacy for each individual patient.

7.8. The Subcommittee considered that it would be appropriate to replace the previously recommended Special Authority criteria, ‘Treatment with deferiprone has resulted in agranulocytosis’ with ‘Treatment with deferiprone is contraindicated due to a history of recurrent episodes of neutropenia or a history of agranulocytosis’. The Subcommittee considered that the definition of ‘recurrent neutropenia’ should be greater than 2 episodes of neutropenia.

7.9. The Subcommittee considered that it would be appropriate to implement 2-yearly renewal Special Authority restrictions for deferasirox based on the efficacy parameters of serum ferritin, cardiac MRI T2* and liver MRI T2*. The Subcommittee considered that improvements in all three parameters above would need to be demonstrated to qualify for further funded treatment of deferasirox in the first renewal. For subsequent renewals, the Subcommittee considered that it would be appropriate that stability (or continued improvement) in all three measures would need to be demonstrated. The Subcommittee also considered that for safety and

7.10. The Subcommittee **recommended** that deferasirox be funded with high priority for patients with transfusional iron overload secondary to congenital anaemias and restricted via the following Special Authority due to its high cost:

Special Authority for Subsidy

Initial application only from a relevant specialist. Approvals valid for 2 years for applications meeting the following criteria:

All of the following:

1. The patient has been diagnosed with chronic transfusional iron overload due to congenital inherited anaemia; and
2. Deferasirox is to be given at a daily dose not exceeding 40mg/kg/day; and
3. Either
   - 3.1. Treatment with maximum tolerated doses of deferiprone monotherapy or deferiprone and desferrioxamine combination therapy have proven ineffective as measured by serum ferritin levels, liver or cardiac MRI T2*; or
   - 3.2. Treatment with deferiprone has resulted in severe persistent gastrointestinal side-effects like vomiting or diarrhoea; or
   - 3.3. Treatment with deferiprone has resulted in arthralgia or arthritis; or
   - 3.4. Treatment with deferiprone is contraindicated due to a history of agranulocytosis (defined as an absolute neutrophil count (ANC) of < 0.5 cells per µL) or recurrent episodes (greater than 2 episodes) of moderate neutropenia (ANC 0.5 - 1.0 cells per µL)

Renewal only from a relevant specialist. Approvals valid for 2 years for applications meeting the following criteria:

Either:

1. For the first renewal following 2 years of therapy, the treatment has been tolerated and has resulted in clinical improvement in all three parameters namely serum ferritin, cardiac MRI T2* and liver MRI T2* levels; or
2. For subsequent renewals, the treatment has been tolerated and has resulted in clinical stability or continued improvement in all three parameters namely serum ferritin, cardiac MRI T2* and liver MRI T2* levels.

7.11. 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*