CONSULTATION

PHARMAC
Pharmaceutical Management Agency

30 August 2012

Proposal for various Pfizer products: voriconazole, azithromycin, minoxifil, midazolam, sunitinib and dalteparin

PHARMAC is seeking feedback on a proposal to fund, from 1 November 2012:

- **voriconazole (Vfend)** for patients with invasive fungal infections ;
- **azithromycin granules for oral liquid (Zithromax)**;
- **minoxidil (Loniten)**for patients with severe refractory hypertension;
- **midazolam injections (Pfizer-Midazolam)**;
- **dalteparin sodium (Fragmin)** for venous thromboembolism treatment and prophylaxis in certain clinical situations; and
- **sunitinib (Sutent)**, for patients with imatinib refractory, or intolerant, unresectable or metastatic malignant gastrointestinal stromal tumour (GIST)

through a provisional agreement with Pfizer New Zealand Limited.

The proposal is consistent with advice from the Pharmacology and Therapeutics Advisory Committee (PTAC) and its relevant Subcommittees.

Further details of this proposal, including how to provide feedback and background information, can be found below and on the following pages.

Feedback sought

PHARMAC welcomes feedback on this proposal. To provide feedback, please submit it in writing by **Friday, 14 September 2012** 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 and background

In relation to voriconazole (Vfend):

- Voriconazole tablets and powder for oral suspension would be listed in Section B and in Part II of Section H of the Pharmaceutical Schedule from 1 November 2012. The

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following prices and subsidies would apply (all prices are ex-manufacturer and exclude GST):

Pharmaceutical	Brand	Pack size	Price and subsidy
Voriconazole 50 mg tablets	Vfend	56	$730.00
Voriconazole 200 mg tablets	Vfend	56	$2,930.00
Voriconazole 40 mg per ml grans for oral liq	Vfend	70ml	$730.00

- Voriconazole injections would be listed in Part II of Section H of the Pharmaceutical Schedule from 1 November 2012. The following price would apply (all prices are ex-manufacturer and exclude GST):

Pharmaceutical	Brand	Pack size	Price
Voriconazole 200 mg injection	Vfend	1	$185.00

- Voriconazole tablets and granules for oral liquid would be funded under the following Special Authority criteria:

Special Authority for Subsidy
Initial application (invasive fungal infection) only from a haematologist or infectious disease specialist. Approvals valid for 1 month for applications meeting the following criteria:
Both:
1. Patient is immunocompromised; and
2. Either:
   2.1. Patient has proven or probable invasive aspergillus infection; or
   2.2. Both:
      2.2.1. Applicant is part of a multidisciplinary team including an infectious disease specialist; and
      2.2.2. Any of the following:
         2.2.2.1. Patient has possible invasive aspergillus infection; or
         2.2.2.2. Patient has fluconazole resistant candidiasis; or
         2.2.2.3. Patient has mould strain such as *Fusarium spp*. and *Scedosporium spp.*

Renewal application (invasive fungal infection) only from a haematologist or infectious disease specialist. Approvals valid for 1 month for applications meeting the following criteria:
Both:
1. Patient is immunocompromised; and
2. Either:
   2.1. Patient continues to require treatment for proven or probable invasive aspergillus infection; or
   2.2. Both:
      2.2.1. Applicant is part of a multidisciplinary team including an infectious disease specialist; and
      2.2.2. Any of the following:
         2.2.2.1. Patient continues to require treatment for possible invasive aspergillus infection; or
         2.2.2.2. Patient has fluconazole resistant candidiasis; or
         2.2.2.3. Patient has mould strain such as *Fusarium spp*. and *Scedosporium spp.*

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- Vfend would have protection from subsidy reduction and delisting until 30 June 2015.

Background

Voriconazole is indicated for the treatment of the following fungal infections: invasive aspergillosis, serious candida infections including oesophageal and systemic candida infections and serious fungal infections caused by Scedosporium spp. and Fusarium spp.

PTAC and its Anti-Infective Subcommittee have recommended funding voriconazole with a high priority under Special Authority for treatment of invasive fungal infections. Relevant minutes can be found at the following links:
http://pharmac.govt.nz/2011/01/17?q=PTACminutes
http://pharmac.govt.nz/2012/06/20

In relation to azithromycin suspension (Zithromax):

- Azithromycin suspension (Zithromax) would be fully funded in Section B and the listing would be amended in Part II of Section H of the Pharmaceutical Schedule from 1 November 2012. The following prices and subsidies would apply (price is ex-manufacturer and excludes GST):

Pharmaceutical	Brand	Pack size	Price and subsidy
Azithromycin grans for oral liq 200 mg per 5ml	Zithromax	15 ml	$6.60

- Zithromax would be funded under the following restriction:

a) Maximum of 5 days treatment per prescription; can be waived by endorsement for the following patients:

Patient has either:

i. Received a lung transplant and requires treatment or prophylaxis for bronchiolitis obliterans syndrome; or

ii. Cystic fibrosis and has chronic infection with Pseudomonas aeruginosa or Pseudomonas related gram negative organisms.

- Zithromax would have protection from subsidy reduction and delisting until 30 June 2015

Background

The Anti-Infective Subcommittee at its 1 March 2012 meeting noted the following with respect to an alternative liquid macrolide for paediatric usage:

> The Subcommittee **recommended** that PHARMAC staff seek an alternative liquid macrolide for paediatric use and suggested either roxithromycin dispersible tablets, clarithromycin liquid or azithromycin liquid.

In July 2012 PHARMAC consulted upon removing all restrictions relating to azithromycin tablets http://pharmac.govt.nz/2012/07/04. After considering feedback received we have issued a further consultation proposing to amend the restriction on the tablets to be consistent with the restrictions proposed for azithromycin suspension. Further details of this proposal can be found at http://pharmac.govt.nz/2012/08/30?q=azithromycin

In relation to minoxidil (Loniten):

- Minoxidil tablets (Loniten) would be fully funded in Section B and listed in Part II of Section H of the Pharmaceutical Schedule from 1 November 2012. The following prices and subsidies would apply (price is ex-manufacturer and excludes GST):

Pharmaceutical	Brand	Pack size	Price and subsidy
Minoxidil 10 mg tablet	Loniten	100	$70.00

- Minoxidil would be funded under the following Special Authority restriction:

Special Authority for Subsidy

Initial application from any relevant specialist. Approvals valid for 2 years where the patient has severe refractory hypertension which has failed to respond to extensive multiple therapies.

Renewal application from any relevant specialist**.** Approvals valid for 2 years where the treatment remains appropriate and the patient is benefiting from the treatment.

- Loniten would have protection from subsidy reduction and delisting until 30 June 2015
- Minoxidil would be removed from the Discretionary Community Supply list.

Background

Minoxidil is indicated as an adjunctive therapy for adults with severe refractory hypertension which has failed to respond to extensive multiple therapy. When used in combination with an accompanying diuretic and beta-blocker, minoxidil has been shown to reverse encephalopathy and retinopathy in patients with severe hypertension. Minoxidil is currently listed on the Discretionary Community Supply list for "indefinite supply for the treatment of severe hypertension that is resistant to other anti-hypertensives or where alternative are not tolerated". Given that it is available for indefinite supply it is more appropriate that it is listed in Section B of the Pharmaceutical Schedule for community supply than being listed on the Discretionary Community Supply list.

In relation to midazolam injections (Pfizer-midazolam):

- Midazolam injections (Pfizer-midazolam) would be fully funded in Section B and listed in Part II of Section H of the Pharmaceutical Schedule from 1 November 2012. The following prices and subsidies would apply (all prices are ex-manufacturer and exclude GST):

Pharmaceutical	Brand	Pack size	Price and subsidy
Midazolam inj 1mg per ml, 5 ml	Pfizer-midazolam	10	$10.00
Midazolam inj 5mg per ml, 3ml	Pfizer-midazolam	5	$11.90

- Pfizer-midazolam would have protection from subsidy reduction and delisting until 30 June 2015

Background

Midazolam injection is used as an anaesthetic and sedative agent. There are currently two brands of midazolam injections funded in Section B of the Pharmaceutical Schedule - Pfizer-midazolam which is partly subsidized and Roche's brand, Hypnovel which is fully subsidized. Hypnovel is also currently listed in Part II of Section H of the Pharmaceutical Schedule. Pfizer-midazolam comes in a plastic ampoule whilst Hypnovel is in a glass ampoule. This proposal would result in two brands of midazolam injection being fully subsidized.

In relation to dalteparin sodium (Fragmin):

- Dalteparin sodium prefilled/graduated syringes would be listed in Section B and the listing will be amended in Part II of Section H of the Pharmaceutical Schedule from 1 November 2012. The following prices and subsidies would apply (all prices are ex-manufacturer and exclude GST):

Pharmaceutical	Brand	Pack size	Price and subsidy
Dalteparin sodium prefilled syringe 2500 IU per 0.2 mL	Fragmin	10	$19.97
Dalteparin sodium prefilled syringe 5000 IU per 0.2 mL	Fragmin	10	$39.94
Dalteparin sodium graduated syringe 7500 IU per 0.75 mL	Fragmin	10	$60.03
Dalteparin sodium graduated syringe 10,000 IU per 1 mL	Fragmin	10	$77.55
Dalteparin sodium prefilled syringe 12,500 IU per 0.5 mL	Fragmin	10	$99.96
Dalteparin sodium prefilled syringe 15,000 IU per 0.6 mL	Fragmin	10	$120.05
Dalteparin sodium prefilled syringe 18,000 IU per 0.72 mL	Fragmin	10	$158.47

- Dalteparin sodium prefilled/graduated syringes would be funded under the following Special Authority restriction:

Special Authority for Subsidy

Initial application - (Pregnancy or Malignancy) from any relevant practitioner. Approvals valid for 1 year for applications meeting the following criteria:
Either:
1 Low molecular weight heparin treatment is required during a patient's pregnancy; or
2 For the treatment of venous thromboembolism where the patient has a malignancy.

Initial application - (Venous thromboembolism other than in pregnancy or malignancy) from any relevant practitioner. Approvals valid for 1 month for applications meeting the following criteria:
Any of the following:
1 For the short-term treatment of venous thromboembolism prior to establishing a therapeutic INR with oral anti-coagulant treatment; or

2 For the prophylaxis and treatment of venous thromboembolism in high risk surgery; or
3 To enable cessation/re-establishment of existing oral anticoagulant treatment pre/post surgery; or
4 For the prophylaxis and treatment of venous thromboembolism in Acute Coronary Syndrome surgical intervention; or
5 To be used in association with cardioversion of atrial fibrillation.

Renewal - (Pregnancy or Malignancy) from any relevant practitioner. Approvals valid for 1 year for applications meeting the following criteria:
Either:
1 Low molecular weight heparin treatment is required during a patient's pregnancy; or
2 For the treatment of venous thromboembolism where the patient has a malignancy.

Renewal -(Venous thromboembolism other than in pregnancy or malignancy) from any relevant practitioner. Approvals valid for 1 month where low molecular weight heparin treatment or prophylaxis is required for a second or subsequent event (surgery, Acute Coronary Syndrome, cardioversion, or prior to oral anti-coagulation).

- Fragmin would have protection from subsidy reduction and delisting until 30 June 2015

Background

Dalteparin sodium is an anticoagulant and is indicated for various conditions including treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), DVT/PE prevention following surgery and in unstable heart disease.

Dalteparin sodium is currently listed in Part II of Section H of the Pharmaceutical Schedule but enoxaparin sodium is the only low molecular weight heparin currently funded in the community (Section B).

This proposal would provide another treatment option for patients who require treatment with a low molecular weight heparin.

In relation to sunitinib (Sutent):

- The Special Authority criteria applying to all strengths of sunitinib capsules (Sutent) in Section B of the Pharmaceutical Schedule would be amended from 1 November 2012 as follows (changes in bold):

Sunitinib - Retail Pharmacy –Special Authority for Subsidy
Initial application - **(RCC)** - 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 The patient has metastatic renal cell carcinoma; and
2 Any of the following:
2.1 The patient is treatment naive; or
2.2 The patient has only received prior cytokine treatment; or
2.3 The patient has only received prior treatment with an investigational agent within the confines of a bona fide clinical trial which has Ethics Committee approval; or
2.4 Both:
2.4.1 The patient has discontinued pazopanib within 3 months of starting treatment due to intolerance; and
2.4.2 The cancer did not progress whilst on pazopanib; and

3 The patient has good performance status (WHO/ECOG grade 0-2); and
4 The disease is of predominant clear cell histology; and
The patient has intermediate or poor prognosis defined as:
5 Any of the following:
- 5.1 Lactate dehydrogenase level > 1.5 times upper limit of normal; or
- 5.2 Haemoglobin level < lower limit of normal; or
- 5.3 Corrected serum calcium level > 10 mg/dL (2.5 mmol/L) ; or
- 5.4 Interval of < 1 year from original diagnosis to the start of systemic therapy; or
- 5.5 Karnofsky performance score of ≤ 70; or
- 5.6 ≥ 2 sites of organ metastasis; and

6 Sunitinib to be used for a maximum of 2 cycles.

Initial application - (GIST) - 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:
Both:
1 The patient has unresectable or metastatic malignant gastrointestinal stromal tumour (GIST); and
2 Either:
- **2.1 The patient's disease has progressed following treatment with imatinib; or**
- **2.2 The patient has documented treatment-limiting intolerance, or toxicity to, imatinib**

Renewal **- (RCC)** - 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:
Both:
1 No evidence of disease progression; and
2 The treatment remains appropriate and the patient is benefiting from treatment.

Renewal – (GIST) - 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:
Both:
The patient has responded to treatment or has stable disease as determined by Choi's modified CT response evaluation criteria as follows:
1. **Any of the following:**
   - **1.1 The patient has had a complete response (disappearance of all lesions and no new lesions), or**
   - **1.2 The patient has had a partial response (a decrease in size of >/= 10% or decrease in tumour density in Hounsfield Units (HU) of >/= 15% on CT and no new lesions and no obvious progression of non measurable disease), or**
   - **1.3 The patient has stable disease (does not meet criteria the two above) and does not have progressive disease and no symptomatic deterioration attributed to tumour progression; and**
2. **The treatment remains appropriate and the patient is benefiting from treatment.**

Notes:
RCC - Sunitinib treatment should be stopped if disease progresses.
Poor prognosis patients are defined as having at least 3 of criteria 5.1-5.6. Intermediate prognosis patients are defined as having 1 or 2 of criteria 5.1-5.6.
GIST - It is recommended that response to treatment be assessed using Choi's modified CT response evaluation criteria (J Clin Oncol, 2007, 25:1753-1759).

Progressive disease is defined as either: an increase in tumour size of >/= 10% and not meeting criteria of partial response (PR) by tumour density (HU) on CT; or: new lesions, or new intratumoral nodules, or increase in the size of the existing intratumoral nodules.

Background

Sunitinib is a small molecule multi-receptor kinase inhibitor currently funded on the Pharmaceutical Schedule for patients with advanced Renal Cell Cancer. Gastrointestinal stromal tumors (GIST) are most often located in the stomach and proximal small intestine, but they can occur in any portion of the alimentary tract including occasionally in the omentum, mesentery, and peritoneum. Complete surgical resection in the early stage of disease offers the only chance for cure of GIST. The goal of chemotherapy in later stages of disease is to induce remission, reduce morbidity, prolong time to disease progression and prevent complications.

Clinical evidence demonstrates that, in imatinib refractory GIST patients, sunitinib treatment can delay tumour progression by around 5 months compared with placebo. The Cancer Treatments Subcommittee of PTAC recommended, with low priority, that sunitinib be funded under Special Authority criteria for patients with GIST after failure of imatinib treatment, due to resistance or intolerance. Relevant minutes can be found at the following link:

http://www.pharmac.govt.nz/2012/04/20