

30 April 2009

## Proposal to List Entecavir and Dasatinib

PHARMAC is seeking feedback on a proposal to fund two new pharmaceuticals, entecavir (Baraclude) for the treatment of Hepatitis B infection and dasatinib (Sprycel) for the treatment of Chronic Myeloid Leukaemia.

In summary, the effect of the proposal would be that:

- Entecavir (Baraclude) tablets would be listed in Section B and Section H of the Pharmaceutical Schedule from 1 July 2009.
- Entecavir would be listed in Section B subject to the same Special Authority restrictions as currently apply to lamivudine, i.e. first-line treatment in hepatitis B treatment-naïve patients.
- Entecavir would be dispensed through community pharmacies and DHB hospital pharmacies with a community pharmacy claiming contract.
- Dasatinib (Sprycel) tablets would be listed in Section B and Section H of the Pharmaceutical Schedule from 1 July 2009
- Dasatinib would be listed in Section B subject to Special Authority restrictions for patients with Chronic Myeloid Leukaemia (CML).
- Approval for subsidies for dasatinib would be upon application.
- Dasatinib would be dispensed and distributed by Healthcare Logistics Limited (HCL).

We have assessed both pharmaceuticals with advice from the Pharmacology and Therapeutics Advisory Committee (PTAC) and relevant subcommittees. Taking into account the provisional agreement with Bristol-Myers Squibb (NZ) Limited (which has rebate and expenditure cap components) our preliminary view is that this proposal is justifiable under our decision criteria compared with other competing options.

### Feedback sought

PHARMAC welcomes feedback on this proposal. To provide feedback, please submit it in writing by 4 pm on **Thursday, 14 May 2009** to:

Jackie Evans  
Therapeutic Group Manager  
PHARMAC  
PO Box 10 254  
Wellington 6143

Email: [jackie.evans@pharmac.govt.nz](mailto:jackie.evans@pharmac.govt.nz)

Fax: 04 460 4995

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.

## Details of the proposal

PHARMAC and Bristol-Myers Squibb (NZ) Limited have entered into a provisional agreement for the listing of entecavir (Baraclude) and dasatinib (Sprycel) in the Pharmaceutical Schedule from 1 July 2009. We are now seeking feedback on this proposal. Details of the proposal are as follows:

### Entecavir

- Entecavir would be listed in Section B and in Part II of Section H of the Pharmaceutical Schedule from 1 July 2009 at the following prices and subsidies (ex-manufacturer, exclusive of GST):

| Chemical  | Presentation | Brand name | Pack size | Price and subsidy |
|-----------|--------------|------------|-----------|-------------------|
| Entecavir | Tab 0.5 mg   | Baraclude  | 30        | \$400.00          |
| Entecavir | Tab 1.0 mg   | Baraclude  | 30        | \$650.00          |

- There would be a risk-sharing expenditure cap arrangement between PHARMAC and Bristol-Myers Squibb (NZ) Limited relating to subsidised dispensings of entecavir.
- The listing of entecavir in Section B would be subject to the following Special Authority restrictions:

#### **Special Authority for Subsidy**

**Initial application** only from a gastroenterologist or infectious disease specialist. Approvals valid without further renewal unless notified for applications meeting the following criteria:

- 1) Patient has confirmed Hepatitis B infection (HBsAg positive for more than 6 months); and
- 2) Patient is Hepatitis B nucleoside analogue treatment-naïve; and
- 3) Entecavir dose 0.5 mg/day; and
- 4) Any of the following:
  - 4.1 ALT greater than upper limit of normal; or
  - 4.2 Bridging fibrosis of cirrhosis (Metavir stage 3 or greater) on liver histology; and
- 5) Any of the following:
  - 5.1 HBeAg positive; or
  - 5.2 patient has  $\geq 2,000$  IU HBV DNA units per ml and fibrosis (Metavir stage 2 or greater) on liver histology; and
- 6) All of the following:
  - 6.1 No continuing alcohol abuse or intravenous drug use; and
  - 6.2 Not co-infected with HCV, HIV or HDV; and
  - 6.3 Neither ALT nor AST greater than 10 times upper limit of normal; and
  - 6.4 No history of hypersensitivity to entecavir; and
  - 6.5 No previous documented lamivudine resistance (either clinical or genotypic).

#### Notes:

- Entecavir should be continued for 6 months following documentation of complete HBeAg seroconversion (defined as loss of HBeAg plus appearance of anti-HBe plus loss of serum HBV DNA) for patients who were HBeAg positive prior to commencing this agent. This period of consolidation therapy should be extended to 12 months in patients with advanced fibrosis (Metavir Stage F3 or F4).
- Entecavir should be taken on an empty stomach to improve absorption.

## Dasatinib

- Dasatinib would be listed in Section B and in Part II of Section H of the Pharmaceutical Schedule from 1 July 2009 at the following prices and subsidies (ex-manufacturer, exclusive of GST):

| Chemical  | Presentation | Brand name | Pack size | Price and subsidy |
|-----------|--------------|------------|-----------|-------------------|
| Dasatinib | Tab 20 mg    | Sprycel    | 60        | \$3,774.06        |
| Dasatinib | Tab 50 mg    | Sprycel    | 60        | \$6,214.20        |
| Dasatinib | Tab 70 mg    | Sprycel    | 60        | \$7,692.58        |
| Dasatinib | Tab 100 mg   | Sprycel    | 30        | \$6,214.20        |

- There would be a rebate arrangement between PHARMAC and Bristol-Myers Squibb (NZ) Limited relating to subsidised dispensings of dasatinib.
- The listing of Sprycel 100 mg tablets would be subject to Bristol-Myers Squibb (NZ) Limited obtaining market approval for this formulation of dasatinib.
- The listing of dasatinib in Section B would be subject to the following Special Authority restrictions:

### **Special Authority for Subsidy**

Special Authority approved by PHARMAC.

Notes: Application details may be obtained from PHARMAC's website <http://www.pharmac.govt.nz>, and prescriptions should be sent to:

The Co-ordinator  
PHARMAC  
PO Box 10 254  
Wellington

Phone: (04) 460 4990  
Facsimile: (04) 916 7571  
Email: [mary.chesterfield@pharmac.govt.nz](mailto:mary.chesterfield@pharmac.govt.nz)

### **Special Authority criteria for CML – access by application to PHARMAC**

- 1) Funded for patients with diagnosis (confirmed by a haematologist) of a chronic myeloid leukaemia (CML) in blast crisis, accelerated phase, or in chronic phase.
- 2) Maximum dose of 140 mg/day for accelerated or blast phase and 100 mg/day for chronic phase CML.
- 3) Subsidised for use as monotherapy only.
- 4) Initial approvals valid seven months.
- 5) Subsequent approval(s) are granted on application and are valid for six months. The first reapplication (after seven months) should provide details of the haematological response. The third reapplication should provide details of the cytogenetic response after 14-18 months from initiating therapy. All other reapplications should provide details of haematological response, and cytogenetic response if such data is available. Applications to be made and subsequent prescriptions can be written by a haematologist or an oncologist.

Note: Dasatinib is indicated for the treatment of adults with chronic, accelerated or blast phase CML with resistance or intolerance to prior therapy including imatinib.

### **Guideline on discontinuation of treatment for patients with CML**

- a) Prescribers should consider discontinuation of treatment if, after 6 months from initiating therapy, a patient did not obtain a haematological response as defined as any one of the following three levels of response:

- 1) complete haematologic response (as characterised by an absolute neutrophil count (ANC)  $> 1.5 \times 10^9/L$ , platelets  $> 100 \times 10^9/L$ , absence of peripheral blood (PB) blasts, bone marrow (BM) blasts  $< 5\%$  (or FISH Ph+ 0-35% metaphases), and absence of extramedullary disease); or
  - 2) no evidence of leukaemia (as characterised by an absolute neutrophil count (ANC)  $> 1.0 \times 10^9/L$ , platelets  $> 20 \times 10^9/L$ , absence of peripheral blood (PB) blasts, bone marrow (BM) blasts  $< 5\%$  (or FISH Ph+ 0-35% metaphases), and absence of extramedullary disease); or
  - 3) return to chronic phase (as characterised by BM and PB blasts  $< 15\%$ , BM and PB blasts and promyelocytes  $< 30\%$ , PB basophils  $< 20\%$  and absence of extramedullary disease other than spleen and liver).
- b) Prescribers should consider discontinuation of treatment if, after 18 months from initiating therapy, a patient did not obtain a major cytogenetic response defined as 0-35% Ph+ metaphases.

## Background

### Entecavir

Hepatitis B is a liver infection caused by the Hepatitis B virus (HBV). HBV is transmitted through blood and infected bodily fluids. HBV infection can lead to cirrhosis of the liver, liver failure and liver cancer. New Zealand has high rates of hepatitis B, particularly in Maori, Pacific Island and Asian peoples. The carrier pool is estimated at 55,000, with 16,000 patients having chronic active infection. Hepatitis B is thought to cause premature death from cirrhosis or liver cancer in 15-25% of those infected. An estimated 80% of primary liver cancer cases are caused by hepatitis B.

The aims of treatment of chronic hepatitis B are to achieve sustained suppression of HBV replication and remission of liver disease. There are currently four treatments listed on the Pharmaceutical Schedule under Special Authority criteria for treatment of chronic hepatitis B: lamivudine (Zeffix), interferon alpha 2A (Roferon-A) and 2B (Intron-A), pegylated interferon alpha-2A (Pegasys) and adefovir dipivoxil (Hepsera).

Entecavir (Baraclude) is a guanosine nucleoside analogue with activity against HBV polymerase. Entecavir is indicated for the treatment of chronic HBV infection in adults with evidence of liver inflammation. The recommended dose of entecavir is 0.5 mg once daily in HBV treatment naïve patients.

The Anti-infective Subcommittee of PTAC reviewed the application for the listing of entecavir in September 2007 and November 2008. The Subcommittee considered there was an unmet clinical need for patients with Hepatitis B. The Subcommittee noted that lamivudine was no longer considered acceptable as a first line therapy for Hepatitis B due to high rates of virological resistance. The Subcommittee considered that the data demonstrated that entecavir was superior to lamivudine in treatment-naïve HBeAg-positive and negative chronic HBV patients as measured by histological improvement, reduction in serum HBV viral load and liver function normalisation.

The Subcommittee considered that compared with lamivudine ETV viral resistance rates in treatment-naïve patients were very low, less than 1% out to four years. However, the Subcommittee noted that in lamivudine-resistant treatment-experienced patients, entecavir resistance rates were 25% at three years increasing by a further 15%, to 40% in the fourth year of treatment. Therefore, the Subcommittee did not recommend the use of entecavir in lamivudine-resistant, treatment-experienced patients.

The Subcommittee recommended that that entecavir be listed as first line monotherapy in Hepatitis B treatment naïve patients. The Subcommittee noted that a number of hepatitis B treatment guidelines recommended entecavir as a preferred first-line treatment option.

## **Dasatinib**

Chronic myeloid leukaemia (CML) is a disease characterised by the increased and unregulated growth of predominantly myeloid cells in the bone marrow and the accumulation of these cells in the blood.

The disease course of CML is grouped into three phases; chronic, accelerated and blast phases, based on clinical characteristics and laboratory findings. Imatinib mesylate (Glivec) is currently funded via a PHARMAC co-ordinated special access program for the treatment of patients with CML (and Gastrointestinal Stromal Tumours – GIST). Patients with CML are funded for up to 400 mg/day imatinib in chronic phase or up to 600 mg/day in accelerated or blast phase. Some patients are unable to tolerate imatinib and some develop imatinib-resistant forms of CML. The 2-year incidence of resistance is estimated to be 80% in blast phase, 40% to 50% in accelerated phase, and at least 10% in chronic phase. Imatinib-resistant patients currently have limited treatment options such as imatinib dosage increases (up to 800 mg daily which may not be tolerated), interferon, or chemotherapy. Allogeneic haematopoietic stem cell transplantation remains the only known curative treatment in CML. Use of this treatment is limited by donor availability and the high risk of the procedure.

Dasatinib is an inhibitor of multiple tyrosine kinases indicated for the treatment of adults with chronic, accelerated or blast phase CML with resistance or intolerance to prior therapy including imatinib. Dasatinib is also indicated for the treatment of Philadelphia chromosome positive acute lymphoblastic leukaemia with resistance or intolerance to prior therapy. Dasatinib is associated with myelosuppression, which can lead to bleeding, infection and fatigue. Other side effects include fluid retention, headache, skin rash and nausea. The recommended dosage of dasatinib in chronic phase CML is 100 mg once daily, in accelerated or blast phase the recommended dose is 140 mg/day administered in two divided doses (70 mg BID), one in the morning and one in the evening with or without a meal.

The application for dasatinib was reviewed by PTAC at its August 2007 and February 2008 meetings. The committee considered that dasatinib was efficacious in imatinib-resistant/intolerant patients and that it has greater potency than high-dose imatinib. The Committee considered that it was likely that future studies would focus on the use of dasatinib as first-line treatment. The Cancer Treatments Sub-committee of PTAC reviewed the application in December 2007 and June 2008. The Subcommittee recommended that dasatinib be listed on the Pharmaceutical Schedule for the treatment of patients with imatinib-resistant or imatinib-intolerant accelerated phase CML and gave this recommendation a medium priority. The Subcommittee also considered that dasatinib may have a role in the treatment of patients with imatinib-resistant or imatinib-intolerant chronic phase CML; however, it noted that the supplier had not sought funding for dasatinib in this patient group. Members considered that if dasatinib were funded it should only be used as monotherapy and not in combination with imatinib or nilotinib. The Subcommittee considered that imatinib remained the preferred first-line treatment for patients with CML.