CONSULTATION

PHARMAC
Pharmaceutical Management Agency

14 January 2013

Proposal to fund unapproved pharmaceutical treatments for various conditions

PHARMAC and Link Pharmaceuticals Limited have entered into a provisional agreement for the funding and supply of 11 pharmaceuticals that do not have Medsafe consent (i.e. are not approved/registered). In summary:

- The following pharmaceuticals would be listed in Section B and/or Part II of Section H of the Pharmaceutical Schedule from 1 April 2013:

  Benzbromarone for gout

  Diazoxide for hyperinsulinism

  Para-amino salicylic acid and protionamide for tuberculosis infection

  Paromomycin for cryptosporidium infection

  Rifaximin for hepatic encephalopathy

  Tetracylcine and tripotassium dictratobismuthate (bismuth) for helicobacter pylori infection

  Stiripentol for Dravet syndrome

  Nitazoxanide for protozoan infection

  Pegaspargase (also known as pegylated asparaginase) for acute lymphoblastic leukaemia in combination with chemotherapy

- All listings in Section B, except bismuth, would be subject to Special Authority and/or prescriber restrictions. Similar access criteria would also apply to the provision of these products in DHB hospitals from 1 July 2013 when PHARMAC assumes responsibility for hospital medicines.

- None of these products are approved by Medsafe so supply, sale and prescribing of all the products would be subject to the requirements of section 25 or section 29 of the Medicines Act 1981, as applicable. Background information on sections 25 and 29 of the Medicines Act is set out near the end of this document.

Feedback sought

PHARMAC welcomes feedback on this proposal. To provide feedback, please submit it in writing by 5 pm on Friday 1 February 2013 to:

Geraldine MacGibbon
Senior Therapeutic Group Manager
PHARMAC

Email: geraldine.macgibbon@pharmac.govt.nz
Post: PO Box 10 254, Wellington 6143

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.

Level 9, 40 Mercer Street, PO Box 10-254, Wellington 6143, New Zealand
Phone: 64 4 460 4990 - Fax: 64 4 460 4995 - www.pharmac.govt.nz

We are not able to treat any part of your feedback as confidential unless you specifically request that we do. If you would like us to withhold any commercially sensitive, confidential proprietary, or personal information included in your submission, please clearly state this in your submission and identify the relevant sections of your submission that you would like withheld.

Feedback we receive is subject to the Official Information Act 1982 (OIA) and we will consider any request to have information withheld in accordance with our obligations under the OIA.

Details of the Proposal

Schedule listings

- From 1 April 2013, the following pharmaceuticals would be listed, fully funded, in Section B and Part II of Section H of the Pharmaceutical Schedule as follows (prices and subsidies ex-manufacturer, excluding GST):

Pharmaceutical	Brand	Form and Strength	Pack Size	Price and Subsidy
Benzbromarone	Benzbromaron	Tablet 100 mg	100	$45.00
Diazoxide	Proglicem	Capsule 25 mg	100	$110.00
Diazoxide	Proglicem	Capsule 100 mg	100	$280.00
Para-amino salicylic acid	Paser	Sachet 4 g	30	$280.00
Paromomycin	Humatin	Capsule 250 mg	16	$126.00
Pegaspargase*	Oncaspar	Inj 3,750 IU per 5 ml	1	$3,005.00
Prothionamide	Peteha	Tablet 250 mg	100	$305.00
Rifaximin	Normix	Tablet 200 mg	12	$60.00
Tetracycline	Tefilin	Capsule 250 mg	100	$76.69
Stiripentol	Diacomit	Capsule 250 mg	60	$509.29
Stiripentol	Diacomit	Sachet 250 mg	60	$509.29

*Pegaspargase is a hospital-administered Pharmaceutical Cancer Treatment (PCT) and would be listed in Section B for claiming purposes only.

- All of the above pharmaceuticals, except pegaspargase, could be dispensed in variable dispensing periods, subject to the conditions set out in Part III of Section F of the Pharmaceutical Schedule.

- In addition, nitazoxanide would be listed in Part II of Section H of the Pharmaceutical Schedule from 1 April 2013 as follows (price ex-manufacturer, excluding GST):

Pharmaceutical	Brand	Form and Strength	Pack Size	Price
Nitazoxanide	Alinia	Tablet 500 mg	30	$1,680.00

- None of the pharmaceuticals listed in Section B would be available funded on a Bulk Supply Order (BSO) or a Practitioner's Supply Order (PSO).

- All of the pharmaceuticals listed in Section B, except pegaspargase, would be subject to the wastage rule (rule 3.3.2 of Part II of the General Rules in Section A of the Pharmaceutical Schedule), which would be amended as follows (additions in bold, deletions in strikethrough):

3.3 Original Packs, ~~and~~ Certain Antibiotics **and Unapproved Medicines**

3.3.2 If a Community Pharmaceutical is **either**:

a) the liquid oral form of an antibiotic to which a diluent must be added by the Contractor at the time of dispensing; **or**

b) an unapproved medicine supplied under Section 29 of the Medicines Act 1981,

and it is prescribed or ordered by a Practitioner in an amount that does not coincide with the amount contained in one or more standard packs of that Community Pharmaceutical, Subsidy will be paid for the amount prescribed or ordered by the Practitioner in accordance with either clause 3.1 or clause 3.3 of the Schedule, and for the balance of any pack or packs from which the Community Pharmaceutical has been dispensed. At the time of dispensing the Contractor must keep a record of the quantity discarded. To ensure wastage is reduced, the Contractor should reduce the amount dispensed to make it equal to the quantity contained in a whole pack where:

a) the difference the amount dispensed and the amount prescribed by the Practitioner is less than 10% (eg; if a prescription is for 105 ml~~s~~ then a 100 ml pack would be dispensed); and

b) in the reasonable opinion of the Contractor the difference would not affect the efficacy of the course of treatment prescribed by the Practitioner.

Note: For the purposes of audit and compliance it is an act of fraud to claim wastage and then use the wastage amount for any subsequent prescription.

- No changes would be made to the Glossary in the Pharmaceutical Schedule which sets out the following information that medical practitioners should be aware of when prescribing unapproved medicines:

Practitioners prescribing this medicine should:

a) be aware of and comply with their obligations under section 29 of the Medicines Act 1981 and otherwise under that Act and the Medicines Regulations 1984;

b) be aware of and comply with their obligations under the Health and Disability Commissioner's Code of Consumer Rights, including the requirement to obtain informed consent from the patient (PHARMAC recommends that Practitioners obtain written consent); and

c) exercise their own skill, judgement, expertise and discretions, and make their own prescribing decisions with respect to the use of an unapproved Pharmaceutical or a Pharmaceutical for an indication for which it is not approved.

Note: Where medicines supplied under section 29 that are used for emergency situations, patient details required under section 29 of the Medicines Act may be retrospectively provided to the supplier.

Restrictions

The following funding restrictions would apply to funding of these pharmaceuticals from 1 March 2013, with similar restrictions applying to the provision of these pharmaceuticals in DHB hospitals from 1 July 2013 when PHARMAC assumes responsibility for hospital medicines:

Benzbromarone (Benzbromaron)

Special Authority for Subsidy
Initial application from any relevant practitioner. Applications valid for six months for applications meeting the following criteria:
Both:

1 Any of:
   1.1 The patient has a serum urate level greater than 0.36 mmol/l despite treatment with allopurinol at doses of at least 600 mg/day and appropriate doses of probenecid; or
   1.2 The patient has experienced intolerable side effects from allopurinol such that treatment discontinuation is required and satisfactory control of serum urate (to less than or equal to 0.36 mmol/l) could not be achieved by probenecid; or
   1.3 Both:
      1.3.1 The patient has renal impairment and serum urate remains greater than 0.36 mmol/l despite optimal treatment with allopurinol (see Note); and
      1.3.2 The patient has a rate of creatinine clearance greater than or equal to 20 ml/min; or
   1.4 All of the following:
      1.4.1 The patient is taking azathioprine and requires urate-lowering therapy; and
      1.4.2 Allopurinol is contraindicated; and
      1.4.3 Appropriate doses of probenecid are ineffective or probenecid cannot be used due to reduced renal function; and
2 The patient is receiving monthly liver function tests.

Renewal from any relevant practitioner. Applications valid for two years for applications meeting the following criteria:
Both:

1 The treatment remains appropriate and the patient is benefitting from treatment; and
2 There is no evidence of liver toxicity.

Note: Optimal treatment with allopurinol in patients with renal impairment is defined as treatment to the creatinine clearance-adjusted dose of allopurinol then, if serum urate remains greater than 0.36 mmol/l, a gradual increase of the dose of allopurinol to 600 mg or the maximum tolerated dose.

Diazoxide (Proglicem)

Special Authority for Subsidy
Initial application from any relevant practitioner. Approvals valid for 12 months where used for the treatment of confirmed hypoglycaemia caused by hyperinsulinism.

Renewal from any medical practitioner. Approvals valid without further renewal where the treatment remains appropriate and the patient is benefiting from treatment.

Para-amino Salicylic Acid (Paser)

Retail Pharmacy – Specialist. Specialist must be an infectious disease physician, clinical microbiologist or respiratory physician.

Paromomycin (Humatin)

Special Authority for Subsidy
Initial application only from an infectious disease physician or clinical microbiologist. Applications valid for one month where the patient has confirmed cryptosporidium infection.*

Renewal only from an infectious disease physician or clinical microbiologist. Applications valid for one month where the patient has confirmed cryptosporidium infection.*

*From 1 July 2013 prescribing of paromomycin in DHB hospitals would be restricted by prescriber type as described here but not by indication.

Protionamide (Peteha)

Retail Pharmacy – Specialist. Specialist must an infectious disease physician, clinical microbiologist or respiratory physician.

Rifaximin (Normix)

Special Authority for Subsidy
Initial application only from a gastroenterologist. Approvals valid for six months where the patient has had two previous episodes of hepatic encephalopathy despite an adequate trial of maximum tolerated doses of lactulose.

Renewal only from a gastroenterologist. Approvals valid without further renewal where the treatment remains appropriate and the patient is benefiting from treatment.

Tetracycline (Tefilin)

Special Authority for Subsidy
Initial application from any relevant practitioner. Approvals valid for three months for applications meeting the following criteria:
Both:

1 For the eradication of helicobacter pylori following unsuccessful treatment with appropriate first-line therapy; and
2 For use only in combination with bismuth.

Renewal application from any relevant practitioner. Approvals valid for three months for applications meeting the following criteria:
Both:

1 For the eradication of helicobacter pylori re-infection following previous successful treatment with tetracycline; and
2 For use only in combination with bismuth.

Stiripentol (Diacomit)

Special Authority for Subsidy
Initial application only from a paediatric neurologist or Practitioner on the recommendation of a paediatric neurologist. Approvals valid for six months for applications meeting the following criteria:
Both:

1 Patient has confirmed diagnosis of Dravet syndrome; and
2 Seizures have been inadequately controlled by appropriate courses of sodium valproate, clobazam and at least two of the following: topiramate, levetiracetam, ketogenic diet.

Renewal from any relevant practitioner. Approvals valid without further renewal where the patient continues to benefit from treatment as measured by reduced seizure frequency from baseline.

Pegaspargase (Oncaspar)

PCT only – 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:
Both:

1 The patient has newly diagnosed acute lymphoblastic leukaemia; and
2 Pegaspargase to be used with a contemporary intensive multi-agent chemotherapy treatment protocol specifically for treatment of paediatric, adolescent or young adult patients; and
3 Treatment is with curative intent.

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:
All of the following:

1 The patient has relapsed acute lymphoblastic leukaemia; and
2 Pegaspargase to be used with a contemporary intensive multi-agent chemotherapy treatment protocol specifically for treatment of paediatric, adolescent or young adult patients; and
3 Treatment is with curative intent.

From 1 July 2013, provision of nitazoxanide (Alinia) in DHB hospitals would be restricted to prescribing by, or on the recommendation of, infectious disease physicians or clinical microbiologists.

Background to the Proposal

Funding of Unregistered Pharmaceuticals

PHARMAC prefers to fund registered pharmaceuticals wherever possible. PHARMAC currently funds less than 20 unregistered pharmaceuticals, which are identified in the Pharmaceutical Schedule by the following symbol: S29 . In most cases these are intended to be temporary listings, pending replacement with a registered version of the same pharmaceutical.

In a very small number of cases, despite our best endeavours, we have been unable to source a registered version of a pharmaceutical that we consider important to fund, and based on the information available to us we consider it unlikely that we would be able to do so in the foreseeable future. Some of these pharmaceuticals are already funded on the Pharmaceutical Schedule; 11 others are contained within this proposal – some of which are currently being funded for individual patients via PHARMAC's Named Patient Pharmaceutical Assessment (**NPPA**) process. If this proposal is approved it would be our intention to work with Link regarding the possibility of registering some or all of these products in the future. Should a registered version of the pharmaceutical become available (whether supplied by Link or another supplier), we would work to ensure that the unregistered version was replaced by the registered version in the Pharmaceutical Schedule.

We would like to highlight that PHARMAC's funding of an unapproved medicines is not an endorsement of the medicine's quality, safety or efficacy, nor does it impact upon a medical practitioner's obligations to comply with relevant legislation and regulations (including the Health and Disability Commissioner's Code of Consumer Rights). As with any pharmaceutical funded by PHARMAC, if this proposal is approved medical practitioners would not have to prescribe these pharmaceuticals; however, funding would be provided if a prescriber chose to do so (providing any funding access criteria are met).

Clinical Advice PHARMAC has Received about the Proposed Medicines

Relevant published minutes of advisory committee discussions referred to below can be found on PHARMAC's website at www.pharmac.govt.nz/PTACminutes and www.pharmac.govt.nz/PTACSCminutes.

Gout Treatment – Benzbromarone

Benzbromarone is a bezofuran derivative which increases urinary uric acid excretion in people with normal and high uric acid levels. It is used in the treatment of gout. Current funded urate-lowering treatments for gout are allopurinol and probenecid.

The Pharmacology and Therapeutics Advisory Committee (PTAC) reviewed benzbromarone in November 2010 and **recommended** that benzbromarone be funded with a high priority subject to Special Authority restrictions for patients in whom the funded treatment options have produced a suboptimal response at appropriately high doses or where the funded treatment options are inappropriate or not tolerated.

The Committee considered that PHARMAC's data showing the relatively low use of probenecid and the low dosing of allopurinol suggest that they are not optimally used in New Zealand.

The Committee noted that benzbromarone is not registered for use in New Zealand and was withdrawn worldwide by the original supplier in 2003 following four reports of serious hepatotoxicity leading to death in two of the patients. It is still marketed in several countries by other suppliers. A review by Lee et al (Drug Safety 2008;31:643-665) reports 11 other cases resulting in nine deaths. The authors estimated the incidence of hepatotoxicity from benzbromarone to be around one in 17,000 and concluded that adverse events are relatively infrequent but potentially severe. The Committee agreed with the author's suggestion that probenecid should be used as the first uricosuric agent before trying benzbromarone, and that the risk of hepatotoxicity with benzbromarone could be reduced by employing a graded dosage increase together with regular liver function monitoring.

If benzbromarone is funded, PHARMAC would work with BPAC to provide updated gout treatment education to prescribers.

The Rheumatology Subcommittee of PTAC reviewed PTAC's minutes and the Special Authority criteria suggested by PTAC for benzbromarone at its meetings in March 2011 and September 2011. The criteria in the current proposal are in line with those **recommended** by the Subcommittee at its most recent meeting (September 2011).

Hyperinsulinaemia Treatment – Diazoxide

Diazoxide is a potassium channel activator which inhibits the secretion of insulin from the pancreas. It is used to counter hypoglycaemia caused by disease states such as insulinoma or congenital hyperinsulinism. At its meeting in April 2012, the Diabetes Subcommittee of PTAC **recommended** that diazoxide be subsidised in the community for patients with confirmed hypoglycaemia caused by hyperinsulinism. Currently, funding of diazoxide is considered through NPPA for this indication. This proposal would eliminate the need for NPPA applications for diazoxide.

Infection Treatments – Para-amino Salicylic Acid, Paromomycin, Protionamide, Nitazoxanide, Rifaximin, Tetracycline in combination with Bismuth

Para-amino salicylic acid and protionamide are both agents for the treatment of tuberculosis. Paromomycin is an agent for the treatment of cryptosporidium infection and nitazoxanide is an anti-protozoal agent.

As a result of PHARMAC's role in assessing pharmaceuticals for inclusion on a nationally consistent hospital medicines list (the Preferred Medicines List, or 'PML') the Anti-Infective Subcommittee of PTAC considered whether certain products should also be included in Section B of the Pharmaceutical Schedule. At its February 2012 and March 2012 meetings the Anti-Infective Subcommittee **recommended** that para-amino salicylic acid, paromomycin, protionamide and nitazoxanide be listed in Section B of the Pharmaceutical Schedule with the proposed restrictions, and included in the PML. PHARMAC has previously consulted on including these medicines in the PML; the consultation document can be found at: www.pharmac.govt.nz/2012/09/25.

Rifaximin is a non-absorbable derivative of rifampicin and can be used to treat hepatic encephalopathy. Currently, lactulose and L-ornithine L-aspartate (LOLA) are funded for this indication. Funding of rifaximin for hepatic encephalopathy was reviewed by PTAC at its November 2012 meeting. This proposal for rifaximin is in line with PTAC's discussion.

Tetracycline is an antibiotic which can be used in combination with bismuth for the eradication of helicobacter pylori. Both products were discontinued in New Zealand several

years ago and, since then, there have been few second-line treatment options for helicobacter pylori eradication available. With resistance to first-line therapies increasing, we propose to fund tetracycline for second-line therapy, only in combination with bismuth.

Dravet Syndrome Treatment – Stiripentol

Stiripentol is an anti-epileptic agent which is used for the treatment of Dravet syndrome. At its July 2012 meeting the Neurological Subcommittee of PTAC **recommended** that stiripentol be listed in a national PML and subsidised in the community for this indication.

During its review of the neurology section of the proposed national PML, PTAC considered advice provided by the Neurological Subcommittee and several paediatric neurologists, and **recommended** that stiripentol be funded for the treatment of Dravet syndrome subject to restrictions essentially as proposed here.

Acute Lymphoblastic Leukaemia Treatment – Pegaspargase

Acute lymphoblastic leukaemia (ALL) is a blood cancer most common in childhood with a peak incidence at 2-5 years of age, and another peak in old age. With appropriate treatment ALL can be cured in about 80% of children and about 45%-60% of adults. Treatment for ALL comprises high dose chemotherapy in combination with asparaginase. Multiple ALL treatment regimens have been developed and patients are commonly enrolled in clinical trials.

In ALL the leukaemic cells are unable to synthesize the amino acid asparagine, whereas normal cells are able to make their own asparagine; thus, leukaemic cells require high amount of circulating asparagine to survive. Asparaginase catalyses the conversion of circulating asparagine to aspartic acid and ammonia thus depriving leukemic cells of vital circulating asparagine and inhibiting their growth.

PHARMAC currently funds Leunase (colaspase, also known as L-asparaginase); this proposal would see a second asparaginase product funded. The funding of pegaspargase has been reviewed by the Cancer Treatments Subcommittee of PTAC (CaTSoP), most recently in October 2012. In summary, CaTSoP noted that pegasparaginase was now part of standard treatment protocols for ALL treatment in paediatrics but it was currently unfunded for adults, which members considered was inequitable. Members considered that there was good evidence in children that pegasparaginase was more efficacious than L-asparginase, had a longer half-life and was less antigenic and considered it was reasonable to extrapolate these benefits to the adult setting.

Registration (approval) and section 29 of the Medicines Act 1981

In order for anyone to market, sell or supply a medicine in New Zealand, the pharmaceutical must be registered (also known as consented, or approved) by Medsafe. The registration process is to ensure that the pharmaceutical is safe and effective, and it involves a comprehensive review of data relating to the safety, efficacy (effectiveness) and physical characteristics of the pharmaceutical.

The majority of medicines available in New Zealand are approved; however, in some circumstances – such as when a supplier has exited, or is unwilling to enter, a market, or where the original data on a medicine is old and not sufficient for current regulatory requirements, or where usage would be very small – there is no approved medicine

available for supply in New Zealand. There are medicines that are effective and safe, and approved in other countries, but are not registered in New Zealand. There are also other medicines that have been approved with a particular set of indications, but for which there are other widely recognised uses not applied for in New Zealand. Some unapproved medicines may be used for rare diseases, for which there are few or no treatments approved in New Zealand.

Prescribers may be aware that section 25 of the Medicines Act 1981 permits registered medical practitioners, midwives and designated providers to procure and administer, or arrange for the administration of, an unapproved medicine for a particular patient in their care. In addition, section 29 of the Medicines Act 1981 enables an authorised supplier or medical practitioner (not midwives or designated prescribers) to supply or sell an unapproved medicine when authorised by a prescriber.

It is the prescriber's responsibility to ensure that they remain aware of any safety issues relating to any unapproved medicines they may be prescribing, and that they comply with all relevant legislation and regulations (including the Health and Disability Commissioner's Code of Consumer Rights) and communicate the risks and benefits of the medicine to their patients.

More information about section 25 and section 29 can be found on Medsafe's website at: www.medsafe.govt.nz/profs/RIss/unapp.asp. The Medicines Act 1981 can be found online at: www.legislation.govt.nz

Reporting requirements associated with section 29 of the Medicines Act 1981

Essentially, section 29 of the Medicines Act 1981 provides for the sale or supply of unregistered medicines to named medical practitioners (not dentists, nurse prescribers or midwives) for use by a particular patient. It requires the party who has supplied or sold the medicine to notify the Director-General of Health (in writing) with:

- the name of the medical practitioner who requested the supply of the medicine;
- the name of the patient the medicine was required for;
- the dose form(s) and strength(s) of the medicine
- the date the medicine was supplied; and
- the name of the place the medicine was supplied to.

If a pharmacist imports an unapproved medicine on behalf of a medical practitioner, the pharmacist must complete the notification. If a pharmacy or medical practitioner obtains an unapproved medicine from a distributor, the pharmacist or medical practitioner must provide the relevant practitioner/patient information to the distributor so the distributor can complete the notification.

In practice, Medsafe only requires the relevant party to notify the generic name, trade name, dose form and month of supply, and to declare that a record of the names of the medical practitioner(s) and patient(s) has been kept.

If a medical practitioner directly imports an unapproved medicine to treat their patient, no notification is necessary (this covered by section 25).

It is our understanding that the most common scenario, for the supply of unapproved medicines, is for a specialist importer (wholesaler) to import the product and distribute it to a

pharmacy for a named patient. This would require the pharmacist to provide the relevant information to the wholesaler, and the wholesaler to report to Medsafe.

More information can be found in Part A, Section 1.13 of the *New Zealand Regulatory Guidelines for Medicines*, which are available on the internet at www.medsafe.govt.nz/regulatory/guidelines.asp#NZRGM. The form for reporting to Medsafe the supply of unapproved medicines is provided in Part E, Section 1.6 of the Guidelines.