26 April 2010

Proposals regarding the Cholesterol Lowering Pharmaceuticals Atorvastatin and Ezetimibe

PHARMAC is seeking feedback on the following proposals relating to the cholesterol lowering pharmaceuticals atorvastatin and ezetimibe, and the combination product ezetimibe with simvastatin. These proposals are summarised as follows:

Sole Supply of Atorvastatin

- Mylan’s brand of atorvastatin (Lorstat) would be the Sole Supply (only funded) brand of atorvastatin until 31 December 2012 – Lipitor would be delisted creating savings in excess of $23 million per year.

Access Changes

- The atorvastatin Special Authority would be removed - atorvastatin would be fully funded without restriction.
- The ezetimibe Special Authority would be amended so that it would be funded for patients who:
  - have rhabdomyolysis following treatment with one statin; or,
  - are intolerant to both simvastatin and atorvastatin; or,
  - have familial hypercholesterolemia.
  Ezetimibe would be able to be used in combination with atorvastatin
- The ezetimibe with simvastatin Special Authority would be amended so that it would only be funded for current patients (no new Special Authority numbers would be issued).

Reference Pricing

- Ezetimibe with simvastatin would be reference priced (the subsidy would be reduced) to the sum of its individual products (the ezetimibe and simvastatin individual tablets) – this would result in a patient surcharge if the supplier of the currently listed ezetimibe with simvastatin (Vytorin) does not reduce its price to the reference price.
- All current ezetimibe with simvastatin (Vytorin) patients would automatically be issued with a Special Authority number for ezetimibe Special Authority to enable them to transition to the individual products if required.

Feedback sought

PHARMAC welcomes feedback on this proposal. To provide feedback, please submit it in writing by Friday 14 May 2010 to:

Stephen Woodruffe
Therapeutic Group Manager
PHARMAC
Email: stephen.woodruffe@pharmac.govt.nz
Fax: 04 460 4995
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.
Details of the proposals

Atorvastatin Sole Supply and Removal of the Special Authority

Following a Sole Supply competitive process we propose that Mylan’s brand of atorvastatin (Lorstat) becomes the only brand of atorvastatin listed in the Pharmaceutical Schedule and that the atorvastatin Special Authority is removed. This would result in the following changes:

- 1 August 2010 - Lorstat would be listed in Sections B and H of the Pharmaceutical Schedule
- 1 September 2010 – The atorvastatin Special Authority would be removed
- 1 September 2010 - Lipitor would be reference priced to Lorstat
- 1 December 2010 - Lipitor would be delisted from the Pharmaceutical Schedule
- 1 December 2010 until 31 July 2012 - Lorstat would have Sole Supply Status

A 1% discretionary variance limit would apply to Lorstat in DHB hospitals.

The proposed pricing of Lorstat is between 88% and 93% lower than the price of Lipitor depending upon the strength (see table below). Therefore, this proposal would reduce expenditure on atorvastatin from approximately $26 million to approximately $3 million per annum. These savings would be used for the funding of other medicines.

<table>
<thead>
<tr>
<th>Strength</th>
<th>Lipitor Price</th>
<th>Lorstat Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 mg</td>
<td>$18.32</td>
<td>$1.77</td>
</tr>
<tr>
<td>20 mg</td>
<td>$26.70</td>
<td>$2.60</td>
</tr>
<tr>
<td>40 mg</td>
<td>$37.02</td>
<td>$4.38</td>
</tr>
<tr>
<td>80 mg</td>
<td>$110.50</td>
<td>$7.73</td>
</tr>
</tbody>
</table>

Prices shown are for 30 tablets and are exclusive of GST

The timing of the proposed changes to the prices and subsidies (ex-manufacturer, excluding GST) for atorvastatin (Lorstat and Lipitor) in the Pharmaceutical Schedule are shown below:

<table>
<thead>
<tr>
<th>Strength (mg)</th>
<th>Brand</th>
<th>Pack Size</th>
<th>Price and subsidy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Current</td>
</tr>
<tr>
<td>10</td>
<td>Lorstat</td>
<td>30</td>
<td>Not listed</td>
</tr>
<tr>
<td></td>
<td>Lipitor</td>
<td>30</td>
<td>$4.03 ($18.32)</td>
</tr>
<tr>
<td>20</td>
<td>Lorstat</td>
<td>30</td>
<td>Not listed</td>
</tr>
<tr>
<td></td>
<td>Lipitor</td>
<td>30</td>
<td>$5.87 ($26.70)</td>
</tr>
<tr>
<td>40</td>
<td>Lorstat</td>
<td>30</td>
<td>Not listed</td>
</tr>
<tr>
<td></td>
<td>Lipitor</td>
<td>30</td>
<td>$8.14 ($37.02)</td>
</tr>
<tr>
<td>80</td>
<td>Lorstat</td>
<td>30</td>
<td>Not listed</td>
</tr>
<tr>
<td></td>
<td>Lipitor</td>
<td>30</td>
<td>$16.28 ($110.50)</td>
</tr>
</tbody>
</table>

1 – Price of Lipitor. An additional subsidy to match this price is available via Special Authority.
2 – From 1 September, the Special Authority for additional subsidy would be removed and a manufacturer’s surcharge would apply to all Lipitor dispensing should the supplier of Lipitor not decrease its price to match the price of Lorstat.
Wholesalers, distributors and pharmacists should be aware that the Lorstat brand of atorvastatin would be available from 26 of July 2010 rather than from 12 of July 2010 for the proposed 1 August 2010 listing in the Pharmaceutical Schedule. This proposed delay is due to the supplier of Lorstat having to wait for a Patent that applies to atorvastatin to expire on 19 July 2010.

Given the size of the savings (about $2 million per month) and, as the referencing pricing is proposed to commence on 1 September 2010, we propose to list Lorstat from the 1 August 2010 even though stock would not be available from the usual 12th of the month prior to listing.

**Ezetimibe – Special Authority Criteria**

We propose that from 1 August 2010, the ezetimibe Special Authority criteria is amended so that it is funded for patients who:

- have a calculated absolute risk of cardiovascular disease >20% over 5 years and develop rhabdomyolysis (defined as muscle aches and creatine kinase more than 10 x normal) following treatment with one statin; or,
- have a calculated absolute risk of cardiovascular disease >20% over 5 years and are intolerant to both simvastatin and atorvastatin; or,
- have familial hypercholesterolemia (defined as a cholesterol level of 8 mmol/L plus a family history of premature coronary heart disease, or tendon xanthelasma)

It is also proposed that:

- ezetimibe could be used in combination with atorvastatin i.e. for patients with familial hypercholesterolemia
- renewals could be applied for by general practitioners as well as specialists

We note that ezetimibe would continue to be funded for all patients with a current valid Special Authority approval.

The proposed Special Authority criteria for ezetimibe is shown below:

**Initial application** - **Rhabdomyolysis** only from a relevant specialist. Approvals valid for 2 years for patients who have a calculated absolute risk of cardiovascular disease >20% over 5 years and develop rhabdomyolysis (defined as muscle aches and creatine kinase more than 10 x normal) when treated with a statin.

**Initial application** - **Intolerant to statins** only from a relevant specialist. Approvals valid for 2 years for patients who have a calculated absolute risk of cardiovascular disease >20% over 5 years and who are intolerant to both simvastatin and atorvastatin.

**Initial application – Familial hypercholesterolemia** only from a relevant specialist. Approvals valid for 2 years for patients who have familial hypercholesterolemia (defined as cholesterol level of 8 mmol/L and a family history of premature coronary heart disease, or tendon xanthelasma)

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

**Note:** Other treatment options including fibrates, resins and nicotinic acid should be considered after failure of statin therapy in addition to ezetimibe.

**Ezetimibe with simvastatin combination tablets - Special Authority Criteria**

It is proposed that the ezetimibe with simvastatin (Vytorin) Special Authority criteria is also amended so that it is consistent with the proposed ezetimibe Special Authority criteria above.

Given the ezetimibe criteria proposed above and on the basis that ezetimibe is unlikely to be prescribed in combination with simvastatin (patients eligible for ezetimibe would be intolerant
to statins, or have familial hypercholesterolemia and therefore likely to use ezetimibe in combination with atorvastatin rather than in combination with simvastatin), we propose that:

- Ezetimibe with simvastatin would continue to be funded but only for patients with a current valid Special Authority approval.
- Renewals could be applied for by general practitioners as well as specialists.

The proposed Special Authority criteria for ezetimibe with simvastatin is as follows:

Renewal – from any practitioner. Approvals valid for 2 years where the treatment remains appropriate and the patient is benefiting from the treatment.

Note: Other treatment options including fibrates, resins and nicotinic acid should be considered after failure of statin therapy as well as ezetimibe.

The new criteria would be effective from 1 August 2010 and would mean that funding would only be available for current patients (there would be no approvals granted for new patients).

**Ezetimibe with simvastatin combination tablets - Reference Pricing**

Finally it is also proposed that from 1 August 2010, the subsidy for combination ezetimibe simvastatin (Vytorin) tablets is reduced, through the application of reference pricing, to the level of the sum of the subsidies for the separate ezetimibe and simvastatin tablets.

Reference pricing would result in Vytorin being partially subsidised – as such it would have a patient charge (unless the supplier reduces its prices to match the proposed subsidies). The following table illustrates the proposed subsidies and resulting patient charges for 30 tablets (the patient charge includes an estimated 85% pharmacy mark-up and is inclusive of GST):

<table>
<thead>
<tr>
<th>Chemical and presentation</th>
<th>Current price/subsidy for combination tablets</th>
<th>Current price/subsidy for separate tablets</th>
<th>Proposed subsidy for combination tablets</th>
<th>Patient charge*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ezetimibe 10mg / simvastatin 10mg</td>
<td>$69.00</td>
<td>$57.60</td>
<td>$0.68</td>
<td>$58.28</td>
</tr>
<tr>
<td>Ezetimibe 10mg / simvastatin 20mg</td>
<td>$75.00</td>
<td>$57.60</td>
<td>$1.00</td>
<td>$58.60</td>
</tr>
<tr>
<td>Ezetimibe 10mg / simvastatin 40mg</td>
<td>$103.50</td>
<td>$57.60</td>
<td>$1.78</td>
<td>$59.38</td>
</tr>
<tr>
<td>Ezetimibe 10mg / simvastatin 80mg</td>
<td>$123.00</td>
<td>$57.60</td>
<td>$3.88</td>
<td>$61.48</td>
</tr>
</tbody>
</table>

* All pricing is per 30 tablets
* The patient charge assumes an 85% pharmacy mark-up and includes the effect of GST. It also assumes that the supplier does not reduce their price.

To assist in any transition of patients to the individual tablets, any outstanding repeats would continue to be fully funded until 31 October 2010 and patients would automatically be issued with an ezetimibe Special Authority approval number.

**Background**

**Atorvastatin**

The patent for atorvastatin is due to expire on 19 July 2010. Proposals for the Sole Supply of atorvastatin were invited from suppliers in November 2009 following the issue of a “Request for Proposals” by PHARMAC. The proposals to award Sole Supply and to remove the Special Authority for atorvastatin are a result of this process.
Ezetimibe / Ezetimibe with Simvastatin combination tablets – Special Authority Criteria

Currently ezetimibe individual tablets (Ezetrol) and ezetimibe simvastatin combination tablets (Vytorin) are funded via Special Authority for:

- Patients with a calculated absolute risk of cardiovascular disease > 20% over 5 years, who cannot tolerate a statin dose ≥ 40 mg day, and who have an LDL cholesterol ≥ 2.0 mmol/litre (if they have a CABG) or ≥ 2.5 mmol/litre (if they do not have a CABG).

- Patients with homozygous familial or heterozygous familial hypercholesterolemia, who are on maximal dose statin therapy and who have an LDL cholesterol ≥ 5 mmol/litre.

However, ezetimibe is not currently funded if it is used in combination with atorvastatin, and both initial and renewal applications require a specialist application.

As a result of the proposal to remove the atorvastatin Special Authority, a number of letters from clinicians’ requesting that general practitioners can apply for Special Authority renewals, the LDL of some patients not being able to be determined due to high triglyceride results, and the below comments from the Cardiovascular Subcommittee of PTAC, we have reviewed the Special Authority criteria for ezetimibe. This has resulted in the proposed criteria for both ezetimibe and the combination tablet, ezetimibe with simvastatin.

The access criteria for ezetimibe and ezetimibe with simvastatin were considered by the Cardiovascular Subcommittee of PTAC in August 2008. The Subcommittee:

- considered that maximal use of statins should be utilised in preference to other lipid modifying agents.
- noted that other treatment options, in addition to ezetimibe, should also be considered after failure of statin therapy.
- recommended that ezetimibe be made available, for use in combination with atorvastatin, for patients who had have failed to reach their LDL-treatment target on simvastatin and then on atorvastatin with a medium priority
- recommended that intolerance of both simvastatin and atorvastatin should be required before a patient can access ezetimibe and that this change occurs with a high priority.
- considered that PHARMAC should wait until the results of further ezetimibe trials become available, such as IMPROVE-IT, before any consideration is given to enabling ezetimibe to be used before the currently available statins.
- considered that in light of the results of the ENHANCE study that atorvastatin plus ezetimibe is preferable to Vytorin; however, it also acknowledged that Vytorin may offer a compliance advantage and therefore considered that it should remain available
- considered that if a patient has rhabdomyolysis (defined as muscle aches and creatine kinase more than 10 x normal) upon treatment with simvastatin then they should be able to access ezetimibe without trialling atorvastatin

Ezetimibe with simvastatin combination tablets - Reference Pricing

The proposal to reference price the ezetimibe with simvastatin combination tablets to the individual tablets is the result of the expiry of a significant rebate which applied to the combination tablet (Vytorin).

Other Activity with respect to Cholesterol Lowering Medications

Gemfibrozil and pravastatin were included in PHARMAC’s current annual tender process, and that process is still open to resolution. Depending on the outcome of the set of proposals outlined in this letter, and the resolution of these tenders, further proposals for access to cholesterol lowering medicines can be anticipated shortly.