

## **5.17 RIVASTIGMINE, 13.3 milligrams/24 hours patch, Exelon® 15, Novartis Pharmaceuticals Australia Pty Limited**

### **1 Purpose of Application**

- 1.1 The minor submission seeks to list an additional strength of rivastigmine transdermal patches. This will provide an additional dosing option for patients with mild to moderately severe Alzheimer-type dementia.

### **2 Requested listing**

- 2.1 The submission seeks to list 13.3 milligrams/24 hours patch strength of rivastigmine with the same General Schedule listing as the existing patch strengths: 4.6 milligrams/24 hours and 9.5 milligrams/24 hours.

### **3 Background**

- 3.1 The currently-listed rivastigmine transdermal patch strengths were TGA approved in March 2008 for the treatment of patients with mild, moderate and severe dementia of the Alzheimer's type. The requested strength was registered on ARTG on 7 April 2015.
- 3.2 The currently-listed rivastigmine transdermal patch strengths were recommended for PBS listing at the March 2008 PBAC meeting for the treatment for Alzheimer's disease. The requested strengths have not previously been considered by the PBAC.

### **4 Clinical place for the proposed therapy**

- 4.1 Dementia of the Alzheimer type is a progressive neurodegenerative condition characterised by deterioration in cognition and memory, progressive impairment in the ability to carry out activities of daily living and a number of neuropsychiatric symptoms.
- 4.2 Rivastigmine is a cholinesterase inhibitor. The requested additional strength would provide an additional dosing option for patients with mild to moderately severe Alzheimer-type dementia.

### **5 Comparator**

- 5.1 As a minor submission, there is no economic comparison.

## 6 Consideration of the evidence

### **Sponsor hearing**

6.1 There was no hearing for this item as it was a minor submission.

### **Consumer comments**

6.2 The PBAC noted that no consumer comments were received for this item.

### **Clinical trials**

6.3 The minor submission presented the following clinical trial:

#### **Trials and associated reports presented in the submission**

Trial ID	Protocol title/ Publication title	Publication citation
<b>Direct randomised trials</b>		
<b>OPTIMA</b>	Cummings, et al, Randomized, double-blind, parallel-group, 48-Week study for efficacy and safety of a higher-dose rivastigmine patch (15 vs. 10cm <sup>2</sup> ) in Alzheimer's Disease]	Dement Geriatr Cogn Disord 2012;33:341-353

### **Comparative effectiveness**

6.4 The submission provides the phase III OPTIMA (OPTimizing Transdermal Exelon In Mild-to-moderate Alzheimer's disease) study. Patients who experienced functional and cognitive decline on the 10cm<sup>2</sup> patch gained additional benefit when their dose was increased to 15cm<sup>2</sup> patch (Cummings, 2012). In this study, patients meeting pre-specified decline criteria were randomised to receive rivastigmine 10 or rivastigmine 15 patch during a 48-week double blind phase. The study co-primary endpoints were change from baseline to week 48 on the Instrumental Activities of Daily Living domain of the Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-IADL) scale and the Alzheimer's Disease Assessment Scale– cognitive subscale (ADAS-cog). OPTIMA study enrolled 1,584 patients, of which 567 met decline criteria and were randomised. At all time-points, ADCS-IADL and ADAS-cog scores favoured the rivastigmine 15cm<sup>2</sup> (13.3mg/24 hours) patch. Rivastigmine 15cm<sup>2</sup> patch was statistically superior to rivastigmine 10cm<sup>2</sup> patch on the ADCS-IADL scale from week 16 (p =0.025) onwards including week 48 (p = 0.002), and ADAS-cog at week 24 (p = 0.027), but not at week 48 (p = 0.227) (Cummings, 2012).

### **Comparative harms**

6.5 The submission claimed that the administration of the higher-dose (13.3mg/24 hours) rivastigmine patch had no new or unexpected concerns relating to safety and tolerability based on the publications of Cummings, 2012 and Frampton, 2014.

### **Economic analysis**

6.6 As a minor submission, there is no economic comparison presented.

**Estimated PBS usage & financial implications**

- 6.7 The submission claims that no incremental cost to the PBS or the government is expected as the majority of the switch to rivastigmine patch 15cm<sup>2</sup> will occur from an identical priced rivastigmine patch 10cm<sup>2</sup> presentation with a DPMQ of \$[REDACTED].

**7 PBAC Outcome**

- 7.1 The PBAC recommended the listing of rivastigmine (13.3 milligrams/24 hours patch) for the treatment of mild to moderately severe Alzheimer disease, under the same conditions as current PBS-listed strengths.
- 7.2 The PBAC was satisfied that rivastigmine (13.3 milligrams/24 hours patch) would provide patient treatment options given the persisting clinical need for treatments of mild to moderately severe Alzheimer disease.
- 7.3 The PBAC noted the data on OPTIMA (OPTimizing Transdermal Exelon In Mild-to-moderate Alzheimer's disease) clinical trial provided with the submission. The PBAC noted that Instrumental Activities of Daily Living domain of the Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-IADL) scale and the Alzheimer's Disease Assessment Scale– cognitive subscale (ADAS-cog) scores favoured the rivastigmine 15cm<sup>2</sup> (13.3mg/24 hours) patch over the 10cm<sup>2</sup> patch. As this was a minor submission, the clinical importance of these differences between 15cm<sup>2</sup> and 10cm<sup>2</sup> patches was not evaluated.
- 7.4 The PBAC noted the submission's claim that no incremental cost to the PBS or the government is expected as the majority of the switch to rivastigmine patch 15cm<sup>2</sup> will occur from an identical priced rivastigmine patch 10cm<sup>2</sup> presentation with same AEMP.
- 7.5 The PBAC considered it was appropriate that the Safety Net 20 day rule should apply to this and other forms of rivastigmine.
- 7.6 The PBAC considered that rivastigmine 13.3 milligrams/24 hours patch is suitable for inclusion in the PBS medicines for prescribing by nurse practitioners as continuing therapy only, as for the currently listed strengths.

**Outcome:**

Recommended

**8 Recommended listing**

Amend existing listing as follows:

Public Summary Document – July 2015 PBAC Meeting

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer	
RIVASTIGMINE 13.3 milligrams/24 hours patch, 30	1	5	Exelon®15	Novartis Pharmaceutical Australia Pty Ltd

<b>Category / Program</b>	GENERAL – General Schedule (Code GE)
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Episodicity:</b>	
<b>Severity:</b>	Mild to moderately severe
<b>Condition:</b>	Alzheimer disease
<b>PBS Indication:</b>	Mild to moderately severe Alzheimer disease
<b>Treatment phase:</b>	Initial
<b>Restriction Level / Method:</b>	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input checked="" type="checkbox"/> Authority Required – Emergency <input checked="" type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
<b>Clinical criteria:</b>	<p>Patient must have a baseline Mini-Mental State Examination (MMSE) or Standardised Mini-Mental State Examination (SMMSE) score of 10 or more,</p> <p>AND</p> <p>The condition must be confirmed by, or in consultation with, a specialist/consultant physician (including a psychiatrist),</p> <p>AND</p> <p>The treatment must be the sole PBS-subsidised therapy for this condition.</p>

Public Summary Document – July 2015 PBAC Meeting

<p><b>Prescriber Instructions</b></p>	<p>The authority application must include the result of the baseline MMSE or SMMSE. If this score is 25 - 30 points, the result of a baseline Alzheimer Disease Assessment Scale, cognitive sub-scale (ADAS-Cog) may also be specified.</p> <p>The application must be made in writing, but initial supply may be sought by telephone.</p> <p>For telephone applications, up to a maximum of 2 months' initial therapy will be authorised. This telephone application must be followed by a written authority application for no more than 1 month's therapy and sufficient repeats to complete a maximum of up to 6 months' initial treatment.</p> <p>For written applications where no prior telephone approval has been issued, up to a maximum of 1 month's therapy plus 5 repeats will be authorised.</p>
<p><b>Administrative Advice</b></p>	<p>Continuing Therapy Only:</p> <p>For prescribing by nurse practitioners as continuing therapy only, where the treatment of, and prescribing of medicine for, a patient has been initiated by a medical practitioner. Further information can be found in the Explanatory Notes for Nurse Practitioners.</p>

<p><b>Category / Program</b></p>	<p>GENERAL – General Schedule (Code GE)</p>
<p><b>Prescriber type:</b></p>	<p><input type="checkbox"/>Dental <input checked="" type="checkbox"/>Medical Practitioners <input type="checkbox"/>Nurse practitioners <input type="checkbox"/>Optometrists <input type="checkbox"/>Midwives</p>
<p><b>Episodicity:</b></p>	
<p><b>Severity:</b></p>	<p>Mild to moderately severe</p>
<p><b>Condition:</b></p>	<p>Alzheimer disease</p>
<p><b>PBS Indication:</b></p>	<p>Mild to moderately severe Alzheimer disease</p>
<p><b>Treatment phase:</b></p>	<p>Initial</p>
<p><b>Restriction Level / Method:</b></p>	<p><input type="checkbox"/>Restricted benefit <input checked="" type="checkbox"/>Authority Required - In Writing <input checked="" type="checkbox"/>Authority Required - Telephone <input checked="" type="checkbox"/>Authority Required – Emergency <input checked="" type="checkbox"/>Authority Required - Electronic <input type="checkbox"/>Streamlined</p>

Public Summary Document – July 2015 PBAC Meeting

<p><b>Clinical criteria:</b></p>	<p>Patient must have a baseline Mini-Mental State Examination (MMSE) or Standardised Mini-Mental State Examination (SMMSE) score of 9 or less,</p> <p>AND</p> <p>The condition must be confirmed by, or in consultation with, a specialist/consultant physician (including a psychiatrist),</p> <p>AND</p> <p>The treatment must be the sole PBS-subsidised therapy for this condition.</p> <p>For written applications where no prior telephone approval has been issued, up to a maximum of 1 month's therapy plus 5 repeats will be authorised.</p>
<p><b>Prescriber Instructions</b></p>	<p>A patient who is unable to register a score of 10 or more for reasons other than their Alzheimer disease, as specified below.</p> <p>Such patients will need to be assessed using the Clinicians Interview Based Impression of Severity (CIBIS) scale. The authority application must include the result of the baseline (S)MMSE and specify to which group(s) (see below) the patient belongs.</p> <p>Patients who qualify under this criterion are from 1 or more of the following groups:</p> <p>(1) Unable to communicate adequately because of lack of competence in English, in people of non-English speaking background;</p> <p>(2) Limited education, as defined by less than 6 years of education, or who are illiterate or innumerate;</p> <p>(3) Aboriginal or Torres Strait Islanders who, by virtue of cultural factors, are unable to complete an (S)MMSE test;</p> <p>(4) Intellectual (developmental or acquired) disability, eg Down's syndrome;</p> <p>(5) Significant sensory impairment despite best correction, which precludes completion of an (S)MMSE test;</p> <p>(6) Prominent dysphasia, out of proportion to other cognitive and functional impairment.</p> <p>The application must be made in writing, but initial supply may be sought by telephone.</p> <p>For telephone applications, up to a maximum of 2 months' initial therapy will be</p>

Public Summary Document – July 2015 PBAC Meeting

	authorised. This telephone application must be followed by a written authority application for no more than 1 month's therapy and sufficient repeats to complete a maximum of up to 6 months' initial treatment.
<b>Administrative Advice</b>	<p>Continuing Therapy Only:</p> <p>For prescribing by nurse practitioners as continuing therapy only, where the treatment of, and prescribing of medicine for, a patient has been initiated by a medical practitioner. Further information can be found in the Explanatory Notes for Nurse Practitioners.</p>

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer	
RIVASTIGMINE 13.3 milligrams/24 hours patch, 30	1	5	Exelon®15	Novartis Pharmaceutical Australia Pty Ltd

<b>Category / Program</b>	GENERAL – General Schedule (Code GE)
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Episodicity:</b>	
<b>Severity:</b>	Mild to moderately severe
<b>Condition:</b>	Alzheimer disease
<b>PBS Indication:</b>	Mild to moderately severe Alzheimer disease
<b>Treatment phase:</b>	Continuing
<b>Restriction Level / Method:</b>	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
<b>Clinical criteria:</b>	<p>Patient must have received six months of sole PBS-subsidised initial therapy with this drug,</p> <p>AND</p> <p>Patient must demonstrate a clinically meaningful response to the initial treatment,</p> <p>AND</p> <p>The treatment must be the sole PBS-subsidised therapy for this condition.</p>

<p><b>Prescriber Instructions</b></p>	<p>Prior to continuing treatment, a comprehensive assessment must be undertaken and documented, involving the patient, the patient's family or carer and the treating physician to establish agreement that treatment is continuing to produce worthwhile benefit.</p> <p>Treatment should cease if there is no agreement of benefit as there is always the possibility of harm from unnecessary use.</p> <p>Re-assessments for a clinically meaningful response are to be undertaken and documented every six months.</p> <p>Clinically meaningful response to treatment is demonstrated in the following areas:</p> <p>Patient's quality of life including but not limited to level of independence and happiness;</p> <p>Patient's cognitive function including but not limited to memory, recognition and interest in environment;</p> <p>Patient's behavioural symptoms, including but not limited to hallucination, delusions, anxiety, marked agitation or associated aggressive behaviour.</p>
<p><b>Administrative Advice</b></p>	<p>Continuing Therapy Only:</p> <p>For prescribing by nurse practitioners as continuing therapy only, where the treatment of, and prescribing of medicine for, a patient has been initiated by a medical practitioner. Further information can be found in the Explanatory Notes for Nurse Practitioners.</p>

**9 Context for Decision**

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicines. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

**10 Sponsor's Comment**

The sponsor had no comment.