

**6.10 LISDEXAMFETAMINE,  
Capsule containing lisdexamfetamine dimesilate,  
20 mg, 30 mg, 40 mg, 50 mg, 60 mg and 70 mg,  
Vyvanse<sup>®</sup>,  
Shire Australia Pty Ltd**

**1 Purpose of Application**

- 1.1 The minor submission sought to remove the age of diagnosis criterion in the Authority Required listings of lisdexamfetamine (LDX) for attention deficit hyperactivity disorder (ADHD) to allow use in patients diagnosed over the age of 18 years.
- 1.2 The minor submission requested a price premium for LDX in the expanded (adult) population only, relative to the nominated comparator, immediate release dexamfetamine (IR DEX). This represents an overall price reduction for lisdexamfetamine across the whole population.

**2 Background**

***Previous PBAC consideration***

- 2.1 At its July 2014 meeting, the PBAC recommended the listing of LDX (30 mg, 50 mg and 70 mg) on a cost-minimisation basis with long-acting methylphenidate (Concerta<sup>®</sup>) for use in both children and adolescents. The PBAC accepted that a modest clinical need existed for alternative treatments for ADHD in children and adolescents as response to one treatment over another appears to be highly individualised. At its July 2019 meeting, the PBAC recommended three new strengths of LDX (20 mg, 40 mg and 60 mg) and considered they would provide greater dosing flexibility to achieve optimal efficacy and tolerability for patients.
- 2.2 LDX is currently listed on the PBS for the treatment of patients with ADHD diagnosed between the ages of 6 and 18 years (inclusive). This same PBS restriction applies to all long-acting stimulant medications used in the treatment of ADHD, i.e. long-acting methylphenidate hydrochloride (Concerta and Ritalin LA<sup>®</sup>) and atomoxetine (Strattera<sup>®</sup>). Under the PBS, an individual diagnosed with ADHD after the age of 18 is only eligible to receive short-acting ADHD medications on the PBS (IR DEX and immediate release methylphenidate (IR MPH)).
- 2.3 At its July 2012 meeting, the PBAC considered a submission from Janssen-Cilag Pty Ltd to extend the listing for Concerta to include patients diagnosed after the age 18 years. The PBAC was unable to make a recommendation to change the PBS listing criteria due to the following issues:

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- Comparator: The submission had inappropriately nominated long-acting MPH used in patients diagnosed with ADHD **aged 18 years or less** as the comparator. The PBAC considered that IR MPH and IR DEX were the appropriate comparators.
  - Clinical relevance of outcome measure: The PBAC noted that the pooled result of the post-hoc subgroup analysis of patients diagnosed with ADHD after 18 years of age from the pivotal trials was a mean difference of -5.83 (-8.02, -3.63) of the ADHD Investigator Symptom Rating Scale (AISRS), the primary outcome of the trials. The PBAC did not accept that the clinical relevance and validity of the outcome measures used in the trials had been adequately established.
  - Safety: The PBAC considered that the safety profile of methylphenidate in adults may be different to that in children and adolescents, including the potential for increase in the incidence of hypertension in adults as an adverse effect.
  - Higher price: The PBAC considered that no evidence was presented in the submission to support the substantially higher price proposed for long-acting MPH over IR MPH in patients diagnosed after 18 years of age.
  - Utilisation: The PBAC considered that the utilisation of long-acting MPH in patients diagnosed after 18 years of age was highly uncertain and that the utilisation estimates provided in the submission and the overall costs to the PBS were likely to be substantially underestimated. The PBAC considered that the proposed extension to PBS listing of long-acting MPH would expand the ADHD market by a much larger extent than that estimated in the submission.
- 2.4 The PBAC had received correspondence from a range of patients, clinicians, and professional organisations who were concerned that some adult patients were disadvantaged by the age of diagnosis criteria associated with PBS-listed long-acting ADHD treatments.
- 2.5 In September 2019, the PBAC sought advice from the Royal Australian & New Zealand College of Psychiatrists (RANZCP) as to whether the age of diagnosis criteria for ADHD medicines on the PBS were problematic for prescribers or for patients, and if the restrictions were inconsistent with the current evidence-based standard of care for ADHD patients. A response from the RANZCP raised the following concerns with the existing PBS listing:
- That access to PBS subsidised ADHD medications is limited by the age of diagnosis criteria;
  - That there is significant cross-over between substance use disorder and ADHD. Some practitioners are reluctant to prescribe short-acting ADHD medications for adults as they are more susceptible to abuse by people with substance use disorder;
  - Short-acting medications require multiple daily doses which can lead to poor compliance and therefore poorer clinical outcomes;
  - Poorly managed ADHD can lead to a greater risk of failure at school, the workplace,

and relationships. Rates of suicide, serious accidents, substance abuse and imprisonment are also significantly increased; and

- that improved access to treatment would significantly reduce the societal costs of ADHD in Australia.

### Registration status

2.6 LDX (30 mg, 50 mg and 70 mg strengths) was TGA registered on 22 July 2013 for the treatment of ADHD. In 2017, the TGA registered 20 mg, 40 mg and 60 mg strengths of LDX.

2.7 The TGA-approved PI also states the following:

- Treatment should be commenced by a specialist as part of a comprehensive treatment plan and re-evaluated periodically during long-term use; and
- A diagnosis of ADHD implies the presence of hyperactive-impulsive or inattentive symptoms that caused impairment and were present before 12 years of age.

*For more detail on PBAC's view, see section 6 PBAC outcome.*

## 3 Requested listing

3.1 The submission proposed two options for changes to the existing restriction.

3.2 Bold text (and bold strikethrough text) indicate the changes to the current restriction proposed by the sponsor.

Name, Restriction, Manner of administration and form	PBS item code	Max. Qty packs	Max. Qty units	No. of Rpts	Proprietary Name and Manufacturer
<b>LISDEXAMFETAMINE</b>					
lisdexamfetamine dimesilate 20 mg capsule, 30	11884L	1	30	5	
lisdexamfetamine dimesilate 30 mg capsule, 30	10486X	1	30	5	
lisdexamfetamine dimesilate 40 mg capsule, 30	11898F	1	30	5	Vyvanse®
lisdexamfetamine dimesilate 50 mg capsule, 30	10474G	1	30	5	Shire Australia Pty Ltd
lisdexamfetamine dimesilate 60 mg capsule, 30	11897E	1	30	5	
lisdexamfetamine dimesilate 70 mg capsule, 30	10492F	1	30	5	

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**Option 1:**

<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>Restriction Level / Method:</b> <input checked="" type="checkbox"/> Authority Required – Telephone/Electronic/Emergency
<b>Administrative Advice:</b> Continuing Therapy Only: 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.
<b>Administrative Advice:</b> Special Pricing Arrangements Apply.
<b>Indication:</b> Attention deficit hyperactivity disorder
<b>Clinical criteria:</b>
Patient must require continuous coverage over 12 hours.
<b>AND</b>
<b>Population criteria:</b>
Patient must be or have been diagnosed <del>between</del> <b>after</b> the age of 6 <del>and 18</del> <b>and 18</b> years <b>inclusive</b> .
<b>Administrative Advice:</b> Care must be taken to comply with the provisions of State/Territory law when prescribing this drug.
<b>Administrative Advice:</b> The treatment must not exceed a maximum daily dose of 70 mg.

3.3 The pre-PBAC response claimed that the criteria presented in Option 1 is the most relevant to current clinical practice and is consistent with the restrictions of ADHD medications currently available to patients diagnosed after the age of 18, IR DEX and IR MPH.

3.4 Option 2 provided alternative wording for the population criteria, reflective of current Diagnostic and Statistical Manual of Mental Disorders criteria<sup>1</sup> and International Classification of Diseases guidelines<sup>2</sup>. The proposed criterion is based on wording included in the UK summary of product characteristics for Elvanse Adult® (lisdexamfetamine dimesilate)<sup>3</sup> and specifies that, in patients who are diagnosed as adults, the presence of symptoms of ADHD that were pre-existing in childhood should be confirmed retrospectively (e.g. from the patient’s medical records, in-depth clinical interview and/or obtaining corroborating evidence from parents, teachers or siblings).

**Option 2:**

<b>Population criteria:</b>
Patient must be or-have been diagnosed between the age of 6 and 18 years inclusive; OR
Patient must be or have been diagnosed after the age of 18 years with retrospective confirmation of the presence of symptoms of ADHD that were pre-existing in childhood (before the age of 12 years).

3.5 Option 2 is consistent with the TGA-approved Product Information for LDX, which states that “a diagnosis of ADHD implies the presence of hyperactive-impulsive or inattentive symptoms that caused impairment and were present before 12 years of age”.

*For more detail on PBAC’s view, see section 6 PBAC outcome.*

<sup>1</sup> DSM5. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Arlington, VA: American Psychiatric Association, 2013

<sup>2</sup> ICD-11 International Classification of Diseases 11th Revision The global standard for diagnostic health information. Available at. <https://icd.who.int/en>

<sup>3</sup> <https://www.medicines.org.uk/emc/product/7504/smpc#PRODUCTINFO>

## 4 Comparator

- 4.1 The minor submission nominated IR DEX as the main comparator, and IR MPH as a secondary comparator, as an individual diagnosed with ADHD after the age of 18 is currently only eligible to receive short-acting ADHD medications on the PBS. The nomination of IR DEX and IR MPH as comparators aligned with the advice provided by the PBAC in consideration of Concerta in July 2012. A DUSC analysis conducted in May 2018 showed that IR DEX was the most widely used PBS subsidised ADHD medication in adults, including those who commence ADHD therapy after the age of 18 years.

*For more detail on PBAC's view, see section 6 PBAC outcome.*

## 5 Consideration of the evidence

### *Sponsor hearing*

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

### *Consumer comments*

- 5.2 The PBAC noted and welcomed the input from individuals (194), health care professionals (18) and organisations (1) via the Consumer Comments facility on the PBS website. The comments from health care professionals described the benefits of treatment with LDX with respect to once daily dosing, such as improved compliance due to ease of use, and sustained response to the medication. Individuals described the significant improvements in quality of life due to LDX, but also the financial hardship associated with having to access the medication via a private prescription due to a diagnosis of ADHD in adulthood.
- 5.3 The PBAC also noted that ADHD Australia was in strong support of the requested change to the listing. The comments emphasised that not all patients with ADHD are afforded the benefit of diagnosis in their early life. The organisation stated that it has been advocating for equity of access for long-acting ADHD medications for some time.

### *Clinical trials*

- 5.4 The minor submission provided the following evidence:
- The results of eight randomised placebo-controlled trials evaluating the efficacy and safety of LDX versus placebo in adults diagnosed with ADHD, to support the submission's claim that LDX is more effective than placebo.
  - Outcomes from recent systematic literature reviews which estimated the treatment effect sizes of LDX, IR DEX and IR MPH versus placebo, based on meta-analyses data from randomised controlled trials conducted in adult ADHD populations, to support the submission's claim that the treatment effect size for LDX is similar to, if not better than, short-acting stimulant therapies in adults.

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- A comparison of the safety information in the TGA-approved Product Information for LDx, IR DEX, long-acting MPH and IR MPH products, to support the submission’s claim that LDx has a similar safety profile to short-acting therapies and other long-acting therapies.

5.5 Details of the trials presented in the submission are provided in the table below.

**Table 1: Randomised control trials and associated reports presented in the submission**

Trial ID	Protocol title/ Publication title	Publication citation
<b>Pivotal</b>		
NRP 104-303	<p>A Phase 3, Randomized, Double-Blind, Multi-Center, Placebo-Controlled, Parallel- Group, Forced Dose Titration, Safety and Efficacy Study of NRP104 in Adults with Attention Deficit Hyperactivity Disorder (ADHD).</p> <p>Adler LA, Goodman DW, Kollins SH, Weisler RH, Krishnan S, Zhang Y, et al. Double-blind, placebo-controlled study of the efficacy and safety of lisdexamfetamine dimesylate in adults with attention-deficit/hyperactivity disorder.</p> <p>Adler LA, Weisler RH, Goodman DW, Hamdani M, Niebler GE. Short-term effects of lisdexamfetamine dimesylate on cardiovascular parameters in a 4-week clinical trial in adults with attention-deficit/hyperactivity disorder.</p> <p>Adler LA, Goodman D, Weisler R, Hamdani M, Roth T. Effect of lisdexamfetamine dimesylate on sleep in adults with attention-deficit/hyperactivity disorder.</p>	<p>Clinical study report</p> <p><i>Journal of Clinical Psychiatry.</i> 2008;69(9):1364-73.</p> <p><i>Journal of Clinical Psychiatry.</i> 2009a;70(12):1652-61.</p> <p><i>Behavioral and Brain Functions.</i> 2009b;5</p>
<b>Supportive</b>		
SPD489-403	<p>A Phase 4, Randomized, Double-blind, Multi-center, Placebo controlled, Parallel-group Study Evaluating the Safety and Efficacy of SPD489 on Executive Function (Self-regulation) Behaviors in Adults with Attention-Deficit/Hyperactivity Disorder (ADHD) Reporting Clinically Significant Impairment of Real-world Executive Function Behavior.</p> <p>Adler LA, Dirks B, Deas P, Raychaudhuri A, Dauphin M, Saylor K, et al. Self-Reported quality of life in adults with attention-deficit/hyperactivity disorder and executive function impairment treated with lisdexamfetamine dimesylate: a randomized, double-blind, multicenter, placebo-controlled, parallel-group study.</p> <p>Adler LA, Dirks B, Deas PF, Raychaudhuri A, Dauphin MR, Lasser RA, et al. Lisdexamfetamine dimesylate in adults with attention-deficit/hyperactivity disorder who report clinically significant impairment in executive function: Results from a randomized, double-blind, placebo-controlled study.</p>	<p>Clinical study report</p> <p><i>BMC psychiatry.</i> 2013a;13:253</p> <p><i>Journal of Clinical Psychiatry.</i> 2013b;74(7):694-702</p>

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Trial ID	Protocol title/ Publication title	Publication citation
SPD489-316	<p>A Phase IIIb Randomized, Double-Blind, Multicenter, Placebo-controlled, Dose Optimization, Crossover, Safety and Efficacy Workplace Environment Study of Lisdexamfetamine Dimesylate (LDX) in Adults with Attention-Deficit Hyperactivity Disorder (ADHD).</p> <p>Wigal T, Brams M, Gasior M, Gao J, Squires L, Giblin J. Randomized, double-blind, placebo-controlled, crossover study of the efficacy and safety of lisdexamfetamine dimesylate in adults with attention-deficit/hyperactivity disorder: novel findings using a simulated adult workplace environment design.</p> <p>Wigal T, Brams M, Gasior M, Gao J, Giblin J. Effect size of lisdexamfetamine dimesylate in adults with attention-deficit/hyperactivity disorder.</p> <p>Wigal T, Gao J, Gasior M, Giblin J, Valliere S, Brams M. Efficacy and safety of lisdexamfetamine dimesylate in adults with attention-deficit/hyperactivity disorder in the simulated adult workplace environment.</p>	<p>Clinical study report</p> <p><i>Behavioral and brain functions.</i> 2010a;6:34</p> <p><i>Postgraduate Medicine.</i> 2011;123(2):169-75</p> <p><i>Pharmacotherapy.</i> 2010b;30(10):422e.</p>
SPD489-401	<p>Phase 4, Double-blind, Multi-center, Placebo-controlled, Randomized Withdrawal, Safety and Efficacy Study of SPD489 in Adults Aged 18-55 with Attention-Deficit/Hyperactivity Disorder (ADHD).</p> <p>Brams M, Weisler R, Findling RL, Gasior M, Hamdani M, Ferreira-Cornwell MC, et al. Maintenance of efficacy of lisdexamfetamine dimesylate in adults with attention-deficit/hyperactivity disorder: Randomized withdrawal design.</p>	<p>Clinical study report</p> <p><i>Journal of Clinical Psychiatry.</i> 2012;73(7):977-83.</p>
Biederman 2012	<p>Biederman J, Fried R, Hammerness P, Surman C, Mehler B, Petty CR, et al. The effects of lisdexamfetamine dimesylate on the driving performance of young adults with ADHD: A randomized, double-blind, placebo-controlled study using a validated driving simulator paradigm.</p> <p>Biederman J, Fried R. The effects of lisdexamfetamine dimesylate on the driving performance of young adults with ADHD.</p>	<p><i>Journal of Psychiatric Research.</i> 2012a;46(4):484-91.</p> <p><i>European Neuropsychopharmacology.</i> 2012b;22:S436.</p>
DuPaul 2012	<p>DuPaul GJ, Weyandt LL, Rossi JS, Vilardo BA, O'Dell SM, Carson KM, et al. Double-blind, placebo-controlled, crossover study of the efficacy and safety of lisdexamfetamine dimesylate in college students with ADHD.</p>	<p><i>Journal of Attention Disorders.</i> 2012;16(3):202-20.</p>
Martin 2014	<p>Martin PT, Corcoran M, Zhang P, Katic A. Randomized, double-blind, placebo-controlled, crossover study of the effects of lisdexamfetamine dimesylate and mixed amphetamine salts on cognition throughout the day in adults with attention-deficit/hyperactivity disorder.</p>	<p><i>Clinical Drug Investigation.</i> 2014;34(2):147-57.</p>
Waxmonsky 2014	<p>Waxmonsky JG, Waschbusch DA, Babinski DE, Humphrey HH, Alfonso A, Crum KI, et al. Does pharmacological treatment of ADHD in adults enhance parenting performance? Results of a double-blind randomized trial.</p> <p>Babinski DE, Waxmonsky JG, Waschbusch DA, Humphery H, Pelham WE. Parent-reported improvements in family functioning in a randomized controlled trial of lisdexamfetamine for treatment of parental attention-deficit/hyperactivity disorder.</p>	<p><i>CNS Drugs.</i> 2014;28(7):665-77.</p> <p><i>Journal of Child and Adolescent Psychopharmacology.</i> 2017;27(3):250-7.</p>

Source: Table 4, Appendix A, of the minor submission

## ***Comparative effectiveness***

### Randomised placebo-controlled trials of LDX in adults

5.6 The minor submission provided a summary of the efficacy results from the randomised controlled trials comparing LDX with placebo in adults. The minor submission claimed that, overall, the body of evidence presented demonstrates:

- In terms of improvement in ADHD-Rating Scale total score (ADHD-RS), the treatment effect is consistently large across the studies (weighted mean difference (WMD) vs placebo = -10.54 points [95% CI: -12.17, -8.91]). The size of the treatment effect for LDX, according to convention, also represents a large Cohen's d treatment effect size (Standardised mean difference (SMD) = -0.97 [95% CI: -0.13, -0.81]).
- The difference between LDX and placebo is greater than the range of minimal clinically important "between treatment" differences (MCIDs of -5.2 to -7.7 estimated for this outcome by Zhang et al 2005 when anchored to the Clinical Global Impressions-ADHD-Severity (CGI-ADHD-S). It is also greater than the "between treatment" MCIDs of -4.0 to -9.9 estimated for the outcome in three key trials of LDX in adults when anchored to the CGI-I.
- The risk ratio for CGI improvement (CGI-I) (much improved, very much improved) is 2.36 [95% CI: 1.93, 2.87]. The number needed to treat based on achieving a CGI-I response (much or very much improved) is between 2 to 3.
- The clinical response to LDX has been shown to be maintained long-term (Study SPD489-401).
- LDX has been shown to significantly improve executive functioning and quality of life, helping adults with ADHD to lead more normal lives (Studies SDP489-316; SDP489-403; DuPaul 2012). This includes facilitating improvements in parent-child interactions (Waxmonsky 2014).
- LDX may also improve reaction times and may help to reduce driving risks of young adults with ADHD (Biederman 2012).
- The long duration lasting up to 14 hours, (SDP489-316) gives patients on LDX the advantage of avoiding supplemental doses of short-acting stimulants in the afternoon or early evening.

5.7 The minor submission stated that the available randomised controlled evidence for LDX supports the drug as being highly effective as a treatment of ADHD in adults, providing day long continuous ADHD symptom control and functional improvement across settings compared to placebo.

### Efficacy of LDX versus immediate release (short-acting) stimulants

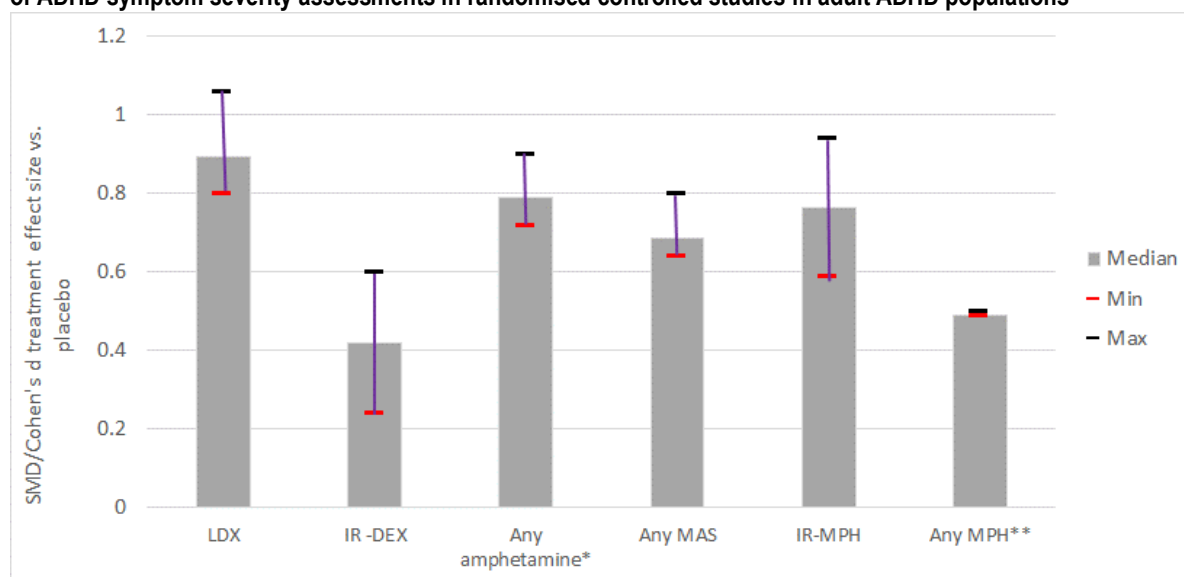
5.8 There are no direct comparative trials between LDX and immediate release stimulant therapies, with widely reported heterogeneity and variable quality of the trial data.

5.9 The minor submission presented outcomes from recent systematic literature reviews which estimated the treatment effect sizes of LDX, IR DEX and IR MPH versus placebo, in terms of ADHD symptom control, based on meta-analyses data from randomised controlled trials conducted in adult ADHD populations.

5.10 The minor submission claimed that (see Figure 1):

- In general, based on Cohen’s d effect size, the findings of the identified systematic literature review and meta-analyses suggest relatively large effect sizes for stimulant therapies in the treatment of ADHD in adults over the study periods.
- The effect sizes reported for amphetamines are, for the most part, larger than those reported for MPH, with those reported for LDX amongst the largest.
- The treatment effect sizes for symptom control based on ADHD-RS scores reported for IR DEX and IR MPH vary considerably.
- Based on a CGI-I score of 1 or 2, i.e. much or very much improved, the response rates with LDX are least comparable to those for mixed amphetamine salts and all formulations of MPH. Data specifically for IR MPH and IR DEX are lacking.
- None of the reviews provide evidence-based support for any treatment hierarchy in adult ADHD.

Figure 1: Treatment effect sizes reported for stimulant therapies in recent systematic reviews based on meta-analyses of ADHD symptom severity assessments in randomised controlled studies in adult ADHD populations



Source: Figure 6, page 23 of the minor submission; Table 7, Appendix A of the minor submission  
 DEX, dexamphetamine; IR, immediate-release; LDX, lisdexamfetamine; MAS, mixed amphetamine salts; max, maximum effect size; min, minimum effect size; MPH, methylphenidate; SLR, systematic review; SMD, standardise mean difference

\*Any amphetamine includes IR DEX, IR or long-acting MAS and LDX

\*\*Any MPH includes IR MPH or long-acting MPH formulations

5.11 The minor submission stated that, whilst not providing robust evidence, the treatment effect sizes reported across the systematic literature reviews and meta-analyses may be considered informative. It also claimed that the large treatment effect size reported for LDX provides reasonable confidence that the level of ADHD symptom

control provided by LDX is similar to, if not better than, that provided by short-acting stimulant therapies in adults, before any consideration of any additional benefits provided by LDX due to once daily dosing.

### ***Comparative harms***

- 5.12 The minor submission presented a review of information available in the respective TGA-approved Product Information leaflets for LDX (Vyvanse®), IR DEX (Aspen Dexamfetamine® and Dexmine®), long-acting MPH (Ritalin LA®), and IR MPH (Ritalin® 10 and Artige®).
- 5.13 The minor submission stated that the adverse effect profiles, contraindications, special warnings and precautions for use are similar across all three therapies, with common adverse effects such as insomnia, nausea, decreased appetite and increased blood pressure.
- 5.14 The minor submission noted that for patients with borderline hypertension and antecedent cardiac disease, sympathomimetic effects (e.g. increases in blood pressure and heart rate), although usually small, could be clinically significant for patients using short-acting or long-acting stimulant therapies.
- 5.15 The minor submission claimed that a key distinguishing feature between LDX and the short-acting stimulants relates to a comparatively lower potential for abuse, misuse, dependence, or diversion for non-therapeutic uses, based on its pharmacokinetic and physiochemical properties.

### ***Clinical claim***

- 5.16 The minor submission claimed that, within the limits of the available evidence, LDX is at least non-inferior to short-acting stimulants IR DEX and IR MPH in terms of efficacy.
- 5.17 The submission also claimed that LDX is non-inferior in terms of safety versus IR DEX and IR MPH.

### ***Economic analysis***

- 5.18 The minor submission did not present a formal economic evaluation. Rather, it proposed that a proportion of the price premium awarded to Concerta (in 2006) and other long-acting formulations over IR MPH in the child/adolescent population also be awarded to LDX in adults (relative to IR DEX). The submission stated that this is based on “analogous, although potentially less valuable, non-clinical benefits” of once daily dosing in the adult population compared to the child/adolescent population.
- 5.19 The minor submission stated that the clinical claim had not taken into account the additional benefits provided to adults by LDX due to once daily dosing. These benefits were acknowledged by the PBAC for long-acting stimulant therapies in the child/adolescent setting in its November 2006 recommendation for Concerta,

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including likely improvements in compliance and in ease of administration, particularly in relation to the removal of the need for a dose of medication at school.

5.20 The minor submission stated that the additional benefits of LDX compared to the nominated comparator in adults include:

- A smoother and a longer duration of effect, thereby avoiding the peaks and troughs and wearing off effects which that occur throughout the day with short-acting therapy;
- Convenience and ease of once-a-day administration which removes the need for a second, third or even fourth doses to be taken during the day in the workplace; with avoidance of the associated social stigma;
- Improved medication compliance (adherence/ persistence); and
- A decreased risk of misuse or diversion.

5.21 The submission acknowledged that the potential benefits of once daily treatment in adults will be different to that for children/adolescents (e.g. the removal of school dosing is not applicable to adults). Conversely, the impact of treatment on driving is not applicable to children/adolescents. The reduced risk of misuse, abuse and diversion however is arguably of greater applicability in an adult population.

5.22 The minor submission used the price premium awarded to Concerta in the child/adolescent population, relative to Ritalin 10, as a benchmark for assigning value to the benefits of once daily ADHD medication in adults (see table below). The premium was \$1.73 per day at the time of listing and has since decreased to \$1.21 per day.

**Table 2: Price premium of Concerta® relative to Ritalin 10®, 2007 to 2019**

	<b>Concerta®<sup>a</sup></b>	<b>Ritalin 10®</b>	<b>Premium</b>
PBS item(s)	2387P, 2172H, 2388Q, 2432B	8839F	-
Daily dose	18 – 54 mg once-daily	3 x 10 mg daily	-
<b>August 2007</b>			
DPMQ/day	\$2.70	\$0.56	\$2.14
AEMP/day	\$2.06	\$0.25	\$1.73
<b>December 2019</b>			
DPMQ/day	\$2.06	\$0.71	\$1.35
AEMP/day	\$1.47	\$0.26	\$1.21

Source: Table 8, p27 of the minor submission

AEMP = approved ex-manufacturer price; DPMQ = dispensed price for maximum amount; PBS = Pharmaceutical Benefits Scheme

a. Price per day calculated as a weighted average across all four doses of Concerta®, see spreadsheet Section 3 spreadsheet\_Vyvanse\_Minor Dec2019.xlsx.

5.23 The minor submission proposed a price premium of \$ [redacted] per day for LDX in the adult population (relative to IR DEX), which is [redacted] of the current premium (\$1.21 per day) and [redacted] of the original price premium applied to Concerta for the child/adolescent population (\$1.73 per day). The submission estimated that the value of long-acting medication in adults is [redacted] that in children/adolescents (using the original premium as the benchmark).

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5.24 The proposed approved ex-manufacturer price (AEMP) for LDX in the adult population was calculated at \$ [REDACTED] (30 units) using the proposed \$ [REDACTED] premium per day (see Table 3). The proposed effective dispensed price for maximum quantity (DPMQ) for LDX in the expanded adult population was calculated by the submission to be \$ [REDACTED].

5.25 The current effective AEMP of LDX in the child/adolescent population is \$ [REDACTED].

**Table 3: Requested LDX price in adult patients**

Row	Parameter	Value	Reference
Price Premium for LA in adult patients			
A	Current DEX price (Ex-man) in ineligible patients (per day)	\$0.18	PBS Item: 1165H; assumes 1 script is equivalent to 100/3 days of therapy
B	Price premium for LDX in ineligible patients	\$ [REDACTED]	-
LDX price (AEMP) in adult patients			
C	Price per day	\$ [REDACTED]	A + B
D	Price per pack	\$ [REDACTED]	C x 30
E	Price cut in LDX ineligible patients (relative to current effective price \$ [REDACTED])	43%	(D - \$ [REDACTED])/\$ [REDACTED]

Source: Table 9, p29 of the minor submission

AEMP = approved ex-manufacturer price; DEX = dexamfetamine; LA = long acting; LDX = lisdexamfetamine; PBS = Pharmaceutical Benefits Scheme

Weighted price calculation

5.26 The minor submission proposed a weighted effective AEMP, which would include two patient populations:

- Patients currently eligible for LDX, that is patients diagnosed before the age of 18 years, in which the current effective AEMP of LDX is \$ [REDACTED] per pack; and
- Patients currently ineligible for LDX, that is patients diagnosed after the age of 18 years, in which the proposed effective AEMP of LDX would be \$ [REDACTED] per pack.

5.27 A weighting of these two prices was proposed based on the size of each patient population based on a 10% sample of longitudinal PBS data for all ADHD medications.

**Table 4: Number of long and short acting ADHD scripts dispensed in ‘children’, ‘continuers’ and ‘adults’ from July 2011 to June 2019**

	2011/12	2012/13	2013/14	2014/15	2015/16	2016/17	2017/18	2018/19
<b>Prescription numbers</b>								
Children	424,400	488,070	526,940	563,330	634,520	707,170	781,580	871,420
Continuers	31,280	46,880	54,740	64,460	75,410	86,610	97,930	113,010
Adults	134,780	230,590	241,710	258,960	290,610	314,350	336,790	375,620
Total	590,460	765,540	823,390	886,750	1,000,540	1,108,130	1,216,300	1,360,050
<b>Proportion by cohort</b>								
Children <sup>a</sup>	72%	64%	64%	64%	63%	64%	64%	64%
Continuers <sup>b</sup>	5%	6%	7%	7%	8%	8%	8%	8%
Adults <sup>c</sup>	23%	30%	29%	29%	29%	28%	28%	28%
<b>Proportions by age at supply</b>								
<18 (Children)	72%	64%	64%	64%	63%	64%	64%	64%
18+ (Continuers/Adults)	28%	36%	36%	36%	37%	36%	36%	36%
<b>Proportions by PBS restriction</b>								
Children/Continuers	77%	70%	71%	71%	71%	72%	72%	72%
Adults	23%	30%	29%	29%	29%	28%	28%	28%

Source: Table 11, p33 of the minor submission

ADHD = attention deficit/hyperactivity disorder; PBS = Pharmaceutical Benefits Scheme

<sup>a</sup> Children: Aged <18 at date of supply and “diagnosed” (i.e. first script) < 18

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<sup>b</sup> Continuers: Aged 18+ at date of supply but “diagnosed” (i.e. first script) < 18

<sup>c</sup> Adults: Aged 18+ at date of supply and “diagnosed” (i.e. first script) > 18.

These definitions assume that the age of the patient when they received their first ADHD script is a proxy for age at diagnosis.

5.28 In 2018/19, 72% of all PBS scripts in the ADHD market were dispensed to patients who received their first PBS-subsidised prescription before 18 years of age and 28% were dispensed to patients who received their first PBS-subsidised prescription after 18 years of age. Using these proportions resulted in an effective AEMP of LDX per pack equal to \$ [REDACTED], an approximate 12% reduction on the current effective AEMP (see Table 5).

**Table 5: Calculation of weighted price of LDX**

Patient population	Number of prescriptions	Weighting	AEMP per pack
Children/Continuers	984,430*	72%	\$ [REDACTED]
Adults	375,620	28%	\$ [REDACTED]
Weighted AEMP			\$ [REDACTED]*
Change in price relative to current effective ex-man	\$ [REDACTED]		~ -12.0%

Source: Table 12, p34 of the minor submission

AEMP = approved ex-manufacturer price; LDX = lisdexamfetamine

\* The sponsor had number of prescriptions for children/continuers at 1,073,320 (this is incorrect, based on Table 4).

\* (72% of \$ [REDACTED]) + (28% of \$ [REDACTED]) gives \$ [REDACTED] (not \$ [REDACTED]).

**Drug cost/patient/year: \$ [REDACTED].**

5.29 The estimated drug cost per patient per month would be \$ [REDACTED] (the proposed weighted DPMQ for 30 tablets) based on a course duration of 30 days (once daily dosing). Therefore, the estimated drug cost per patient per year would be \$ [REDACTED].

**Estimated PBS usage & financial implications**

5.30 With respect to the new adult market, the minor submission estimated a net cost to the PBS of less than \$10 million in Year 5 of listing, with a total net cost to the PBS of \$20 - \$30 million over the first 5 years of listing. This is summarised in the table below. The submission did not provide estimated usage or financial implications for Year 6 of listing.

**Table 6: Estimated use and financial implications**

	Year 1	Year 2	Year 3	Year 4	Year 5
Projected size of adult ADHD market	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Uptake of LDX	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
LDX items dispensed	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Substituted IR MPH and IR DEX items	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
LDX expenditure (at adult price, \$ [REDACTED])	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Substituted IR MPH and IR DEX expenditure	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
<b>Net cost to PBS/RPBS</b>	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]

Source: Table 14, p37 of the minor submission

ADHD = attention deficit/hyperactivity disorder; DPMQ = dispensed price for maximum quantity; IR DEX = immediate release dexamfetamine; IR MPH = immediate release methylphenidate; LDX = lisdexamfetamine; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme

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All units for IR MPH, IR DEX and LDX are presented as natural units. However, prescription equivalence was applied when calculating uptake of LDX and substitution of stimulant medication in the 'adult' ADHD market, see Section 4 spreadsheet\_VYVANSE\_Minor\_Dec19.xls for calculations. As such, the number of dispensed LDX items are not equal to the % uptake of LDX in the adult ADHD market. Also, substituted IR MPH and IR DEX items are not equal to the number of LDX items despite the assumption that no additional LDX items will grow the adult ADHD market due to the reversal of prescription equivalence. Costs are presented as total cost to the PBS/RBS and hence are based on DPMQ for each ADHD medication less patient co-payments.

- 5.31 The estimated use and financial impact of LDX in the adult population was estimated by way of a market share analysis. The submission stated that the analysis followed these steps:
- Summary of the units of short-acting ADHD medications dispensed on the PBS (including below co-payment items).
  - Inclusion of additional units of LDX dispensed on a private prescription. Sales of non-PBS LDX are increasing and expected to represent approximately █% of PBS sales by the end of 2019 based on sales data.
  - Units dispensed to “children” and to “continuers” are removed from this potential market because they are already eligible for LDX (and other long-acting ADHD medications) and would be using LDX (or other long-acting ADHD medication) if that was their preference.
  - Uptake of LDX within this “adult” market is based on market share of long-acting medication in “continuers” (estimated from 10% PBS data) as a proxy.
  - Units of LDX dispensed, and units of other short-acting ADHD medications substituted in the proposed adult patient population is then calculated.
  - The financial impact of LDX on the PBS is then calculated by applying the adult price of \$█ in the adult population to calculate the incremental cost of adding adults to the PBS.
  - Substituted costs of short-acting medications are incorporated to calculate the net financial impact to the PBS.
- 5.32 The minor submission suggested that, if other sponsors of long-acting medication decide to apply for expansion of their listings, the financial estimates would reflect the budget impact of all long-acting medication in ADHD patients diagnosed after the age of 18 years.
- 5.33 As a minor submission, the financial estimates have not been independently evaluated.
- 5.34 LDX is currently listed with a Special Pricing Arrangement (SPA). The sponsor requested that an SPA be maintained for PBS listing to occur at the proposed weighted effective price in this submission.
- 5.35 The minor submission also requested that the current risk sharing arrangement (RSA) for LDX be terminated. It claimed that because LDX is listed as a first-line treatment option, and with the expansion of indication into adults diagnosed after 18 years, there is no risk of utilisation outside of the proposed population. The submission also stated that LDX has four years of PBS history, with relative certainty in the expected utilisation for the “children” and “continuers” segments of the currently eligible

market compared to when LDX was first listed on the PBS. The PBAC noted that the financial cap in place for LDX was originally proposed by the sponsor as a way to offer further rebate and reduction in the price of the listing, and not to manage a particular utilisation risk.

*For more detail on PBAC's view, see section 6 PBAC outcome.*

## **6 PBAC Outcome**

- 6.1 The PBAC recommended expanding the listing of lisdexamfetamine (LDX) to include treatment of patients with attention deficit hyperactivity disorder (ADHD) who are diagnosed after the age of 18. The PBAC's recommendation was based on, among other matters, its assessment that the cost-effectiveness of LDX in adults would be acceptable if LDX was no more costly on a per day basis (at ex-manufacturer price) for this population than the drug cost per patient per day of immediate release dexamfetamine (IR DEX), without the requested price premium.
- 6.2 In addition to the advice and support received from the Australian ADHD Professionals Association and the Royal Australian & New Zealand College of Psychiatrists (RANZCP), the PBAC noted that the consumer comments were strongly supportive of the requested listing.
- 6.3 The PBAC noted several reasons for why a diagnosis of ADHD may have been missed in childhood, including:
  - Lack of access to clinicians with the relevant expertise and associated referral pathways;
  - ADHD in adults may only be recognised when a person has a child diagnosed with ADHD; and
  - The presence of masking or overlapping comorbidities.
- 6.4 The PBAC considered that there is a moderate unmet clinical need for effective treatments for this cohort of patients, acknowledging that there is now greater acceptance in the medical community of the diagnosis of ADHD in adulthood. The PBAC noted that RANZCP recommends the Canadian ADHD Practice Guidelines (CADDRA 4th Edition, 2018) and the UK National Institute for Health Care and Excellence Guidelines (NICE, 2018), both of which consider the use of long-acting stimulant medications as first-line pharmacotherapy in adults with ADHD.
- 6.5 The PBAC considered it appropriate that the restriction should be amended to require retrospective confirmation of symptoms before age 12, as this aligns with the TGA-approved Product Information for LDX, as well as the Diagnostic and Statistical Manual of Mental Disorders criteria (5<sup>th</sup> edition) and International Classification of Diseases guidelines (11<sup>th</sup> revision). The PBAC requested that the Department work with the Australian ADHD Professionals Association and RANZCP to develop an appropriate definition of a retrospective confirmation of symptoms.

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- 6.6 The PBAC reiterated its previous advice that IR DEX and immediate release methylphenidate (IR MPH) were the appropriate comparators.
- 6.7 The PBAC noted that no direct comparative evidence for LDX versus IR DEX (or IR MPH) in patients diagnosed after 18 years of age was presented. Rather, evidence of LDX versus placebo was presented in order to demonstrate the efficacy of LDX in adults, as well as an estimation of the relative treatment effect sizes of LDX and immediate release (short-acting) therapies versus placebo. The PBAC considered these comparisons to be informative. The PBAC also considered that LDX is likely to be as effective at improving measures of ADHD core symptoms in adults as the short-acting stimulant therapies.
- 6.8 The PBAC also noted that safety data specific to the use of LDX in adults was not presented in the minor submission. Rather, a review of information available in the TGA-approved Product Information for LDX, long-acting MPH, IR DEX, and IR MPH was presented. The PBAC considered that, compared with the short-acting stimulants, LDX may have a lower potential for abuse or dependence, and was likely to be similar in relation to other potential harms.
- 6.9 Overall, the PBAC considered that the evidence base for the clinical claim was not robust, but recalled the additional benefits of long-acting stimulant therapies (over short-acting stimulants) that were accepted in 2006 for children and adolescents (see paragraphs 5.20 and 5.21). On balance, the PBAC considered that the evidence presented supports the proposed listing.
- 6.10 The PBAC noted that the proposed effective approved ex-manufacturer price (AEMP) of LDX per pack (i.e. 30 days' worth of treatment) for patients diagnosed after the age of 18 years was \$ [REDACTED], derived from the current ex-manufacturer cost per day of IR DEX of \$0.18 with a \$ [REDACTED] per day price premium. The PBAC considered that because evidence of superiority of LDX over IR DEX was limited, it did not support the requested price premium.
- 6.11 Under Section 101 (3B) of the *National Health Act 1953*, the PBAC noted that it could not recommend listing LDX at a higher price than the alternative therapy (IR DEX) as it was not satisfied that it provides, for some patients, a significant improvement in efficacy, or reduction of toxicity, over the alternative therapy.
- 6.12 The PBAC noted that the proposed weighted effective AEMP of LDX per pack was equal to \$ [REDACTED], inclusive of the price premium and based on a 28%:72% split for patients diagnosed after the age of 18 and patients diagnosed before the age of 18, respectively. The PBAC considered that the submission's proposed weighting was appropriate, and noted that the resulting price proposed was approximately a 12% reduction on the current effective AEMP of \$ [REDACTED]. The PBAC considered that, in order to ensure cost-effectiveness of LDX in the expanded population, an effective AEMP for the expanded population equivalent to the cost per day of IR DEX would be appropriate. The PBAC noted that this would equate to a revised weighted AEMP that is approximately 25% lower than the current effective AEMP.

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- 6.13 The PBAC considered that there was uncertainty with respect to uptake rate and the size of the expanded adult population, and therefore considered that this uncertainty could be managed by increasing the LDX RSA but only to capture the additional patient numbers at the level estimated in the submission, with a [REDACTED] % rebate above these caps.
- 6.14 The PBAC considered that the recommended changes to the restriction for LDX should flow-on to all other long-acting ADHD medicines on the PBS, including methylphenidate hydrochloride (Concerta and Ritalin LA) and atomoxetine (Strattera), at a similarly reduced price based on the accepted weighting of 28% diagnosed after the age of 18 years and 72% diagnosed before the age of 18.
- 6.15 The PBAC previously recommended that LDX is suitable for inclusion in the PBS medicines for prescribing by nurse practitioners as continuing therapy, noting that some state based laws may prevent this from occurring in practice.
- 6.16 The PBAC previously considered that it is not appropriate to apply the Early Supply Rule to LDX.
- 6.17 The PBAC previously considered, under Section 101(3BA) of the *National Health Act 1953*, that LDX should not be treated as interchangeable with any other drugs.
- 6.18 The PBAC advised that, because lisdexamfetamine is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over immediate release dexamfetamine, or address an urgent unmet clinical need given the presence of alternative therapies, the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009* for Pricing Pathway A were not met.
- 6.19 The PBAC advised that this submission would not meet the criteria for an Independent Review as it received a positive recommendation.

**Outcome:**

Recommended

## 7 Recommended listing

### 7.1 Amend existing listings to read as follows:

Name, Restriction, Manner of administration and form	PBS item code	Max. Qty packs	Max. Qty units	No. of Rpts	Proprietary Name and Manufacturer
LISDEXAMFETAMINE					
lisdexamfetamine dimesilate 20 mg capsule, 30	11884L	1	30	5	
lisdexamfetamine dimesilate 30 mg capsule, 30	10486X	1	30	5	
lisdexamfetamine dimesilate 40 mg capsule, 30	11898F	1	30	5	Vyvanse®
lisdexamfetamine dimesilate 50 mg capsule, 30	10474G	1	30	5	Shire Australia Pty Ltd
lisdexamfetamine dimesilate 60 mg capsule, 30	11897E	1	30	5	
lisdexamfetamine dimesilate 70 mg capsule, 30	10492F	1	30	5	

<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 - CTO <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Restriction Level / Method:</b> <input checked="" type="checkbox"/> Authority Required – Telephone/Electronic/Emergency
<b>Administrative Advice:</b> Continuing Therapy Only: 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.  Special Pricing Arrangements Apply.
<b>Indication:</b> Attention deficit hyperactivity disorder <b>Clinical criteria:</b> <ul style="list-style-type: none"> <li>▪ Patient must require continuous coverage over 12 hours.</li> </ul> <b>Population criteria:</b> <ul style="list-style-type: none"> <li>▪ Patient must be aged between the ages of 6 and 18 years inclusive; or</li> <li>▪ Patient must have had a diagnosis of ADHD prior to turning 18 years of age if PBS-subsidised treatment is continuing beyond 18 years of age; or</li> <li>▪ Patient must have a retrospective diagnosis of ADHD if PBS-subsidised treatment is commencing after turning 18 years of age; or</li> <li>▪ Patient must have had a retrospective diagnosis of ADHD if PBS-subsidised treatment is continuing in a patient who commenced PBS-subsidised treatment after turning 18 years of age</li> </ul>
<b>Prescriber Instructions:</b> A retrospective diagnosis of ADHD for the purposes of administering this restriction is: (i) the presence of pre-existing childhood (before the age of 12 years) symptoms of ADHD documented in the patient's medical records; and (ii) thorough conduct of an in-depth clinical interview and/or obtaining corroborating evidence from parents, teachers or siblings, which is documented in the patient's medical records
<b>Administrative Advice:</b> Care must be taken to comply with the provisions of State/Territory law when prescribing this drug. The treatment must not exceed a maximum daily dose of 70 mg.

### 7.2 Flow-on changes:

*Pending implementation of the above recommendation, amend the following population criterion where it appears in the restrictions for methylphenidate modified release tablets and atomoxetine capsules ADHD listings, to be consistent with lisdexamfetamine.*

**Population criteria:**

- Patient must be or have been diagnosed between the ages of 6 and 18 years inclusive.

***These restrictions may be subject to further review. Should there be any changes made to the restriction the Sponsor will be informed.***

## **8 Context for Decision**

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

## **9 Sponsor's Comment**

Shire Australia (now part of Takeda) welcomes the PBAC's decision to recommend lisdexamfetamine for the treatment of ADHD in patients diagnosed over the age of 18. Shire also wishes to thank those patients, clinicians, and organisations who took time to submit comments during the PBAC process.