Public Summary Document

Product: Lisdexamfetamine, capsules, 30 mg, 50 mg, and 70 mg, Vyvanse®
Sponsor: Shire Australia Pty Ltd
Date of PBAC Consideration: July 2013

1. Purpose of Application

The submission requested an Authority required listing for treatment of attention deficit hyperactivity disorder (ADHD) in a patient diagnosed between the ages of 6 and 18 years who requires continuous coverage over 13 hours.

This application was considered under the TGA/PBAC parallel process. TGA Clinical Evaluator comments and Delegate's Overview were provided during the evaluation.

2. Background

This drug had not been previously considered by the PBAC.

3. Registration Status

Lisdexamfetamine was TGA registered on 22 July 2013for the "treatment of Attention Deficit Hyperactivity Disorder (ADHD). Treatment should be commenced by a specialist. A diagnosis of ADHD implies the presence of hyperactive –impulsive or inattentive symptoms that caused impairment and were present before 12 years of age"

4. Listing Requested and PBAC's View

Authority required
Treatment of attention deficit hyperactivity disorder (ADHD) in a patient diagnosed between the ages of 6 and 18 years (inclusive), who requires continuous coverage over 13 hours.

Note:
In accordance with State/Territory law

The PBAC noted that the proposed listing was similar to other ADHD drugs with respect to restriction and patient ages.

5. Clinical Place for the Proposed Therapy

Lisdexamfetamine is a pro-drug of dexamphetamine. Lisdexamfetamine is hydrolysed to dexamphetamine and an inactive compound L-lysine in the blood after absorption. This activation step is rate limiting and is responsible for the prolonged systematic bioavailability and duration of action of lisdexamfetamine compared to dexamphetamine.

The submission proposed that lisdexamfetamine will provide an alternative single daily morning dose treatment option for patients with ADHD. The once a day dosing of lisdexamfetamine may assist with compliance with therapy for ADHD.

6. Comparator

The submission nominated methylphenidate osmotic controlled-release oral delivery system (methylphenidate OROS, Concerta®) as the main comparator and placebo as a secondary comparator.

The PBAC agreed that the selection of comparator in the submission was not completely consistent with the PBAC submission Guidelines. The PBAC considered that some use of lisdexamfetamine (LDX) would replace dexamphetamine but the majority of use would replace the long acting methylphenidate formulations, as represented by methylphenidate OROS (MPH-OROS). Therefore, dexamphetamine was also a suitable comparator for patients in the first-line or initiating treatment setting and methylphenidate OROS was a suitable comparator in the second-line or treatment experienced patients who require longer duration therapy.

7. Clinical Trials

The submission presented three trials:

- one three-arm trial (SPD489-325) comparing lisdexamfetamine to methylphenidate OROS and placebo (n=332);
- two forced-dose trials of lisdexamfetamine versus placebo (SPD489-301 and -305), n=604; and
- a network meta-analysis (Roskell et al 2012), including the trial for lisdexamfetamine that are in the submission (SPD489-325, -301, -305).

The PBAC noted that the submission's claim of superiority for comparative effectiveness and non-inferiority for comparative safety was based on Trial SPD489-325. The primary comparison of Trial SPD489-325 was between lisdexamfetamine and placebo, the comparisons versus methylphenidate OROS were conducted post-hoc. The PBAC further noted that the SPD489-325 trial was not powered to compare lisdexamfetamine and methylphenidate OROS, rather the comparison of each product versus placebo. Given the comparisons did not adjust for multiple comparisons and the inflation of type I errors, the possibility of detecting differences simply by chance could not be excluded.

The PBAC also noted that there was a risk of bias in Trial SPD489-325 due to the possibility of unblinding as investigators were aware of the results of drug screening tests for amphetamines in some patients.

The PBAC noted that the population enrolled in Trial SPD489-325 were representative of the likely PBS population but approximately 50% of the population had prior treatment with methylphenidate and prior success was not required in the methylphenidate OROS arm. The PBAC agreed that this would not be exactly the same as the current use of methylphenidate OROS in the PBS population.

The table below details the published trials presented in the submission.

Trial ID/ First author	Protocol title/ Publication title	Publication citation
Direct randomised trials		

LDX vs OROS-MPH (main comparison)		
SPD489-325	A Phase III, Randomised, Double-Blind, Multicentre, Parallel-Group, Placebo- and Active-Controlled, Dose-Optimisation Safety and Efficacy Study of Lisdexamfetamine Dimesylate (LDX) in Children and Adolescents Aged 6-17 With Attention-Deficit/Hyperactivity Disorder (ADHD)	19 August 2011
Coghill et al	European, randomized, phase 3 study of Lisdexamfetamine dimesylate in children and adolescents with attention-deficit/hyperactivity disorder.	European Neuropsychopharmacology, 2013; http://dx.doi.org/10.1016/j.euroneuro.2012.11.012 (in press) full publication.
Zuddas et al	Clinical efficacy of lisdexamfetamine dimesylate in children and adolescents with ADHD: A post-hoc analysis.	Neuropsychopharmacol 2012;22:S431 (conference abstract)
Soutullo et al	Effect of lisdexamfetamine dimesylate on functional impairment in children and adolescents with attention-deficit/hyperactivity disorder	Eur Psychiatry 2012;27. (conference abstract)
Setyawan et al	Health utility scores in children and adolescents with attention-deficit/hyperactivity disorder: Response to stimulant treatment.	Value Health 2012;15:A284. (conference abstract)
Hodgkins et al	Effect of lisdexamfetamine dimesylate on functional impairment in children and adolescents with attention-deficit/hyperactivity disorder.	Acta Neuropsychiatr 2012;24:27-28 (conference abstract)
Gasior et al	Efficacy and safety of lisdexamfetamine dimesylate in children and adolescents with ADHD: A phase 3, randomized, double-blind, multicenter, parallel-group, placebo-and active-controlled, dose-optimized study in Europe	Acta Neuropsychiatr 2012;24:24 (conference abstract).
LDX versus placebo (secondary comparison)		
SPD489-301	Phase 3 Randomized Double-Blind Placebo-Controlled Study of NRP104 in Children Aged 6-12 With ADHD	2 November 2005
Biederman et al	Efficacy and Tolerability of Lisdexamfetamine Dimesylate (NRP-104) in Children with Attention-Deficit/Hyperactivity Disorder: A Phase lll, Multicenter, Randomized, Double- Blind, Forced-Dose, Parallel-Group Study.	Clinical Therapeutics, Volume 29, Number 3, 2007
Childress et al	The effects of lisdexamfetamine dimesylate on emotional lability in children aged 6-12 years with attention-deficit/hyperactivity disorder in a double-blind, placebo-controlled trial.	European Child and Adolescent Psychiatry 2010a, Volume 19, S78
Findling et al	Clinical Response and Symptomatic Remission in Children Treated With Lisdexamfetamine Dimesylate for Attention-Deficit/Hyperactivity Disorder.	CNS Spectr 15:9, September 2010, p559-568.

Jain et al	Efficacy of lisdexamfetamine dimesylate in children with attention-deficit/hyperactivity disorder previously treated with methylphenidate: a post hoc analysis.	Child and Adolescent Psychiatry and Mental Health 2011, 5:35
Lopez et al	Effect of lisdexamfetamine dimesylate on parent-rated measures in children aged 6 to 12 years with attention-deficit/hyperactivity disorder: A secondary analysis.	Postgraduate Medicine, 2008, Volume 120, Issue 3, p89-102.
Waxmonsky et al	Prediction of placebo response in 2 clinical trials of lisdexamfetamine dimesylate for the treatment of ADHD	Journal of Clinical Psychiatry, 2011, Volume 72, Issue 10, p1366-1375.
SPD489-305	Efficacy and Safety of Lisdexamfetamine Dimesilate (LDX) in Adolescents With Attention-Deficit/Hyperactivity Disorder (ADHD)	17 August 2009
Childress et al	Double-blind, placebo-controlled efficacy and safety study of lisdexamfetamine dimesylate in adolescents with Attention Deficit Hyperactivity Disorder (ADHD).	Journal of Child and Adolescent Psychopharmacology, 2010b, Volume 20, Issue 6, p533. (conference abstract)
Findling et al	Efficacy and safety of lisdexamfetamine dimesylate in adolescents with attention-deficit/hyperactivity disorder.	Journal of the American Academy of Child and Adolescent Psychiatry, 2011a, Volume 50, Issue 5, p395-405
Findling et al	Long-term safety of lisdexamfetamine dimesylate (LDX) in adolescents with attention-deficit/hyperactivity disorder.	European Child and Adolescent Psychiatry, 2011b, Volume 20, S117-S118 (conference abstract)
Gasior et al	Double-blind, placebo-controlled efficacy and safety study of lisdexamfetamine dimesylate in adolescents with attention-deficit/ hyperactivity disorder.	Neuropsychopharmacology, 2010, Volume 35, S103-S104
IST-NRP104 Giblin et al	Effect of lisdexamfetamine dimesylate on sleep in children with ADHD.	Journal of Attention Disorders, 2011, Volume 15, Issue 6, p491-498.
NRP401-201 Biederman et al	Lisdexamfetamine Dimesylate and Mixed Amphetamine Salts Extended-Release in Children with ADHD: A Double-Blind, Placebo-Controlled, Crossover Analog Classroom Study	Biol Psychiatry. 2007 Nov 1;62(9):970-6. Epub 2007 Jul 12.
López et al	Physician perception of clinical improvement in children with attention-deficit/hyperactivity disorder: a post hoc comparison of lisdexamfetamine dimesylate and mixed amphetamine salts extended release in a crossover analog classroom study.	Neuropsychiatric Disease and Treatment 2011:7 267–273
SPD489-311 Wigal et al	A 13-hour laboratory school study of lisdexamfetamine dimesylate in school-aged children with attention-deficit/hyperactivity disorder.	Child Adolesc Psychiatry Ment Health. 2009 Jun 9;3(1):17.
Wigal et al	Efficacy and Tolerability of Lisdexamfetamine Dimesylate in Children With Attention-Deficit/Hyperactivity Disorder: Sex and Age Effects and Effect Size Across the Day.	Child and Adolescent Psychiatry and Mental Health, 14 December 2010; 4:32

8. Results of Trials

The PBAC noted the results from Trial SPD489-325 (refer Table below) and that the mean change in ADHD-Rating Scale-IV total score from baseline to endpoint was the primary outcome nominated in the submission. ADHD-RS-IV total score measures symptoms and quality of life measures. The Committee considered that all outcomes favoured lisdexamfetamine and many comparisons were statistically significantly different, including the primary outcome mean change in ADHD-RS-IV total score.

The results of patient-relevant outcomes across SPD489-325 trial –Continuous outcomes are shown in the following table:

Mean change from baseline to endpoint+	**Mean change (SD)**			**Mean difference across treatments (95%CI) p-value**			
	LDX N=104*	**PBO N=106***	**MPH-OROS N=107***	**LDX v PBO**	**MPH-OROS v PBO**	**LDX v MPH -OROS**	**Exceeds MCID[b] (Target)**
Efficacy outcomes (a negative change indicates improvement)							
ADHD-RS-IV Total score^	-24.7 (10.15)	-6.3 (10.02)	-18.9 (12.92)	**-18.6 (-21.5, -15.7)**	**-13.0 (-15.9, -10.2)**	**-5.8 (-9.0, -2.6)**	NO (6.6 or 7.6)
ADHD-RS-IV: H/I subscale	-11.2 (5.5)	-3.0 (5.7)	-8.7 (6.9)	**-8.7 (-10.3, -7.2)**	**-6.0 (-7.5, -4.5)**	**-2.50 (-4.22, -0.79)**	NR
ADHD-RS-IV: Inattention subscale	-13.5 (6.3)	-3.4 (5.3)	-10.3 (7.0)	**-9.9 (-11.5, -8.3)**	**-7.0 (-8.6, -5.4)**	**-3.20 (-5.0, -1.4)**	NR
CRPS-R:S	-24.9 (17.76)	-5.0 (13.33)	-19.1 (20.48)	**-21.3 (25.5, 17.0)**	**-15.1 (-19.3, -10.9)**	**-5.8 (-11.2, -0.4)**	NR
HRQoL outcomes							
CHIP-CE: PRF global score[a] (+ve better)	9.1 (8.91) n=75%	-0.9 (8.14) n=75.5%	5.9 (9.4) n=72.8%	**10.5 (7.9, 13.0)**	**7.5 (4.9, 10.0)**	**3.20 (0.33, 6.07)**	NO (4 - 5.7)
CHIP-CE: PRF global score[a] (+ve better)	8.4 (9.53)	0.2 (8.59)	7.1 (9.33)	**8.8 (6.1, 11.5)**	**7.3 (4.6, 10.0)**	1.30 (-1.69, 4.29)	NR
WFIRS-P: Global Score (-ve better)	-0.30 (0.54) n=76%	-0.04 (0.32) n=82.1%	-0.27 (0.33) n=77.6%	**-0.3 (-0.4, -0.2)**	**-0.2 (-0.3, -0.1)**	-0.03 (-0.17, 0.11)	NO (11 - 15)

Note: Bold typography indicate statistically significant results

Abbreviations: MCID=minimally clinically important difference; ADHD-RS-IV= Attention-Deficit/Hyperactivity Disorder Rating Scale – IV; H/I subscale=hyperactivity/impulsivity subscale; CRPS-R= Conners' Parent Rating Scale – Revised; HRQoL=health related quality of life; CHIP-CE: PRF= Child Health and Illness Profile, Child Edition: Parent Report Form; WFIRS-P: Global Score= Weiss Functional Impairment Rating Scale – Parent, NR=not reported, i.e., MCID was not defined by submission.

^ primary outcome

* the numbers of patients that had completed the rating scales to enable a estimation of mean change from endpoint to baseline was consistently >90% in all outcomes except where annotated.

\+ Definitions of the rating scales used are summarised in Attachment 3 of the Commentary.

[a] a positive change indicates improvement.

[b] Need to exceed the MCID target to claim superiority, if the mean difference is within the MCID specified, then can only claim non-inferiority

The PBAC noted that the Pre-Sub-Committee Response cited Zhang (2005) where it suggested that a "between-treatment" MCID of 5.2 is applicable in paediatric subjects with a baseline ADHD-RS-IV score >=45 (mean change was -5.3 [95% CI: -1.2, -11.8]) and that 32% of patients in Trial SPD489-325 study were in this group. The Committee noted that the results indeed reached the MCID, but also noted that lisdexamfetamine was superior in only 32% of the population (i.e. more severe group) while the data for the remaining 68% of patients support non-inferiority.

The PBAC noted that Clinical Global Impression – Improvement (CGI-I) score was also used in the submission to identify a responder (and non-responder), defined in several categories. The Committee noted that treatment with lisdexamfetamine resulted in approximately 18% additional responders compared to methylphenidate OROS under each definition. Response defined as CGI-I 1 or 2; and ADHD reduction >50% was used in the base case modelled economic evaluation presented in the submission.

Overall, the PBAC did not accept the submission's claim of superiority for comparative effectiveness as the data presented did not support superiority of lisdexamfetamine over methylphenidate OROS.

With regard to comparative harms, the PBAC noted that in general, patients treated with lisdexamfetamine reported a significantly higher incidence of anorexia, decreased appetite, weight loss and insomnia versus placebo. By comparison, patients treated with methylphenidate OROS experienced fewer serious and severe adverse events versus placebo. When lisdexamfetamine was compared to methylphenidate OROS, the only significant difference was the effect of the treatments on weight loss. More patients treated with lisdexamfetamine experience weight loss compared to those randomised to methylphenidate OROS (RD (95% CI): 0.09 (0.02, 0.2)).

The PBAC further noted that more patients randomised to lisdexamfetamine experienced a clinically important weight loss (i.e., greater than or equal to 7% decrease in body weight from baseline to trial end) compared to those randomised to methylphenidate OROS treatment (RD (95% CI): 0.22 (0.11, 0.32) but it was unclear how the patient numbers were tallied in the submission. The Committee agreed that the 7% or greater decrease in body weight was a clinically important difference between lisdexamfetamine and methylphenidate OROS and would be of importance to children and their carers.

The submission provided additional data on potential safety concerns beyond those identified in the short term clinical trials (up to 7 weeks of follow up). The PBAC noted that no long-term data directly comparing lisdexamfetamine and methylphenidate OROS was presented. Overall safety outcomes from the longer-term studies were generally consistent with the adverse events reported in Trial SPD489-325 and the known effects of amphetamine treatment.

The PBAC noted that the proportion of patients who reported weight loss was higher in the extension studies than in the lisdexamfetamine arm of Trial SPD489-325 (13.5%). The Committee noted that Farone et al (2010) (identified during the evaluation) reported the result of NRP104-302 and noted that lisdexamfetamine was significantly associated with diminished gains in height, weight, and BMI compared to levels that would be expected based on age-appropriate standards from the Centers for Disease Control (in the USA). The

delays were largest for weight and BMI, and there was a 13 percentile point decrease in height, even though at study entry, children were taller and heavier than average.

9. Clinical Claim

The submission described lisdexamfetamine as superior in terms of comparative effectiveness and non-inferior in terms of comparative safety over methylphenidate OROS.

The PBAC did not accept the submission's claim of superior comparative effectiveness. The PBAC noted that the mean difference between lisdexamfetamine and methylphenidate OROS was -5.8 (95% CI: -9.0, -2.6), favouring lisdexamfetamine but that it did not reach the nominated MCID, which was between 6.6 and 7.6. A difference up to -7.6 and +7.6 points on this scale was indicative of non-inferiority. The PBAC noted that only the lower bound of the confidence interval (-9.0) exceeded the MCID and therefore considered that the results only supported a claim of non-inferiority.

The PBAC did not accept the submission's claim of non-inferior comparative safety as the safety outcomes of Trial SPD489-325 indicated that lisdexamfetamine treatment is associated with significantly higher incidence of anorexia and weight loss compared with methylphenidate OROS. This difference was likely to be clinically important in the requested patient population and the PBAC considered this as a significant problem, especially in young children.

The PBAC agreed that a more appropriate conclusion would be non-inferiority of lisdexamfetamine to methylphenidate OROS in terms effectiveness but inferior to methylphenidate OROS in terms of safety.

10. Economic Analysis

The PBAC noted that the submission presented a modelled economic evaluation (cost utility analysis) based on superiority claim for comparative benefit. The submission presented an ICER of $15,000 –$ 45,000/QALY based on taking the post-hoc, reanalysed response outcome from Trial SPD489-325, applied to the child and adolescent population (similar to Trial SPD489-325) and extrapolated to 5 years (from 7 weeks in the trial) and applying utility weights from Trial SPD489-325.

The PBAC considered concerns regarding the uncertainty in the long term maintenance of response to treatment beyond the 7 weeks in the trial. The Committee agreed that the economic claim is not justified based on the clinical evidence.

The PBAC noted that there were issues with transforming utilities collected in the trial to 'responder' and 'non-responder' health states. The trial showed little difference in changes from baseline in HUI-2 derived utilities between lisdexamfetamine (0.067) and methylphenidate OROS (0.065) but when the submission translated the trial results, the difference in HUI-2 utility weights in responders and non-responders was much larger between lisdexamfetamine (0.12) and methylphenidate OROS (0.076). The Committee noted that the ICER was very sensitive to the method chosen.

The PBAC noted that the model was most sensitive to the probabilities of achieving response and the assumed health state utilities. Disutilities associated with treatment emergent side effects of lisdexamfetamine were not incorporated into the model, which resulted in a biased ICER in favour of lisdexamfetamine. The Committee noted that the model was in general not very sensitive to cost assumptions.

The PBAC considered the results of the sensitivity analyses for lisdexamfetamine versus methylphenidate OROS and agreed with the ESC that the model was most sensitive to:

i. the probability of achieving response with lisdexamfetamine relative to methylphenidate OROS, when the lower 95% CI of the difference over methylphenidate OROS is applied, the ICER nearly tripled; and
ii. assumed utilities for the health states:
   - the model did not incorporate any disutilities associated with treatment emergent side effects, which occurred more frequently amongst patients treated with lisdexamfetamine. The potential disutility due to these events may have been captured in the lower utilities reported amongst lisdexamfetamine compared with methylphenidate OROS non-responders in Trial SPD489-325. The PBAC noted that when treatment dependent health state utilities were used to attempt to capture these potential differences, the ICER increased to $45,000 - $75,000.
   - the model was also very sensitive to the difference in utility between the health states of response and non-response, when the utility improvement between responders and non-responders was reduced to 0.04 (similar to what was recorded for placebo in Trial SPD489-325) the ICER increased to $45,000 - $75,000.

Overall, the PBAC agreed that there significant variability in the cost-effectiveness of lisdexamfetamine in the model as presented.

11. Estimated PBS Usage and Financial Implications

The submission's estimated net cost per year to the PBS was less than $10 million in Year 5. The PBAC considered the estimated net cost to the PBS was likely underestimated given that the assumed uptake rates (7%-18%) were low.

12. Recommendation and Reasons

The PBAC acknowledged the consumer comments received in relation to the submission from individuals, individual health care professionals and organisations.

The PBAC acknowledged that a modest clinical need exists for alternative treatments for ADHD in children and adolescents.

The PBAC considered that the clinical evidence provided in the submission supported the claim of statistical superiority of lisdexamfetamine but was insufficient to support claims of clinical superiority. In terms of claims for non-inferiority on comparative safety, PBAC agreed that lisdexamfetamine was inferior in terms of safety as the safety outcomes of Trial SPD489-325 indicated that lisdexamfetamine is associated with significantly higher

incidence of weight loss compared with methylphenidate OROS. The PBAC considered this as a significant problem especially in young children.

The PBAC therefore rejected the submission for lisdexamfetamine on the basis of insufficient clinical evidence to support claims of superiority in comparative effectiveness, non-inferiority in comparative safety and unacceptable cost-effectiveness compared with methylphenidate OROS.

The PBAC did not accept the cost utility analysis (CUA) presented in the submission because there was no clear additional benefit from lisdexamfetamine compared with methylphenidate OROS. The PBAC noted that in the pre PBAC response, the sponsor accepted that an MCID was only seen in patients with ADHD-RS-IV score of $\geq$45 therefore, the sponsor proposed a new price for lisdexamfetamine, acknowledging that a cost-minimisation analysis (CMA) is appropriate for a proportion of patients against methylphenidate OROS and the proposed price for the remaining proportion. However, the PBAC noted that this was only applied to 50% of the total population with the other 50% assumed to fail methylphenidate OROS and requested a higher price (compared to placebo).

The PBAC considered that given the clinical evidence presented and the issues raised regarding the appropriate economic evaluation and choice of comparators, a possible alternative approach could be a CMA of lisdexamfetamine against a weighted price of methylphenidate OROS and a cost-effective analysis against methylphenidate OROS. The PBAC further advised that to maintain a higher price, the sponsor would need to reconstruct the comparator and identify a patient population where superiority can be justified. The sponsor would also need to identify a patient population where height/weight is not an issue.

Outcome:
Rejected

13. 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 medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment

Shire agrees with the PBAC that a clinical need exists for alternative treatments for ADHD in children and adolescents. Shire will continue to work with the PBAC so that patients with ADHD may access lisdexamfetamine on the PBS.