7.3 LISDEXAMFETAMINE DIMESILATE, capsules, 30 mg, 50 mg & 70 mg, Vyvanse®, Shire Australia Pty Ltd

1 Purpose of Application

1.1 The resubmission requested an Authority Required listing for lisdexamfetamine (LDX) on the PBS for treatment of Attention Deficit Hyperactivity Disorder (ADHD). The first submission was in July 2013.

2 Requested listing

2.1 The resubmission requested the following restriction:

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
LISDEXAMFETAMINE				
30mg Capsules	30	5	Vyvanse®	Shire Australia
50mg Capsules	30	5		
70mg Capsules	30	5		

Authority required	
Option 1 Treatment of attention deficit hyperactivity disorder (ADHD) in a patient diagnosed between the ages of 6 and 18 years (inclusive), [who has demonstrated a response to immediate release dexamphetamine sulphate with no emergence of serious adverse events^] and who requires continuous coverage over 12 hours.	**Option 2** Treatment of attention deficit hyperactivity disorder (ADHD) in a patient diagnosed between the ages of 6 and 18 years (inclusive), [who has demonstrated a response to immediate release dexamphetamine sulphate with no emergence of serious adverse events^] and who requires continuous coverage over 12 hours AND whose response to previous methylphenidate treatment is considered clinically inadequate.

NOTE:

- Patients requiring long term therapy should be carefully monitored. Patients who are not growing or gaining weight as expected should have their treatment interrupted.
- Care must be taken to comply with the provisions of State/Territory law when prescribing lisdexamfetamine.
- 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.

[redacted] calculated as a weighted average price of first line use in children, first line use in adolescents and second line use in children and adolescents.

2.2 The resubmission presents the following economic evaluations:

- Cost minimisation analysis versus long-acting methylphenidate (MPH-OROS) in children aged 6 to 12;
- Cost-utility analysis versus MPH-OROS in adolescents aged 13 to 17; and
- Cost-utility analysis versus "no pharmacological treatment" or "placebo" as proxy for standard of care in patients who have failed MPH-OROS.

3 Background

3.1 LDX was TGA registered on 22nd July, 2013 for the treatment of Attention Deficit Hyperactivity Disorder (ADHD).

3.2 This is the second submission for LDX for the management of ADHD.

3.3 The previous submission was rejected 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 MPH-OROS.

4 Clinical place for the proposed therapy

4.1 LDX is an alternative once daily morning therapy for patients with ADHD.

5 Comparator

5.1 The nominated comparators for LDX are MPH-OROS for first line use and placebo for patients who have not demonstrated an adequate response to MPH-OROS but need longer acting treatment. The ESC did not consider placebo an appropriate comparator on the basis that it would be highly unlikely for clinicians to leave patients completely untreated in the event that they don't respond to MPH-OROS. The ESC considered the appropriate comparators for LDX to be DEX (where MPH-OROS could be used as the price reference to account for increased compliance and extended duration of effect compared with DEX) and MPH-OROS.

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (7), health care professionals (22) and organisations (2) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with lisdexamfetamine, including a significant improvement in children's overall behaviour, an increased ability to complete work, a more convenient and manageable treatment regimen with fewer and more manageable side effects. The PBAC also noted public concern that currently using the medication imposes a significant financial strain on families accessing it through the private market, and that the age of diagnosis potentially discriminates against those who fail to get appropriately diagnosed in the required timeframe. This medication was also noted as not easily able to be diverted to others and therefore is less attractive to recreational drug users.

For more detail on PBAC's view, see section 7 "PBAC outcome"

Clinical trials

6.3 The trials included in the submission are listed below:

Trial	Protocol title/ Publication title	Publication citation
Direct randomised trials **LDX vs MPH-OROS (main comparison)**		
SPD489-325	A Phase III, Randomised, Double-Blind, Multicentre, Parallel-Group, Placebo- and Active-Controlled, Dose-Optimisation Safety and	19 August 2011

	Efficacy Study of Lisdexamfetamine Dimesylate (LDX) in Children and Adolescents Aged 6-17 With Attention-Deficit/Hyperactivity Disorder (ADHD)	
Coghill et al	European, randomized, phase 3 study of Lisdexamfetamine dimesylate in children and adolescents with attention-deficit/hyperactivity disorder.	European Neuropsychopharmacology, 2013; 23(10):1208-18. [redacted]
Coghill et al	Post hoc comparison of the efficacy of lisdexamfetamine dimesylate and osmotic release oral system methlyphenidate in children and adolescents with ADHD.	Eur Psychiatry 2013c;28.
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).
Lecendreux et al	Efficacy of lisdexamfetamine dimesylate in children and adolescents with attention-deficit/hyperactivity disorder: Effect of age, sex and baseline disease severity.	Eur Psychiatry 2013a;28.
Soutullo et al	A post hoc comparison of the effects of lisdexamfetamine dimesylate and osmotic release oral system-methylphenidate on symptoms of attention-deficit hyperactivity disorder in children and adolescents.	CNS Drugs 2013;27(9):743-51.
Banaschewski et al	Health-related quality of life and functional outcomes from a randomized, controlled study of lisdexamfetamine dimesylate in children and adolescents with attention deficit hyperactivity disorder.	CNS Drugs 2013;27(10):829-40.
Banaschewski et al	The child health and illness profile as a measure of health-related quality of life in stimulant-treated children and adolescents with ADHD.	Eur Child Adolesc Psychiatry 2013;22(2):S125-S126.
Coghill et al	Impact of previous ADHD medication on the efficacy of lisdexamfetamine dimesylate in the treatment of ADHD: Post hoc analyses.	Eur Neuropsychopharmacol 2013b;23:S599-S600
Coghill et al	The first European studies of lisdexamfetamine dimesylate in children and adolescents with attention-deficit/hyperactivity disorder.	Eur Child Adolesc Psychiatry 2013d;22(2):S125.
Hodgkins et al	Health utility scores in children and adolescents with attention-deficit/hyperactivity disorder: Response to stimulant treatment.	Eur Child Adolesc Psychiatry 2013;22(2):S127.
Lecendreux et al.	Weight related safety outcomes of lisdexamfetamine dimesylate in children and adolescents with attention-deficit/hyperactivity disorder.	Eur Child Adolesc Psychiatry 2013;22(2):S223b.
LDX versus placebo		
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 III, 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

Source: Table 22, pp90-91 of the main body and Table 3, of Appendix A.2 of the resubmission.

6.4 A summary of the key features of the trials presented in the submission are presented in the table below.

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
LDX versus MPH-OROS and LDX versus placebo						
SPD489-325	332 (3 arms LDX, PBO and MPH-OROS^)	R, DB, MC, PC 7 weeks screening and washout 7 weeks treatment period	High (potential treatment unblind)	Children and adolescents (6-17yrs) with ADHD* Excluded: Patients well controlled on current ADHD medications and patients who do not fully respond to MPH-OROS. ≈50% of subjects were MPH naïve.	Change from baseline: in ADHD symptoms measured by (ADHD-RS-IV total score+, hyperactivity/impulsivity and inattentiveness subscales, CGI– S; CGI-I, CPRS-R) Qol/health utility (CHIP:CE PRFI; WFIRS-P; HUI-2 parent or carer as proxy)	Yes
LDX versus placebo						
SPD489-	290	R, DB, MC,	Low	Children (6-12 years)	Rating scales measuring	NO

301	(4 arms: PBO, LDX30, 50 & 70mg fixed dose arms)	PC 4 weeks treatment period		with ADHD* (combined subtype or the predominantly hyperactive-impulsive subtype)	improvements in ADHD symptoms (ADHD-RS-IV total score+, hyperactivity/impulsivity subscale and inattentiveness subscales), CGI– S; CGI-I, CPRS-R)	
SPD489-305	314 (4 arms: PBO, LDX30, 50,&70mg fixed dose arms)	R, DB, MC, PC 4 weeks treatment period	Low	Adolescents (13-17 years) with ADHD*		NO

DB=double blind; MC=multi-centre; OL=open label; R=randomised. PC, placebo controlled; PG, parallel group; WFIRS-P, Weiss Functional Impairment Rating Scale – Parent – Severity of Illness; CHIP-CE: PRF, Child Health and Illness Profile, Child Edition: Parent Report Form; CPRS-R, Connors' Parent Rating Scale – Revised; d, daily; DB, double-blind; DD, double dummy; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; HUI-2, Health Utilities Index – Mark 2; LDX, lisdexamfetamine; PBO, placebo;
^the comparison of LDX versus MPH-OROS was a post hoc analysis. The primary comparison is LDX versus placebo.
*ADHD diagnosis as per DSM-IV, with baseline ADHD-RS-IV total score ≥28
+primary outcome of the trial
Source: Table 1 7.3.COM.3

Sub-group analysis in clinical trials

6.5 To support Option 1 listing: the efficacy and safety outcomes from SPD489-325 comparing LDX and MPH-OROS are presented as subgroups by age: adolescents (13-17 years) and children (6-12 years).

6.6 To support Option 2 listing: the results of trials SPD489-325, -301 and -305 comparing LDX and placebo are summarised in Appendix A.2 of the resubmission, although only the results of the full analysis set (FAS) from Trial SPD489-325 are used in the model.

6.7 Trial SPD489-325 enrolled both children and adolescents, and provided a head-to-head comparison of LDX and MPH-OROS (albeit post hoc). The ESC considered that the resubmission's approach to performing sub-group analyses was inappropriate as it lacked scientific rigour, was confounded due to unblinding of the trial, and was not supported by consistent results from other trials.

6.8 ESC did not believe that a post-hoc sub group analysis was PBAC's intended guidance when it stated in the July 2013 Minutes: "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." (para 7.6, July 2013 PBAC Minutes). The ESC also noted that differences in LDX efficacy were observed when stratifications other than age were applied in post-hoc sub group analyses (e.g. differing severities of disease), casting further doubt on the legitimacy of applying post hoc sub-stratifications.

Comparative effectiveness

6.9 A summary of the relevant trial results used to demonstrate comparative effectiveness shown below:

Results of patient-relevant outcomes across SPD489-325 trial –Continuous outcomes

Mean change	**Mean change (SD)**			**Mean difference across treatments (95%CI)**			
from baseline to	**LDX**	**PBO**	**MPH-**	**LDX v**	**MPH-**	**LDX v**	*Exceeds*

endpoint +			OROS	PBO	OROS v PBO	MPH-OROS	*MCID[b](LDX vs MPH-OROS)?*
EFFICACY OUTCOMES (A NEGATIVE CHANGE INDICATES IMPROVEMENT)							
Attention Deficit Hyperactivity Disorder rating scale IV (ADHD-RS-IV) Total score (primary outcome)							
FAS(6-17 years)	n=104 -24.7 (10.15)	n=106 -6.3 (10.02)	n=107 -18.9 (12.92)	**-18.6 (-21.5, -15.7)**	**-13.0 (-15.9, -10.2)**	**-5.8(-9.0, -2.6) P<0.001**	*NO (6.6 or 7.6)*
13-17 years	[redacted]						*YES (6.6 or 7.6)*
6-12 years	[redacted]						*NO (6.6 or 7.6)*

Note: Bold typography indicate statistically significant results, italics indicate results extracted and/or estimated during the evaluation, mean differences were estimated in RevMan 5.2.
+Definitions of the rating scales used are summarised in Attachment B.5 of the Commentary.
[b] Need to exceed the minimal clinically important difference (MCID) target to claim superiority, if the mean difference is within the MCID specified, then can only claim non-inferiority. See Table B.5.1 of Attachment B of the commentary.
Source: Table B.6.1 of the July 2013 Commentary; Tables 25, 27, 30, 31, 32 of the main body and Attachment 4 of the resubmission.

Results of patient-relevant outcomes across the SPD489-325 trial–dichotomous outcomes

	LDX N=104 n /N^ (%)]	PBO N=106 n /N^ (%)	MPH-OROS N=107 n /N^ (%)	RD (95%CI)		LDX versus MPH-OROS		
				LDX vs PBO	MPH-OROS vs PBO	RD (95%CI) p-value NNT[95%C])	OR (95%CI) p-value	RR (95%CI) p-value
Proportions of patients defined as responders [a]								
FAS (6-17 years)	72/97 (74.2%)	11/103 (10.7%)	57/102 (55.9%)	**0.64 (0.53, 0.74)**	**0.54 (0.34, 0.57)**	**0.18 (0.05, 0.31) P=0.006 NNT: 6[3-20]**	**2.27 (1.25, 4.14) P=0.0007**	**1.33 (1.08, 1.64) P=0.008**
13-17 years	[redacted]							
6-12 years	[redacted]							

Note: Bold typography indicates statistically significant results; italics indicate results estimated during the evaluation using RevMan Version 5.2. ^number of patients for whom results are available.
[a]response is defined as proportion of subjects achieving at least 30% change from baseline ADHD-RS-IV AND a CGI-I score of 1 or 2 at endpoint. Source: Table B.6.2 of the July 2013 Commentary, Tables 28 and 29 of the main body and Attachment 4 of the resubmission.

Summary of results of commonly reported outcomes for Trials SPD489-301 (children), -305 (adolescents) and -325 (children and adolescents)

Trials	Outcomes	LDX versus placebo			LDX v. MPH-OROS (Tables B.6.1, B.6.2)	Exceeds MCID* versus placebo? (Target)
		LDX 30mg v PBO	LDX 50mg v PBO	LDX 70mg v PBO		
ADHD-RS-IV total score mean change (SD) from baseline to endpoint						
325 (6-17yrs)	Mean Diff#	**-18.6 (-21.5, -15.7)**			**-5.8 (-9.0, -2.6)**	Yes (10-15)
325 (6-12 yrs)	Mean Diff#		[redacted]		[redacted]	Yes (10-15)
301 (6-12 yrs)	Mean Diff#	**-15.6(-19.4, -11.7)**	**-17.2(-21.3, -13.1)**	**-20.5(-24.5, -16.5)**	-	Yes (10-15)
325 (13-17 yrs)	Mean Diff#		[redacted]		[redacted]	Yes (10-15)
305 (13-17yrs)	Mean Diff#	**-5.60(-9.41, -1.79)**	**-7.9(-11.3, -4.6)**	**-7.4(-10.8, -4.0))**	-	**No (10-15)**
CGI-I improvement^						
325 (6-17 yrs)	RD	**0.64 (0.53, 0.74)**			**0.17 (0.05, 0.3)**	NR
	RR	**5.41 (3.34, 8.73)**			**1.29 (1.07, 1.55)**	
325 (6-12 yrs)	RD		[redacted]		[redacted]	
	RR		[redacted]		[redacted]	
301 (6-12 yrs)	RD:	**0.52 (0.37, 0.66)**	**0.52 (0.39, 0.66)**	**0.59 (0.46, 0.72)**	-	
	RR:	**3.85 (2.30, 6.46)**	**3.90 (2.33, 6.53)**	**4.25 (2.56, 7.06)**	-	
325 (13-17 yrs)	RD		[redacted]		[redacted]	
	RR		[redacted]		[redacted]	
305 (13-17yrs)	RD	**0.18 (0.03, 0.34)**	**0.34 (0.19, 0.49)**	**0.37 (0.22, 0.51)**	-	
	RR	**1.47 (1.05, 2.06)**	**1.86 (1.4, 2.54)**	**1.93 (1.42, 2.61)**	-	

Note: Italics indicate results estimated during the evaluation, bold typography indicates statistically significant differences.
Abbreviations: MPH-OROS; extended release methylphenidate (Concerta®), PBO; placebo; RD=risk difference, RR=relative risk, ADHD-RS=ADHD rating scale, CGI-I=investigator rated clinical global impression-improvement. NR=not stated, i.e. MCID was not defined by submission.

mean difference in changes from baseline to endpoint

^ Improvement includes CGI-I categories 'very much improved' and much improved (no improvement includes all other categories)

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

Source: Table B.6.4 of the July 2013 Commentary, Results form Table B.6.1 above for SPD489-325.

6.10 While increased efficacy of LDX versus MPH-OROS was observed amongst adolescents compared with children in the sub-group analyses conducted for Trial SPD489-325, this was not supported by the results of SPD489-301 and -305. In fact, the results of the SPD489-301 and -305 suggest the opposite, that LDX may be more efficacious in children than adolescents. While the Pre-Sub-Committee Response (PSCR, p2) argued that this finding is an artefact of forced dosing, where the adolescents were under-dosed, the ESC felt that a higher dose in adolescents may not have increased efficacy, and that this is not a reasonable explanation as to why LDX was less efficacious in adolescents in SPD489-301 and -305. Furthermore, no dose response effect was observed from 50 mg to 70 mg lisdexamfetamine compared to placebo amongst adolescents.

For more detail on PBAC's view, see section 7 "PBAC outcome"

Comparative harms

6.11 The pattern of adverse effects (AEs) in the subgroups is similar to what was observed for the overall population. No formal statistical comparisons were conducted for the subgroups; however, given the smaller sample sizes of the subgroups, statistical tests are unlikely to have sufficient power to detect any meaningful differences in AEs.

6.12 Given Trial SPD489-325 enrolled both children and adolescents and provided a head-to-head comparison of LDX and MPH-OROS (albeit post hoc), the

resubmission's approach to performing sub-group analyses is considered inappropriate and unnecessary..

6.13 A summary of comparative benefits and harms for LDX versus MPH-OROS in the FAS of Trial SPD489-325 are shown below:

Trial	LDX	MPH-OROS	RR (95% CI)	Event rate/100 patients*		RD (95% CI)
				LDX	MPH-OROS	
Benefits						
Proportions of patients defined as responders [a]						
325	72/97	57/102	1.33 (1.08, 1.64)	74.2	55.9	0.18 (0.05, 0.31)
ADHD-RS-IV Total score (primary outcome) mean change from baseline to endpoint						
	LDX			**MPH-OROS**		**Mean difference*: LDX vs MPH-OROS (95% CI) MCID (6.6 or 7.6)**
	n	**Mean Δ**	**SD**	**n**	**Mean Δ**	**SD**	
325	104	-24.7	10.15	107	-18.9	12.92	-5.8 (-9.0, -2.6) Difference not clinically meaningful based on MCID
Harms						
	LDX	**MPH-OROS**	**RR^ (95% CI)**	**Event rate/100 patients***		**RD (95% CI)**
				LDX	**MPH-OROS**	
Patients with weight decrease						
325	15/111	5/111	3.00 (1.13, 7.97)	13.5	4.5	0.09 (0.02, 0.2)
Patients with weight decrease ≥7%						
325	35/107	12/108	2.94 (1.62, 5.36)	32.7	11.1	0.22 (0.11, 0.32)

Abbreviations: PBO = placebo; MPH-OROS=methylphenidate OROS, LDX=lisdexamfetamine; RD = risk difference; RR = risk ratio; SD=standard deviation; MCID=minimally clinically meaning difference; ADHD-RS-IV =Attention Deficit Hyperactivity Disorder rating scale IV; * Median duration of follow-up: 7 weeks; ^ estimated during the evaluation using RevMan 5.2; [a] response is defined as proportion of subjects achieving at least 30% change from baseline ADHD-RS-IV AND a CGI-I score of 1 or 2 at endpoint.

Source: Compiled during the evaluation from Tables B.6.1, B.6.2 of this commentary and Table B.6.5 of the July 2013 commentary.

6.14 On the basis of direct comparative evidence presented by the submission, for every 100 patients treated for a median of 7 weeks with LDX in comparison to MPH-OROS:

- Approximately 18 additional patients would meet the definition of a responder (defined as the proportion of subjects achieving at least 30% change from baseline ADHD-RS-IV AND a CGI-I score of 1 or 2 at endpoint). The clinical meaning of being a responder under this definition is unclear.
- There would be an average reduction of 5.8 points in the ADHD-RS-IV Total score; it is considered that a reduction of 6.6 or 7.6 is clinically significant.
- Approximately 22 additional patients would experience clinically significant weight loss of 7% or more.

Clinical claim

6.15 A Summary of clinical claims for LDX by treatment setting are shown below:

Treatment setting	Comparisons	Patient population	Clinical claim	Evidence base	Economic evaluation proposed
"First-line"	LDX vs MPH-OROS	Adolescents (13-17 years)	Superior efficacy; Non-inferior safety (caveat for BMI effects)	SPD489-325	Cost effectiveness analysis
		Children (6-12 years)	Non-inferior efficacy; Non-inferior safety		Cost minimisation analysis

"Second-line"	LDX vs PBO (as proxy for no treatment)	Patients with inadequate clinical response to MPH	Superior efficacy; Inferior safety	SPD489-325 Supported by SPD489-301; SPD489-305	Cost effectiveness analysis

Source: Table 41, p127 of the resubmission.

6.16 The results of the FAS were considered to be the most relevant, given Trial SPD489-325 enrolled both children and adolescents and provided a head-to-head comparison of LDX and MPH-OROS (albeit post hoc). As per the PBAC's determination in July 2013 and based on the results of the SPD489-325 trial, the data supports a claim that LDX is non-inferior in terms of effectiveness and inferior in terms of safety (given the increased weight loss observed) to MPH-OROS.

6.17 The ESC provided the following summary of the clinical claim and relevant supportive evidence:

Summary of clinical claims for LDX by treatment setting – ESC comment

Treatment setting	Comparisons	Patient population	Clinical claim	Why not supported	What data supports
"First-line"	LDX vs MPH-OROS	Adolescents (13-17 years)	Superior efficacy; Non-inferior safety (caveat for BMI effects)	Subgroup analysis not appropriate and direction of effect with age differs between trials.	Non-inferior efficacy and inferior safety for 6-17 year olds
		Children (6-12 years)	Non-inferior efficacy; Non-inferior safety		
"Second-line"	LDX vs PBO (as proxy for no treatment)	Patients with inadequate clinical response to MPH-OROS	Superior efficacy; Inferior safety	Inappropriate comparator.	Comparison with MPH-OROS or DEX

For more detail on PBAC's view, see section 7 "PBAC outcome"

Economic analysis

6.18 The resubmission presents the following economic evaluations:

- Cost minimisation analysis versus MPH-OROS in children aged 6 to 12;
- Cost-utility analysis versus MPH-OROS in adolescents aged 13 to 17; and
- Cost-utility analysis versus "no pharmacological treatment" or "placebo" as proxy for standard of care in patients who have failed MPH-OROS.

6.19 The model presented in this resubmission is identical to that presented in July 2013, but with additional pre-modelling studies to update the model inputs. The ESC noted that disutilities associated with weight loss over time had still not been adequately accounted for, despite the inclusion of drug holidays as a proxy, and that this was a concerning limitation in the model. With regards to supporting evidence for the extrapolated efficacy of LDX, the ESC noted that the prevalence of ADHD decreases over time, though psychopathology continues to exist. It was also considered that currently there is no clear evidence for the efficacy of psychostimulant treatment beyond 3 years (Tonge Aust Presc 2013), compared with behavioural management and a combination of treatment and behavioural management.

6.20 The only appropriate economic evaluation is a cost minimisation analysis of LDX versus MPH-OROS. A cost minimisation analyses is presented in Section D(i).2 of the resubmission for children aged 6 – 12; this analysis is relevant for all the populations requested in the listing. The cost minimisation price of LDX is estimated to be [redacted] as a best case (given no cost for AEs have been

incorporated). As a contrast, using the resubmission's approach the ICER for LDX versus MPH-OROS in adolescents was in the range of $15,000/QALY - $45,000/QALY [redacted] irrespective of daily dose (due to flat pricing); when the drug holiday variable was included, the ICER increased to $15,000/QALY - $45,000/QALY [redacted]. The ICER of LDX versus placebo was $15,000/QALY - $45,000/QALY [redacted] in patients who failed MPH [redacted]; when the drug holiday variable was included, the ICER changed to $15,000/QALY - $45,000/QALY [redacted]. The ESC noted that a series of sensitivity analyses demonstrated that the model was mostly sensitive to utilities used and the definition of benefit.

6.21 The price of LDX requested in the submission exceeds that of MPH-OROS, despite the lack of clinical benefit demonstrated in the trials. If the proportion of patients accessing LDX on the PBS differs from what the resubmission assumes, it is likely that LDX will be dominated by MPH-OROS as an alternative medication with a higher cost yet similar or inferior clinical benefit.

6.22 The drug cost/patient/year is [redacted], listing option 1) or [redacted] listing option 2), both assuming [redacted] compliance and [redacted] scripts per patient year of treatment.

6.23 The PBAC did not accept the cost-utility analysis for LDX versus MPH-OROS in adolescent patients nor did the Committee accept the cost-utility analysis of LDX versus placebo in patients who have failed MPH-OROS. The PBAC agreed with the ESC that cost minimisation analysis of LDX versus MPH-OROS is the most appropriate economic analysis.

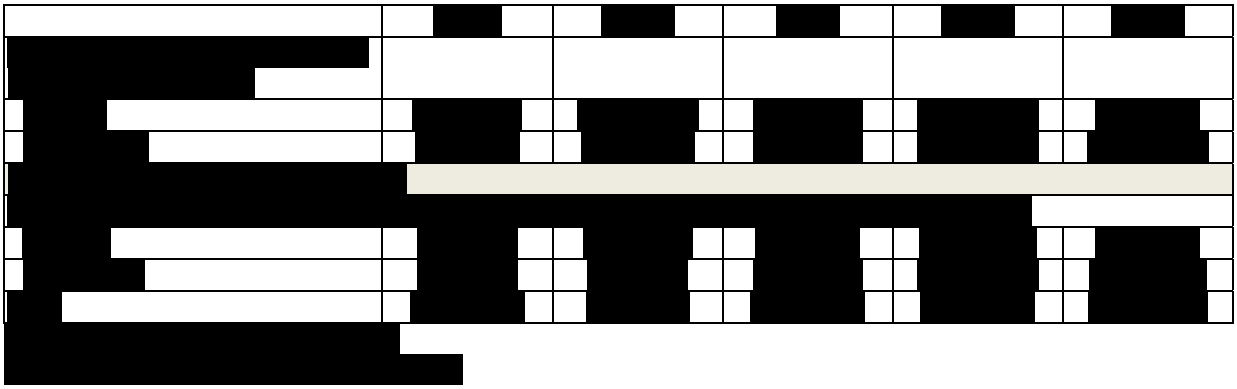
6.24 The PBAC noted that the sponsor proposed a Managed Entry Scheme in their pre-PBAC response based on forthcoming results from a new head to head trial of LDX versus MPH-OROS in adolescents due to report in late 2014. The PBAC considered this trial would be relevant to the re-submission's clinical claims. However, the Committee did not accept the current price offer for initial PBS listing as it was not justified on the basis of the evidence presented. The PBAC recommended that LDX could initially be listed at the price that is cost-minimised to MPH-OROS, and that this price could be re-assessed based on any evidence of superiority presented in a future submission to PBAC.

For more detail on PBAC's view, see section 7 "PBAC outcome"

Estimated PBS usage & financial implications

6.25 This submission was not considered by DUSC.

[redacted]



6.26 The biggest impact on expenditure would be if PBS listing Option 2 is implemented thereby restricting LDX to second-line use only. In this case, the expected uptake of LDX is expected to be reduced by [redacted] because this reflects the proportion of patients who will respond to MPH and therefore not be eligible for LDX on the PBS. The net financial impact of a PBS of listing for LDX in the second-line setting assuming [redacted]% reduction in uptake is [redacted] by Year 5 of listing.

7 PBAC Outcome

7.1 The PBAC recommended the listing of lisdexamfetamine on a cost-minimisation basis with MPH-OROS in both children and adolescents. During the maintenance phase of Trial SPD 489-325 (FAS), the average daily doses of MPH-OROS and LDX were [redacted]mg/day and [redacted]mg/ respectively.

7.2 The PBAC accepted that a modest clinical need exists for alternative treatments for ADHD in children and adolescents as patient response to one treatment over another appears to be highly individualised.

7.3 The PBAC recommended Option 1 of the proposed PBS restrictions for the listing of LDX as an Authority Required benefit for the treatment of attention deficit hyperactivity disorder (ADHD) in a patient diagnosed between the ages of 6 and 18 years (inclusive).

7.4 For the restriction, PBAC considered there should be no requirement for patients to demonstrate response to DEX before being eligible for treatment with LDX, as use of DEX gives no guide as to dose or tolerability of LDX. The PBAC noted that no evidence was presented for the additional treatment resistant population proposed in Option 2 for patients who failed to respond to MPH-OROS.

7.5 The PBAC accepted MPH-OROS as the main comparator. The comparison versus placebo was not considered appropriate for the clinical place of therapy.

7.6 The PBAC considered that the quality of the clinical trial data was limited, and noted the unblinding in key trial SPD 489-325. The post-hoc sub group analysis was rejected on the basis that it lacked scientific rigour, as evidenced by inconsistent results across differing trials and an implausibly low response rate to MPH-OROS, which was not consistent with clinical experience with MPH-OROS.

7.7 The PBAC considered that the claim of superior comparative effectiveness in adolescent patients and patients with inadequate clinical response to MPH-OROS

was not adequately supported by the data, and reiterated its July 2013 determination that lisdexamfetamine is non-inferior to MPH-OROS.

7.8 The PBAC considered that the claim of non-inferior comparative safety in the first line was not adequately supported by the data, and that the claim of inferior safety in second line was reasonable. The PBAC noted that the most worrying adverse effect was weight loss.

7.9 The PBAC recommended that the only appropriate interpretation of trial SPD489-325 was to support cost minimisation to MPH-OROS in both children and adolescents, with LDX demonstrating non-inferiority to MPH-OROS in terms of effectiveness and inferiority to MPH-OROS in terms of safety.

7.10 The PBAC recommended that lisdexamfetamine should not be treated as interchangeable with any other drugs.

7.11 The PBAC recommended that lisdexamfetamine is only suitable for prescribing by nurse practitioners as continuing therapy.

7.12 The PBAC recommended that the Safety Net 20 Day Rule should not apply.

Outcome:
Recommended

8 Recommended listing

8.1 Add new item:

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
LISDEXAMFETAMINE DIMESILATE				
Capsule 30 mg , 30	1	5	Vyvanse®	ZI
Capsule 50 mg , 30	1	5	Vyvanse®	ZI
Capsule 70 mg , 30	1	5	Vyvanse®	ZI

Category/ Program:	General Schedule
Episodicity:	
Severity:	
Condition:	Attention deficit hyperactivity disorder
Indication	Attention deficit hyperactivity disorder
Restriction:	Authority required
Clinical criteria:	Patient must require continuous coverage over 12 hours
Population criteria:	Patient must be diagnosed between the ages of 6-18 years inclusive

Administrative Advice	Note: Special Pricing Arrangements apply Note: Care must be taken to comply with the provisions of State/Territory law when prescribing methylphenidate hydrochloride. Note: No increase in the maximum quantity or number of units may be authorised. Note: No increase in the maximum number of repeats may be authorised. CAUTION: Patients requiring long term therapy should be carefully monitored. Patients who are not growing or gaining weight as expected should have their treatment interrupted. Note: 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.

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

10 Sponsor's Comment

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