Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 3

Extract from the Supplementary Clinical Evaluation Report for Lisdexamfetamine dimesilate

Proprietary Product Name: Vyvanse

Sponsor: Shire Australia Pty Ltd

October 2017

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <https://www.tga.gov.au/product-information-pi>.

Contents

List of abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
ACSA	Amphetamine Cessation Symptom Assessment
ADHD	Attention deficit hyperactivity disorder
AE	Adverse event
BED	Binge eating disorder
BMI	Body mass index
CBT	Cognitive behaviour therapy
CER	Clinical evaluation report
CI	Confidence interval
CMI	Consumer Medicines Information
CV	Cardiovascular
DA	Dopamine
DB	Double-blind
DBP	Diastolic blood pressure
EDE-Q	Eating Disorder Examination-Questionnaire
EMA	European Medicines Agency
CGI-I	Clinical Global Impressions – Global Improvement
CGI-S	Clinical Global Impressions – Severity of Illness
C-SSRS	Columbia-Suicide Severity Rating Scale
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders Fourth Edition –Text Revision
DSM-5	Diagnostic and Statistical Manual of Mental Disorders Fifth Edition
GFR	Glomerular filtration rate
LS	Least squares

Abbreviation	Meaning
NE	Noradrenaline
PI	Product information
RANZCP	Royal Australian and New Zealand College of Psychiatrists
SBP	Systolic blood pressure
SSRI	Selective serotonin reuptake inhibitor
TGA	Therapeutic Goods Administration
US	United States

1. Introduction

Submission PM-2016-01092-1-1 was an application to extend the indications of lisdexamfetamine to include the treatment of binge eating disorder (BED) in adults.

In response to this submission, the first round clinical evaluation report (CER) was produced by the Therapeutic Goods Administration (TGA) on 10 November 2016. The clinical evaluator did not support the proposed indication of 'the treatment of BED in adults', stating: 'The product's risks and current data are such that there needs to be significant tightening of the indication and the safety warnings, as well as further restrictions on the product's availability.' In the second round CER dated 3 March 2017, the clinical evaluator also did not support the following revised indication:

> *Binge Eating Disorder (BED)*
>
> *Vyvanse is indicated for the treatment of moderate to severe BED in adults. Treatment should be commenced by a specialist.*
>
> *Need for comprehensive treatment programme: Vyvanse is indicated as an integral part of a total treatment program for BED that may include other measures (nutritional, psychological, and medical) for patients with this syndrome. When remedial measures including psychotherapy are insufficient, the decision to prescribe stimulant medication will depend upon the physician's assessment of the chronicity and severity of the patient's symptoms.*
>
> *Limitation of Use: Vyvanse is not indicated or recommended for weight loss. Use of other sympathomimetic drugs for weight loss has been associated with serious cardiovascular adverse events. The safety and effectiveness of Vyvanse for the treatment of obesity have not been established.*

In the request for Advisory Committee on Medicines (ACM) advice (dated 14 April 2017) the Delegate was not in a position to say at that time that the application to extend the indications for lisdexamfetamine as proposed by the sponsor should be approved for registration. The ACM (ratified minutes of ACM meeting 3: 2.02 lisdexamfetamine dimesilate; 2 June 2017) also had several concerns regarding the use of lisdexamfetamine for BED. The sponsor provided further information addressing the concerns of the TGA. The concerns of the Delegate and the ACM, and the sponsor's response to these concerns, are considered in Section 7.

The submission also proposed changes to the PI in relation to attention deficit hyperactivity disorder (ADHD) which are not the focus of this report.

1.1. Drug class and therapeutic indication

Lisdexamfetamine is a pharmacologically inactive prodrug of dexamfetamine, a centrally acting sympathomimetic agent.[1] Lisdexamfetamine is pharmacologically inactive; it is thought to be absorbed intact and then hydrolysed to l-lysine and the pharmacologically active dexamfetamine. In Australia, the approved indication is:

> *Vyvanse is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). Treatment should be commenced by a specialist.*
>
> *A diagnosis of Attention Deficit Hyperactivity Disorder (ADHD) implies the presence of hyperactive-impulsive or inattentive symptoms that caused impairment and were present before 12 years of age.*
>
> *Need for comprehensive treatment programme: Vyvanse is indicated as an integral part of a total treatment program for ADHD that may include other measures (psychological,*

educational and social) for patients with this syndrome. Stimulants are not intended for use in the patient who exhibits symptoms secondary to environmental factors and/or other primary psychiatric disorders, including psychosis. Appropriate educational placement is essential and psychosocial intervention is often helpful. When remedial measures alone are insufficient, the decision to prescribe stimulant medication will depend upon the physician's assessment of the chronicity and severity of the patient's symptoms.

Long term use: The physician who elects to use Vyvanse for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

1.2. Dosage forms, strengths and dosage instructions

The following strengths of lisdexamfetamine, in capsule form, are currently registered as shown in Table 1.

Table 1: Strengths of lisdexamfetamine capsules registered in Australia

STRENGTH	AUST R
30mg	199227
50mg	199226
70mg	199228

An application (PM-2016-03516-1-1);[1] to register additional strengths of lisdexamfetamine (20 mg, 40 mg and 60 mg) has been submitted to the TGA. These strengths are available in the United States (US) and Canada, and in the United Kingdom (as Elvanse).

In terms of dosage instructions, the following information is contained in the current PI;[1] in relation to ADHD:

> 'In patients who are either starting treatment for the first time or switching from another medication, 30 mg once daily in the morning is the recommended starting dose. If the decision is made to increase the dose beyond 30 mg/day, daily dosage may be adjusted in increments of 20 mg in intervals no more frequently than weekly. The maximum recommended dose is 70 mg/day; doses greater than 70 mg/day of Vyvanse have not been studied. Vyvanse has not been studied in children under 6 years of age. The effectiveness of Vyvanse has not been studied in adults over 55 years of age. Due to reduced clearance in patients with severe renal insufficiency (GFR 15 to < 30 mL/min/1.73 m^2) the maximum dose should not exceed 50 mg/day. Further dosage reduction should be considered in patients undergoing dialysis.'

For BED, the dosage proposed by the sponsor was as follows:

> 'The recommended starting titration dose is 30 mg/day to be adjusted in increments of 20 mg at approximately weekly intervals to achieve the recommended target dose of 50 or 70 mg/day. Dose titration should be guided by clinical outcome to an optimal dose, with a maximum dose of 70 mg/day.'

1.3. Information on the condition being treated

BED is a psychiatric disorder, the essential features of which are recurrent episodes of binge eating with associated distress and the absence of the regular use of inappropriate weight

[1] Approved 14 November 2017.

control or compensatory behaviours characteristic of bulimia nervosa[2]. Due to the absence of compensatory behaviours, individuals with BED are often overweight or obese. During the episodes of binge eating, which occur on average at least once a week for 3 months, individuals eat an amount of food in a discrete period of time (for example, 2 hours) that is definitely larger than most people would eat in a similar period of time under similar circumstances[3]. In DSM-IV, BED was diagnosable under the category 'eating disorder not otherwise specified'; however, BED was included as a separate diagnosis in DSM-5 (Table 2). The lifetime prevalence of BED is approximately 3.5% in women and 2.0% in men, and the estimated point prevalence in Australia is 2%; BED is thus more prevalent than anorexia nervosa or bulimia nervosa [3, 4]. The onset is usually in later adolescence and young adulthood. [4]

Common psychiatric comorbidities include anxiety, mood, impulse control and substance use disorders.[4] Individuals with a history of BED also have an increased risk of developing medical comorbidities such as diabetes mellitus, hypertension and chronic pain.[4,5] The results of observational studies suggest the course of BED is often chronic.[5]

Table 2: DSM-5 Criteria for BED[4]

DSM-5 Criteria for BED
Episodes of binge eating, defined as consuming an amount of food in a discrete period of time (for example, two hours) that is definitely larger than what most people would eat in a similar amount of time under similar circumstances. During episodes, patients feel they lack control over eating (for example, patients feel they cannot stop eating or control the amount or what they are eating).
Binge eating episodes are marked by at least three of the following: · Eating more rapidly than normal · Eating until feeling uncomfortably full · Eating large amounts of food when not feeling physically hungry · Eating alone because of embarrassment by the amount of food consumed · Feeling disgusted with oneself, depressed, or guilty after overeating
Episodes occur, on average, at least once a week for three months.
No regular use of inappropriate compensatory behaviours (for example, purging, fasting, or excessive exercise) as are seen in bulimia nervosa
Binge eating does not occur solely during the course of bulimia nervosa or anorexia nervosa.
The current level of severity is based upon the number of binge eating episodes per week: · Mild – 1 to 3 · Moderate – 4 to 7 · Severe – 8 to 13 · Extreme – 14 or more

1.4. Current treatment options

Treatment goals may include reducing binge eating episodes, excess weight (if overweight or obese), excessive concerns with body image and psychiatric and physical comorbidity.[3] Psychotherapy including cognitive behaviour therapy (CBT), interpersonal psychotherapy and dialectical behaviour therapy is first-line treatment for BED.[3] Other non-pharmacological options include self-help CBT and behavioural weight loss treatment; the latter may be combined with psychotherapy.[3]

Pharmacotherapy is thought to be less efficacious than psychotherapy, although there have been no head-to-head comparisons of pharmacotherapy with psychotherapy or self-help therapy.[3] Although findings have been inconsistent, some trials have found an additive benefit for combined psychological and pharmacological treatment.[4] It may be appropriate however to use medications first-line in patients who do not have access to or who decline psychotherapy.[3] Some authors prefer selective serotonin reuptake inhibitors (SSRIs) due to efficacy and tolerability, with consideration of either an antiepileptic (such as topiramate) or lisdexamfetamine in those patients who do not respond to 1 to 2 courses of an SSRI.[3] The potential side effects of lisdexamfetamine include anorexia, gastrointestinal distress, headaches, insomnia and sympathetic nervous system arousal, and lisdexamfetamine has the potential for abuse and dependence.[3]

There are currently no medications approved for the treatment of BED in Australia.

2. Clinical rationale

The following information was included in the Clinical Overview:

> *'(Lisdexamfetamine) is thought to treat the symptoms of ADHD through a mechanism of action that is presumed to be related to the blockade of DA (dopamine) and NE (noradrenaline) reuptake, which has the effect of increasing the availability of both of these neurotransmitters. Amelioration of dopaminergic and noradrenergic hypofunction may play a similar therapeutic role in BED. Data suggests that agents that facilitate DA and/or NE neurotransmission may reduce pathological overeating (for example binge eating) in both animals and humans.*
>
> *Stimulants such as (lisdexamfetamine) might relieve binge eating in BED by stabilizing a deficient DA reward system via blockade of DA reuptake. Norepinephrine blockade also appears to be a potentially effective therapy for eating disorders. The selective NE reuptake inhibitor atomoxetine has been shown to reduce binge eating and body weight in 1 placebo controlled study of BED in adults (McElroy et al 2008[2]).'*

2.1. Approach to the preparation of this report

This evaluator consulted the following documents in consideration of the issues raised by the TGA and the sponsor's response to these issues:

- The CER produced by the TGA (second round report dated 3 March 2017(Attachment 2))
- The request for ACM advice (dated 14 April 2017)
- Ratified minutes of ACM meeting 3: Item 2.02 lisdexamfetamine dimesilate (dated 2 June 2017)

[2] McElroy, SL. et al. Atomoxetine in the treatment of binge-eating disorder: a randomized placebo controlled trial. *J Clin Psychiatry* 2007; 68: 390-8.

- Information provided by the sponsor subsequent to the above, (located in sequence 0010: Response to Request for Information – BED), and appendices, including a report by Professors [information redacted], hereafter referred to as the 'expert report'
- The US label (revised January 2017) and the Canadian Product Monograph (revised September 2016) for lisdexamfetamine
- Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the treatment of eating disorders (2014).[2]

There were no relevant European Medicines Agency (EMA) guidelines.

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier in relation to the BED indication

The following 5 clinical studies were submitted in support of the BED indication:

- Study SPD489-208; a Phase II dose finding study.
- Studies SPD489-343 and SPD489-344; Phase III efficacy and safety studies with the same design.

The above studies had treatment durations of 11 to 12 weeks.

- Study SPD489-345; an open label 52 week safety and tolerability extension study for subjects who completed Studies 208, 343 and 344.
- Study SPD489-346; a randomised, controlled withdrawal study, which provided data on efficacy maintenance and relapse risk.

In the CER it was considered that the scope of the clinical studies was sufficient to undertake an evaluation relating to the BED indication, and that the dossier was well presented.

4. Clinical efficacy

The BED studies were evaluated in the CER. The studies including the efficacy results are summarised below; safety results are considered in Section4.2

4.1. Study summaries and efficacy results

4.1.1. Study 343

This was a Phase III, randomised, multicentre, placebo controlled, double blind (DB), parallel group, dose optimisation study in 383 adults (18 to 55 years) with moderate to severe BED. Subjects were randomised in a 1:1 ratio to receive placebo or lisdexamfetamine. Those randomised to the latter were commenced on lisdexamfetamine 30 mg per day; the dose was increased to 50 mg daily after 1 week, and was further increased at the end of Weeks 2 or 3 to 70 mg per week if indicated and the treatment was tolerated; 1 down titration to 50 mg was allowed during the dose optimisation period. The optimised dose was fixed during the subsequent 8 week dose maintenance period. Statistically significant results in favour of lisdexamfetamine were seen for the primary outcome: in terms of the mean number of binge days per week (at baseline these were 4.78 for lisdexamfetamine and 4.59 for placebo), the least squares (LS) mean changes from baseline were -3.87 and -2.51 days in the lisdexamfetamine and placebo groups respectively. The difference in the LS mean of -1.35 days (95% confidence interval (CI): -1.7,-1.0) was statistically significant ($p < 0.001$).

4.1.2. Study 344

This study, which had the same design as Study 343, was conducted in 390 adult subjects. The mean number of binge days per week at baseline was 4.66 for lisdexamfetamine and 4.85 for placebo. The LS mean changes from baseline were -3.92 and -2.26 days in the lisdexamfetamine and placebo groups respectively. The difference in the LS mean of -1.66 days (95% CI: -2.04,-1.28) was again statistically significant ($p < 0.001$).

The results for Studies 343 and 344 were supported by sensitivity analyses, and subgroup analyses on the combined dataset of the 2 studies based on age, gender, race, ethnicity, region, body mass index (BMI) category and binge eating category found generally consistent results. Statistically significant results in favour of lisdexamfetamine were also seen for all of the key secondary endpoints. The rate of binge eating cessation in the 28 days prior to study end were 40% versus 14% for Study 343 and 36% versus 13% for Study 344 for the lisdexamfetamine and placebo groups respectively.

The following were noted in the CER in relation to Studies 343 and 344:

- The vast majority (> 97%) of patients had no history of prior treatment with psychotherapy, and the use of prior pharmacotherapy was rare. As psychotherapy is the recommended initial therapy for BED, an assessment of efficacy in subjects who had failed psychotherapy would have been useful.
- The study duration of 12 weeks was relatively short for a treatment which was proposed to be used long term.
- Subjects were predominantly White (> 73%) and female (> 85%) with a mean age of approximately 38 years and a mean BMI of 33.5 kg/m^2.
- There are no efficacy data in adults > 55 years.
- There was a 5 to 6% decrease in body weight in the lisdexamfetamine treated subjects, with little change in those treated with placebo, in spite of a reduction in binge eating in this group. In response to a question by the TGA clinical evaluator in the first round CER, the sponsor proposed that the weight loss seen in the lisdexamfetamine group was due to the known effects of stimulants of decreased appetite and 'increased metabolism'. In the sponsor's ACM response, it was noted that the weight loss observed in the BED programme was modest relative to typical weight loss goals in the treatment of obesity, and that results from a rodent model of BED provided strong evidence that the primary pharmacological action of lisdexamfetamine is on cognitive impulsivity, rather than appetite suppression leading to weight loss.

4.1.3. Study 208

This was a Phase II, randomised, multicentre, placebo controlled, DB, parallel group, forced dose titration study in 271 adults (18 to 55 years) with moderate to severe BED. Subjects were randomised in a 1:1:1:1 ratio to receive placebo or lisdexamfetamine 30 mg, 50 mg or 70 mg per day. Those randomised to active treatment were commenced on lisdexamfetamine 30 mg per day, and the dose was increased by 20 mg each week until the appropriate dose was reached; there were no dose reductions. An 8 week dose maintenance period followed this phase. In terms of the primary efficacy endpoint, the LS mean changes from baseline in the log transformed binge days per week over the 11 week treatment period were -1.17, -1.26, -1.50, and -1.58 in the placebo, 30 mg, 50 mg and 70 mg groups respectively; there was a statistically significant LS mean difference between the 50 mg ($p = 0.0006$) and 70 mg ($p < 0.0001$) groups and placebo. In terms of secondary endpoints, results for the number of binge episodes per week and binge response were supportive; the rates of subjects with a 4 week remission were 20.3%, 36.9%, 44.8% and 52.3% in the placebo, 30 mg, 50 mg and 70 mg groups respectively.

Although there appeared to be a dose response relationship, inter-dose comparisons were not made.

4.1.4. Study 346

This was a Phase III, randomised, multicentre, placebo controlled, DB, randomised withdrawal study in 418 adults (18 to 55 years) with moderate to severe BED. Following the 4 week screening phase, there was a 12 week open label treatment phase (4 weeks dose optimisation and 8 weeks dose maintenance), a 26 week DB treatment withdrawal phase and a 1 week follow up period. Dose optimisation was as in Studies 343 and 344, with titration to the optimal dose of 50 mg (the lowest allowed dose during the subsequent phase) or 70 mg daily, with the dose fixed during the 8 week dose maintenance period. To enter open label treatment, subjects needed to have ≥ 3 binge days per week during the 14 days prior and a Clinical Global Impressions - Severity of Illness (CGI-S) score of ≥ 4. After 12 weeks treatment, those who responded (reported ≤ 1 binge day per week for the 4 consecutive weeks (28 days) and had a CGI-S score of ≤ 2) were randomised in a 1:1 ratio to lisdexamfetamine (on their optimal dose) or matching placebo capsules for 26 weeks. There were 275 subjects randomised; completion rates for this phase were higher in the lisdexamfetamine group (74.5% versus 36.2%) and the main reasons for study withdrawal were meeting relapse criteria (3.6% versus 29.0%) and 'subject withdrawal' (6.6% versus 18.1%). In the Full Analysis Set, the rate of relapse was 3.7% for lisdexamfetamine and 32.1% for placebo, and the difference in the time to relapse was statistically significant ($p < 0.001$). The Kaplan Meier estimate of the proportion of subjects who relapsed was 4% (95% CI: 1%, 7%) for lisdexamfetamine and 36% (95% CI: 27%, 45%) for placebo group. The majority of relapses occurred within 30 days of randomised withdrawal (60% for lisdexamfetamine and 62% for placebo). Sensitivity analyses were supportive of the primary analysis. The percentages of subjects reported to be 'normal, not at all ill' on the CGI-S were 83.8% and 74.8% for lisdexamfetamine and placebo at the randomised withdrawal baseline; the respective figures at the end of the randomised withdrawal phase (Week 38/early termination) were 81.6% and 45.0%.

Comment: The clinical evaluator thought that the relapse definition was appropriate and that a withdrawal period of 26 weeks was appropriate to assess relapse. However, although the relapse rate was notably lower in the lisdexamfetamine group than placebo, 68% of the placebo subjects did not relapse during the randomised withdrawal period. The clinical evaluator suggested that this may indicate a placebo effect, or the possibility that the majority of subjects may no longer require lisdexamfetamine after the initial 12 weeks of treatment.

4.1.5. Study 345

This was a Phase III, open label extension study for subjects who had completed Studies 208, 343 or 344. There was a 2 week screening period, followed by a 52 week open label treatment phase. If the gap from the previous study was > 30 days, the 52 week open label treatment phase included an initial 4 week dose optimisation period: all subjects recommenced treatment on 30 mg daily, were force titrated to 50 mg daily after 1 week, and further titrated to 70 mg daily if indicated from week 2. Down titration to 50 mg was allowed however subjects were discontinued if further down titration was needed. Of the 815 subjects who completed the 3 feeder studies, 604 (74%) were enrolled in Study 345. The completion rate in this study was 61.1%, with subject withdrawal (10.8%), adverse event (AE, 9.1%), lost to follow up (7.9%) and 'other' (9.6%) the main reasons for premature discontinuation. In terms of the Clinical Global Impressions – Global Improvement (CGI-I) scale, at week 4 the rate of subjects 'improved' was 88.5%, and this was maintained over the study period with a rate of 89.9% at week 52. The mean Eating Disorder Examination-Questionnaire (EDE-Q) global score at baseline was 3.34; the mean decrease at week 4 was -1.66, which was maintained at week 52 (mean decrease -1.90).

Comment: The clinical evaluator indicated in the CER that as only 74% of primary completers continued on to the extension study, the completion rate was 61% and the study was open label and uncontrolled in design, no definitive efficacy conclusions could be drawn from this study. The evaluator concluded that there were only clear efficacy data for treatment up to 12 weeks' duration. This evaluator does believe that Study 345 does suggest continued efficacy in those who continued lisdexamfetamine treatment.

4.2. Safety results

There were no new safety issues from the BED studies. The following summary was contained in the request for ACM advice:

'Overall, in the clinical development program for BED there were 1244 subjects in the safety analysis set with a mean duration of exposure of 212 days and an average daily dose of 57.5 mg. There were 380 subjects with ≥ 361 days of exposure. In the pivotal studies 29.2% of study subjects given lisdexamfetamine were optimised to 50 mg daily and 61.7% to 70 mg daily (Table 3).

Table 3: Investigational product exposure in the short term, placebo controlled studies (Safety analysis set)

		SPD489-208				SPD489-343/-344		SPD489-208/-343/-344		
Exposure Variable	Statistic	Placebo (N=63)	SPD489 30 mg (N=66)	SPD489 50 mg (N=65)	SPD489 70 mg (N=65)	Placebo (N=372)	SPD489 (N=373)	Placebo (N=435)	SPD489 50/70 mg (N=503)	SPD489 All Doses (N=569)
Duration of exposure (days)[a]	n	63	66	65	65	371	372	434	502	568
	Mean	66.9	67.2	69.1	68.1	74.8	75.7	73.7	73.9	73.1
	SD	22.36	21.98	20.01	22.11	21.91	20.46	22.13	20.82	21.05
	Median	77	77	77	77	84	84	84	83	82
	Min, Max	2, 89	3, 81	3, 82	5, 81	2, 91	3, 92	2, 91	3, 92	3, 92
Optimized dose										
50 mg/day	n (%)	NA	NA	NA	NA	NA	109 (29.2)	NA	NA	NA
70 mg/day	n (%)	NA	NA	NA	NA	NA	230 (61.7)	NA	NA	NA
Average daily dose [b] (mg/day)	n	NA	66	65	65	NA	372	NA	502	568
	Mean	NA	29.8	47	61.6	NA	57.3	NA	56.5	53.4
	SD	NA	1.38	4.77	10.2	NA	9.48	NA	9.91	12.65
	Median	NA	30	47.9	64.5	NA	63.2	NA	62.5	57
	Min, Max	NA	20, 32	30, 66	30, 85	NA	26, 68	NA	26, 85	20, 85
Cumulative duration of exposure (days)[a]										
≥1	n (%)	63 (100)	66 (100)	65 (100)	65 (100)	371 (99.7)	372 (99.7)	434 (99.8)	502 (99.8)	568 (99.8)
≥8	n (%)	60 (95.2)	62 (93.9)	61 (93.8)	61 (93.8)	361 (97.0)	367 (98.4)	421 (96.8)	489 (97.2)	551 (96.8)
≥15	n (%)	59 (93.7)	61 (92.4)	61 (93.8)	60 (92.3)	353 (94.9)	357 (95.7)	412 (94.7)	478 (95.0)	539 (94.7)
≥22	n (%)	57 (90.5)	59 (89.4)	60 (92.3)	58 (89.2)	346 (93.0)	349 (93.6)	403 (92.6)	467 (92.8)	526 (92.4)
≥29	n (%)	55 (87.3)	59 (89.4)	60 (92.3)	57 (87.7)	336 (90.3)	342 (91.7)	391 (89.9)	459 (91.3)	518 (91.0)
≥36	n (%)	54 (85.7)	57 (86.4)	59 (90.8)	56 (86.2)	330 (88.7)	338 (90.6)	384 (88.3)	453 (90.1)	510 (89.6)
≥43	n (%)	53 (84.1)	57 (86.4)	58 (89.2)	56 (86.2)	325 (87.4)	333 (89.3)	378 (86.9)	447 (88.9)	504 (88.6)
≥50	n (%)	52 (82.5)	56 (84.8)	56 (86.2)	55 (84.6)	318 (85.5)	329 (88.2)	370 (85.1)	440 (87.5)	496 (87.2)
≥57	n (%)	51 (81.0)	54 (81.8)	55 (84.6)	55 (84.6)	317 (85.2)	323 (86.6)	368 (84.6)	433 (86.1)	487 (85.6)
≥64	n (%)	50 (79.4)	53 (80.3)	55 (84.6)	54 (83.1)	314 (84.4)	318 (85.3)	364 (83.7)	427 (84.9)	480 (84.4)
≥71	n (%)	48 (76.2)	52 (78.8)	52 (80.0)	52 (80.0)	309 (83.1)	314 (84.2)	357 (82.1)	418 (83.1)	470 (82.6)
≥78	n (%)	22 (34.9)	21 (31.8)	20 (30.8)	26 (40.0)	302 (81.2)	303 (81.2)	324 (74.5)	349 (69.4)	370 (65.0)
Total person-time (days)		NA	4456	4518	4437	NA	28241	NA	37196	41652

NA=not applicable; SD=standard deviation

Note: Percentages are based on all subjects in the Safety Analysis Set.

[a] Duration of exposure (days) is the number of days on investigational product based on the first and last days of treatment (last day of investigational product - first day of investigational product + 1) for each individual study.

Source: ISS, Module 5.3.5.3, Table 3.1.1

In the BED studies the most frequent SOCs for adverse event reports were gastrointestinal disorders (50.1% versus 19.3%), psychiatric disorders (31.1% versus 12.2%) and nervous system disorders (24.8% versus 14.5%). The most frequent events, all of which were more common with lisdexamfetamine, were: dry mouth (36.4% versus 7.4%), headache (14.2% versus 9.0%), insomnia (13.7% versus 4.8%), decreased appetite (12.3% versus 3.0%) and

nausea (8.3% versus 5.1%). Other frequent events that were more common with lisdexamfetamine were irritability (6.3% versus 5.3%), constipation (6.2% versus 1.4%), feeling jittery (5.3% versus 0.5%) and anxiety (5.1% versus 0.7%) (Table 4). Feeling jittery had a dose response in Study 208 (0%, 1.5%, 4.6% and 7.7% in the placebo, 30 mg, 50 mg and 70 mg lisdexamfetamine groups, respectively).

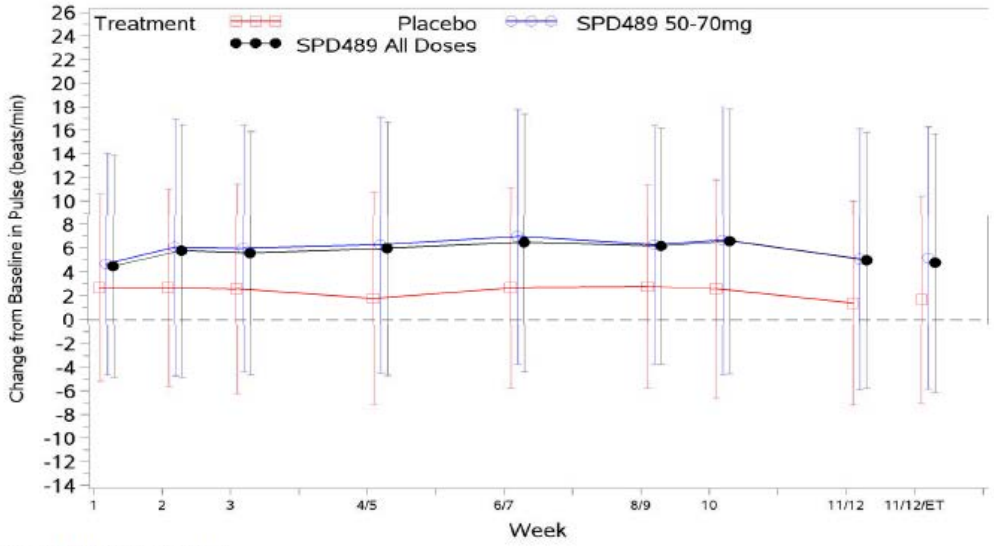
Table 4: Treatment-emergent AEs occurring in ≥ 5 of subjects in the short term, placebo controlled studies by preferred term (Safety analysis set)

	SPD489-208				SPD489-343/-344		SPD489-208/-343/-344		
Preferred term	Placebo (N=63) n (%)	SPD489 30 mg (N=66) n (%)	SPD489 50 mg (N=65) n (%)	SPD489 70 mg (N=65) n (%)	Placebo (N=372) n (%)	SPD489 (N=373) n (%)	Placebo (N=435) n (%)	SPD489 50/70 mg (N=503) n (%)	SPD489 All Doses (N=569) n (%)
Dry mouth	5 (7.9)	22 (33.3)	22 (33.8)	27 (41.5)	27 (7.3)	136 (36.5)	32 (7.4)	185 (36.8)	207 (36.4)
Headache	6 (9.5)	9 (13.6)	9 (13.8)	5 (7.7)	33 (8.9)	58 (15.5)	39 (9.0)	72 (14.3)	81 (14.2)
Insomnia	1 (1.6)	6 (9.1)	10 (15.4)	9 (13.8)	20 (5.4)	53 (14.2)	21 (4.8)	72 (14.3)	78 (13.7)
Decreased appetite	4 (6.3)	17 (25.8)	13 (20.0)	12 (18.5)	9 (2.4)	28 (7.5)	13 (3.0)	53 (10.5)	70 (12.3)
Nausea	0	5 (7.6)	6 (9.2)	4 (6.2)	22 (5.9)	32 (8.6)	22 (5.1)	42 (8.3)	47 (8.3)
Irritability	4 (6.3)	5 (7.6)	3 (4.6)	3 (4.6)	19 (5.1)	25 (6.7)	23 (5.3)	31 (6.2)	36 (6.3)
Constipation	1 (1.6)	6 (9.1)	3 (4.6)	5 (7.7)	5 (1.3)	21 (5.6)	6 (1.4)	29 (5.8)	35 (6.2)
Fatigue	2 (3.2)	2 (3.0)	3 (4.6)	2 (3.1)	19 (5.1)	24 (6.4)	21 (4.8)	29 (5.8)	31 (5.4)
Feeling jittery	0	1 (1.5)	3 (4.6)	5 (7.7)	2 (0.5)	21 (5.6)	2 (0.5)	29 (5.8)	30 (5.3)
Anxiety	0	4 (6.1)	4 (6.2)	1 (1.5)	3 (0.8)	20 (5.4)	3 (0.7)	25 (5.0)	29 (5.1)

Note: Percentages are based on all subjects in the Safety Analysis Set
Note: Subjects were counted once per preferred term.
Source: ISS, Module 5.3.5.3, Table 4.1.2.2.8

No new safety issues were apparent from these studies. Cardiovascular and psychiatric adverse events are the safety issues of most interest. In the short term BED studies (Studies 208, 343 and 344), pulse rate increased with lisdexamfetamine (mean increase of 5.0 bpm at Weeks 11 to 12) and a smaller increase was also noted in the placebo group (1 to 3 bpm) (Figure 1). The rate of subjects with an increase in SBP of > 10 mmHg was higher with lisdexamfetamine (13 to 18% versus 7 to 11%). A similar trend was seen for an increase in DBP > 10 mmHg (8 to 12% versus 4 to 7%). Potentially clinically important increases in SBP, DBP and pulse rate are shown in Table 5. A SBP of ≥ 140 mmHg and an increase of > 10 mmHg from baseline on two consecutive visits was more frequent with lisdexamfetamine (1.6% versus 0.7%). A pulse rate of ≥ 110 bpm occurred in 3.4% and 0.5% of lisdexamfetamine and placebo subjects, respectively. In the long term extension study (Study 345) there was a mean increase in HR of 6.6 bpm.

Figure 1: Mean (SD) change from baseline in pulse rate by visit for the short term, placebo controlled studies (Safety Analysis Set)



ET=early termination; SD=standard deviation
Source: ISS, Module 5.3.5.3, Figure 3.3

Table 5: Potentially clinical important vital signs values in the short term, placebo controlled studies (Safety analysis set)

Parameter (units) PCI Criteria	SPD489-208				SPD489-343/-344		SPD489-208/-343/-344		
	Placebo (N=63) n (%)	SPD489 30 mg (N=66) n (%)	SPD489 50 mg (N=65) n (%)	SPD489 70 mg (N=65) n (%)	Placebo (N=372) n (%)	SPD489 (N=373) n (%)	Placebo (N=435) n (%)	SPD489 50/70 mg (N=503) n (%)	SPD489 All Doses (N=569) n (%)
Number of subjects with a baseline and at least 1 postbaseline result	62	66	65	64	370	370	432	499	565
Systolic blood pressure (mmHg)									
<100	6 (9.7)	4 (6.1)	2 (3.1)	9 (14.1)	117 (31.6)	84 (22.7)	123 (28.5)	95 (19.0)	99 (17.5)
≥140	4 (6.5)	5 (7.6)	2 (3.1)	8 (12.5)	21 (5.7)	26 (7.0)	25 (5.8)	36 (7.2)	41 (7.3)
>10 increase from baseline	19 (30.6)	21 (31.8)	19 (29.2)	32 (50.0)	121 (32.7)	184 (49.7)	140 (32.4)	235 (47.1)	256 (45.3)
>10 increase from baseline on 2 consecutive visits	8 (12.9)	9 (13.6)	6 (9.2)	13 (20.3)	38 (10.3)	84 (22.7)	46 (10.6)	103 (20.6)	112 (19.8)
≥140 and increase >10 from baseline	4 (6.5)	5 (7.6)	2 (3.1)	6 (9.4)	15 (4.1)	19 (5.1)	19 (4.4)	27 (5.4)	32 (5.7)
≥140 and increase >10 from baseline on 2 consecutive visits	0	1 (1.5)	0	2 (3.1)	3 (0.8)	6 (1.6)	3 (0.7)	8 (1.6)	9 (1.6)
≥140 and increase >10 from baseline on 2 consecutive visits including the last study visit	0	1 (1.5)	0	0	0	1 (0.3)	0	1 (0.2)	2 (0.4)
Diastolic blood pressure (mmHg)									
<50	0	0	0	0	2 (0.5)	1 (0.3)	2 (0.5)	1 (0.2)	1 (0.2)
≥90	5 (8.1)	9 (13.6)	10 (15.4)	11 (17.2)	43 (11.6)	72 (19.5)	48 (11.1)	93 (18.6)	102 (18.1)
>10 increase from baseline	10 (16.1)	10 (15.2)	13 (20.0)	15 (23.4)	84 (22.7)	139 (37.6)	94 (21.8)	167 (33.5)	177 (31.3)
>10 increase from baseline on 2 consecutive visits	2 (3.2)	4 (6.1)	7 (10.8)	3 (4.7)	24 (6.5)	53 (14.3)	26 (6.0)	63 (12.6)	67 (11.9)
≥90 and increase >10 from baseline	2 (3.2)	3 (4.5)	3 (4.6)	6 (9.4)	22 (5.9)	43 (11.6)	24 (5.6)	52 (10.4)	55 (9.7)
≥90 and increase >10 from baseline on 2 consecutive visits	0	1 (1.5)	0	0	5 (1.4)	5 (1.4)	5 (1.2)	5 (1.0)	6 (1.1)
≥90 and increase >10 from baseline on 2 consecutive visits including the last study visit	0	0	0	0	2 (0.5)	0	2 (0.5)	0	0
Pulse rate (bpm)									
<50bpm	0	0	0	0	9 (2.4)	2 (0.5)	9 (2.1)	2 (0.4)	2 (0.4)
≥110bpm	0	1 (1.5)	3 (4.6)	2 (3.1)	2 (0.5)	13 (3.5)	2 (0.5)	18 (3.6)	19 (3.4)
≥110bpm and increase >15 from baseline	0	1 (1.5)	2 (3.1)	2 (3.1)	2 (0.5)	11 (3.0)	2 (0.5)	15 (3.0)	16 (2.8)
≥110bpm and increase >15 from baseline on 2 consecutive visits	0	0	0	2 (3.1)	0	1 (0.3)	0	3 (0.6)	3 (0.5)
≥110bpm and increase >15 from baseline on 2 consecutive visits including the last study visit	0	0	0	0	0	0	0	0	0
Temperature (C)									
<35 (oral or tympanic)	0	1 (1.5)	0	0	3 (0.8)	2 (0.5)	3 (0.7)	2 (0.4)	3 (0.5)
>39 (oral or tympanic)	0	0	0	0	1 (0.3)	0	1 (0.2)	0	0

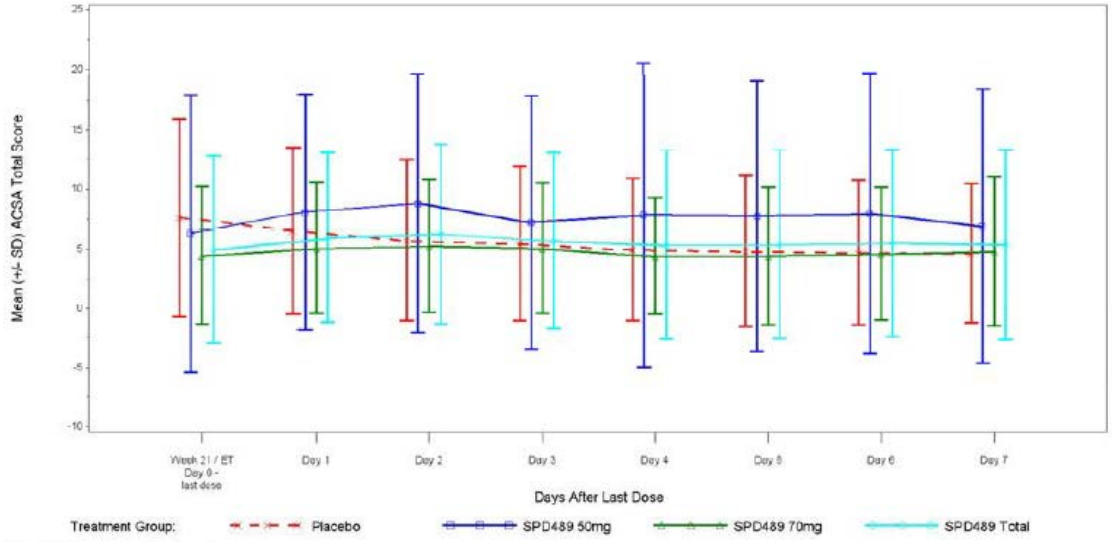
PCI=potentially clinically important
Note: Percentages are based on all Safety Analysis Set subjects with a baseline and at least 1 postbaseline assessment.
Source: ISS, Module 5.3.5.3, Table 6.1.2

The most frequently reported psychiatric adverse events were related to mood and were more common in the lisdexamfetamine group (10.2% versus 3.4%). The most frequent event in this group was insomnia. Aggression related events (8.8% versus 6.0%) were more common in the lisdexamfetamine group and the most frequent event in this group was irritability (6.3% versus 5.3%). Psychosis/hallucination/mania events were more frequent with lisdexamfetamine (2.8% versus 0.2%) with the most common event in this group being affect lability (1.1% versus 0%). None of the events in the lisdexamfetamine group were serious, although two led to discontinuation.

Suicidal ideation and behaviour was assessed using the C-SSRS data. There were no suicide related TEAEs in the short term studies. There were 10 subjects (0.8%) treated with lisdexamfetamine who had TEAEs of overdose (intake of more than one capsule per day in double blind studies or exceeding 70 mg/day in open label studies). In 8 cases only one extra capsule was taken, in one case one extra capsule was taken on two days and in the last case

≤ 3 capsules were taken (precise number unknown). There were two lisdexamfetamine treated subjects (0.2%) with a TEAE of withdrawal syndrome 1 to 2 days post treatment cessation. One reported 'withdrawal symptoms' and one 'fatigue/ withdrawal symptoms'. One subject (0.1%) discontinued due to drug dependence ('intermittent drug craving'). Withdrawal symptoms were assessed using the self-reported Amphetamine Cessation Symptom Assessment (ACSA) questionnaire in Studies 343, 344 and 346. Higher scores are associated with greater withdrawal symptom severity. In the pooled data from Studies 343 and 344, mean ACSA total scores were slightly higher in the lisdexamfetamine group than the placebo group 2 to 7 days post last dose and after this scores were comparable. Mean scores didn't rise above 8 on a 0 to 64 point scale. Similarly no indication of clinical withdrawal syndrome was seen following abrupt discontinuation of therapeutic doses of lisdexamfetamine after up to 38 weeks of treatment. Figure 2 shows ACSA scores by dose in the 7 day period following the last dose of study drug for all BED studies.

Figure 2: Mean (± SD) ACSA total aggregate scores presented by treatment group for the 7 day period following the last dose of investigational product (Randomised Safety Analysis Set)



Note: RW=Randomized-withdrawal
Cross reference: Table 4.11.2
Program: f_acsa.sas; Output: f_acsa-1.rtf; Generated on: 10JUL2015 01:30
Page 1 of 1
ACSA=Amphetamine Cessation Assessment Scale; ET=early termination; SD=standard deviation
Source: Section 14, Figure 4.2.1.

A report titled *'Nonmedical Use and Diversion of Prescription Stimulants: Evidence from Utilization Patterns and Post-marketing Surveillance in the United States'* (2013) prepared for the sponsor by [information redacted] was included in the submission. This report did not consider use of lisdexamfetamine or dexamfetamine when prescribed as a treatment for BED. In its conclusions it was stated that post-marketing surveillance studies show little difference in rates of abuse of amphetamine and methylphenidate. It was also stated that, at this time, there is no evidence to suggest that lisdexamfetamine will alter patterns or rates of nonmedical use of prescription stimulants in Europe, or emerge as a major drug abuse problem in its own right.

5. First round benefit-risk assessment

Assessment and recommendation of the clinical evaluator.

5.1. Benefits

The following benefits were identified by the clinical evaluator in the first round CER (Table 6).

Table 6: Benefits and strengths, uncertainties of Vyvanse for BED

Indication – Binge Eating Disorder	
Benefits	**Strengths and Uncertainties**
Statistically significant efficacy over placebo as measured by the number of binge eating days per week.	Superiority demonstrated in two randomised, placebo controlled trials. The placebo-corrected effect size was 1.5 binge days per week.
Efficacy on the primary endpoint was supported by positive effect across the secondary endpoints in both pivotal trials.	The benefit of lisdexamfetamine was confirmed on CGI-I score, proportion ceasing all binge eating for the last 4 weeks of the trial, percentage reduction in body weight, the change in the Y-BOCS-BE total score and triglyceride levels.
Efficacy was consistent across subgroups	Generally consistent results from the combined Phase III study dataset on all subgroups apart from non-US subjects where numbers were small.
A positive response on the clinically relevant endpoint of 4 week binge eating cessation.	In the lisdexamfetamine groups, the 4 week cessation of binge eating rate was 36 to 40% compared to 13 to 14% in the placebo group with a difference of 23 to 26%.
Lower risk of relapse.	The randomised controlled withdrawal study found a relapse rate of 4% in those on SPD489 compared to 32% in those on placebo.
Safety generally in line with what is known from the ADHD population.	The safety dataset for BED was moderately large in size including 1244 subjects with a mean treatment duration of 212 days.
Weight reduction.	In a population which is typically obese, there was a 5.5% reduction in body weight over 12 weeks of treatment (compared to no change with placebo) and up to 8.6% in the one year study. Weight reduction was seen to stabilise at around week 34 of treatment.
Lack of significant withdrawal symptoms.	Treatment-emergent AEs of withdrawal syndrome were infrequent (0.2%) and specific questionnaire data (ACSA) did not indicate a significant issue.
First pharmaceutical treatment option for BED in Australia.	A novel therapeutic option for patients, particularly for those who may not have access to psychotherapy.

5.2. Risks

The risks identified in the first round CER were as follows (Table 7).

Table 7: Risks and strengths, uncertainties of Vyvanse for BED

Indication – Binge Eating Disorder	
Risks	**Strengths and Uncertainties**
Treatment-related adverse events are very frequent (for example drug mouth, insomnia, headache, decreased appetite, irritability, nausea, feeling jittery).	The rate of treatment-related AEs in the short term studies was 71%. Despite the high rate, the serious AE risk is moderately low (2.3%). In addition, the risk of discontinuation due to AEs was 4.4% in the short term studies and 9% in the 1 year study indicating the risks may be tolerable.
Increased blood pressure and heart rate	There is a well-documented increase in BP of 1-2 mmHg and an increase in heart rate of 5-7 bpm.
Populations where stimulant treatment is contraindicated.	As already stated in the PI, contraindicated populations include: those with symptomatic cardiovascular disease, advanced arteriosclerosis, moderate to severe hypertension, glaucoma, hyperthyroidism, phaeochromocytoma, other psychiatric disorders, agitated states, tics or Tourette's syndrome, drug dependence and alcohol abuse.
No firm long term efficacy data	The efficacy was established over a 12 week treatment period. Supportive studies did not provide firm evidence of efficacy over longer treatment durations.
No long term safety data beyond 1 year.	Safety data in the BED population were only available to 1 year and this is a risk given the proposal that treatment could be prescribed indefinitely.
Cardiovascular risk.	Cardiovascular events (apart from the effects on vital signs) were not evident in the BED clinical program; however the studies were not aimed at assessing this risk. The risk has been associated with weight loss therapies and is applicable to lisdexamfetamine.
Risk of normalising amphetamine use for appetite suppression.	Given the widespread problem in our community of overeating, the availability of lisdexamfetamine for the BED population may have an impact on normalising amphetamine use for appetite suppression and weight loss.
Risk of off label use for weight loss, risk of abuse and of diversion out of the clinical setting.	Off label use for weight loss is a real risk given the positive effects on weight reduction seen in the clinical trials. While treatment abuse was not seen, the clinical trial setting is very controlled. The risk of diversion has not been elucidated; however, due

Indication – Binge Eating Disorder	
Risks	**Strengths and Uncertainties**
	to the nature of the drug, it is an evident possibility.

5.3. Recommendation of the clinical evaluator in the second round CER

The sponsor's revised indication following the first round CER was as follows:

> *Binge Eating Disorder (BED)*
>
> *Vyvanse is indicated for the treatment of moderate to severe BED in adults. Treatment should be commenced by a specialist.*
>
> *Need for comprehensive treatment programme: Vyvanse is indicated as an integral part of a total treatment program for BED that may include other measures (nutritional, psychological, and medical) for patients with this syndrome. When remedial measures including psychotherapy are insufficient, the decision to prescribe stimulant medication will depend upon the physician's assessment of the chronicity and severity of the patient's symptoms.*
>
> *Limitation of Use: Vyvanse is not indicated or recommended for weight loss. Use of other sympathomimetic drugs for weight loss has been associated with serious cardiovascular adverse events. The safety and effectiveness of Vyvanse for the treatment of obesity have not been established.*

In the second round CER, the clinical evaluator did not support the approval of lisdexamfetamine for the revised indication for the following reasons:

1. Due to inherent product risks and guideline recommendations that advocate psychotherapy as the first line treatment option for BED, Vyvanse treatment should be used as second line therapy after an unsatisfactory response to psychotherapy. It is recommended that it is used as first line therapy only in those who do not have access to psychotherapy.
2. In the absence of further longer term efficacy, safety and cardiovascular outcome data, treatment duration for BED should be limited to a maximum of 12 weeks.

In Section 6, the issues of concern of the Delegate are considered. This evaluator's assessment and recommendations are located in Section 7 of this report, in which the clinical evaluator's concerns above are addressed.

6. Consideration of issues raised by the Delegate

In this section the issues of concern of the Delegate are considered. The ACM response is summarised, and information from the sponsor's response and the expert report relevant to the concerns of the Delegate is included in the relevant section.

6.1. Acceptance of BED as a distinct psychiatric condition in Australia

The ACM noted that BED is recognised as a distinct condition in ICD 10 and DSM 5, and that the reliance on subjective measures is standard for psychiatric diagnoses. However, there was concern that this reliance may reduce the reliability of individual diagnoses.

Information included in the sponsor's response included the recognition of BED in Australia as a distinct disorder with specific diagnostic criteria, disease course and treatment recommendations, [4] with BED prevalence estimates in Australia similar to those reported globally. In terms of the reliability of individual BED diagnoses, the sponsor indicated that formal assessment of the validity and test retest reliability of diagnostic criteria for BED demonstrated that DSM criteria identify a group of patients whose symptoms are distinct from those of patients with other eating disorders, and that substantial inter-rater reliability between clinicians and research assessors has been shown for both DSM-IV (84% agreement) and DSM 5 (83% agreement) criteria (Thomas et al, 2014).

In the expert report, Professors [information redacted] indicate that as BED is now included as a distinct psychiatric diagnosis in DSM 5, it is 'core business' for Australian psychiatrists. The role of the RANZCP in producing bi-national guidelines and disseminating new evidence based treatments was outlined. Recent publications concerning BED were discussed, including those concerning the Australian population, in which the 3 month prevalence of BED was reported to be 1.5%, the mean BMI was in the obese range, and physical and mental health related quality of life was poor. Comorbidities including other psychiatric disorders, chronic pain, obesity and diabetes mellitus (with possibly more severe complications), in addition to dysfunctional relationships and interpersonal functioning, were discussed.

Comment: The evaluator agrees that BED appears to be a valid and reliable diagnosis.

6.2. The appropriateness of days of binge eating per week as the primary efficacy measure in the pivotal studies

The ACM suggested that the primary assessment of change in number of binge eating days per week was incomplete as it lacked assessment of other BED severity criteria and only assessed binge eating frequency; elsewhere in the report, the ACM noted that while the primary efficacy measure was subjective, it was appropriate. Questionnaires contained 300 to 400 questions but included few directly relevant to the criteria. The ACM suggested that using so many questions may lead to bias such as trawling data for apparently statistically significant results which may occur by chance with multiple efficacy endpoint assessments and selective reporting bias where only positive results are presented.

The sponsor indicated that the number of binge eating days per week was selected as the primary endpoint as this is a core symptom by which BED is diagnosed (Guerdjikova et al, 2017), is the basis for the DSM 5 severity criteria, has been shown to be highly clinically relevant (correlated with psychopathology; Gianini et al, 2017), and has been used widely in formal assessments of the efficacy of both behavioural and pharmacologic treatments of BED (Peat et al, 2017). Additionally, the NICE 2017 Eating Disorders guideline states: 'The committee discussed the importance and relevance of various outcomes when assessing the effectiveness of pharmacotherapies for treating binge eating disorder. For this population, it was agreed binge eating frequency and remission were of greatest concern'.

The sponsor indicated that the endpoints included in the BED development program sought to measure a range of core and comorbid symptoms commonly associated with BED, with a pre-specified hierarchical testing procedure used in the comparisons between the lisdexamfetamine and placebo groups on the primary and key secondary efficacy endpoints to minimise the risk of Type I error. The clinical evaluator noted that 'Efficacy data were robust and were supported by sensitivity and secondary endpoint analyses'.

Comment: This evaluator notes the absence of EMA guidelines on BED, which would usually be consulted by a clinical evaluator when considering the appropriateness of an efficacy measure. The DSM 5 diagnosis and severity criteria depend upon binge eating episodes and not binge eating days (Table 2, above); however, the clinical

evaluator found that basing the primary efficacy endpoint on binge days rather than binge episodes was sensible as it could be difficult discerning the end of one binge episode and the start of another episode. This evaluator considers days of binge eating per week as the primary efficacy measure in the pivotal efficacy studies of BED to be acceptable.

6.3. The appropriateness of subject selection for the pivotal studies

The ACM agreed that the selection criteria for the pivotal clinical trials restricted study participation to patients with BED who did not have comorbid Axis I or Axis II disorders and on prohibited medication or that was not controlled by medication, and who did not have significant concurrent physical disorders, including symptomatic or significant cardiovascular disease. The ACM considered these were very frequent comorbidities and thus the clinical trial population did not reflect the patient population presenting with BED in real world practice.

The ACM agreed that whilst the diagnostic criteria were applied in the subject selection by a clinical assessment by selected assessors, these assessors were chosen by the sponsor which raises further possibilities of bias. The ACM were of the view that the subject selection process was highly selective and excluded co-morbidities which occur frequently in the BED patient population. This raises a further possibility of bias by selection of subjects who were in better health than the general BED population and thus safety assessment would not be reflective of the safety of lisdexamfetamine were it to be used in the general BED patient population.

The sponsor indicated that sites and investigators selected for participation in the lisdexamfetamine BED programme were identified, evaluated and selected if they were part of or led a team that diagnosed and treated BED patients using current standards of care, including pharmacological and non-pharmacological approaches to treatment. Diagnostic assessments were performed using structured clinical interviews (SCID-I Eating Disorders Module H) to enhance validity and consistency of diagnosis.

The BED studies enrolled male and non-pregnant female subjects who were 18 to55 years of age at the time of consent, and the Phase III studies required subjects to have a BMI of ≥ 18 to ≤ 45 kg/m^2; the majority of the included subjects were obese or morbidly obese. The demographic inclusion criteria were chosen to ensure that subjects included in these studies reflected the typical demographic features of patients with BED. All of the BED studies used DSM-IV-TR BED diagnostic criteria; the studies included subjects with BED of at least moderate severity.

It was maintained that the key safety related exclusion criteria in the BED clinical trials reflected known or potential risks of stimulants for subjects with concurrent illnesses and are consistent with proposed labelling for BED patients (for example, seizures or unstable cardiovascular disease) or acute concurrent illnesses or medications that could confound the interpretation of study data (for example, comorbid unstable psychiatric diagnoses, use of concurrent medications affecting the CNS, blood pressure or heart rate; abnormal thyroid function). Subjects with stage I hypertension that was controlled on an antihypertensive regimen and subjects with dyslipidaemias who were on lipid lowering treatment were included in the study.

Comment: This evaluator believes that the process to select sites and investigators for participation in the lisdexamfetamine BED programme, and the use of structured clinical interviews, would have ensured the validity and consistency of the BED diagnoses. It is thought that the demographic characteristics of the included subjects would be generally consistent with the target population in Australia. The current lisdexamfetamine PI includes several contraindications, including symptomatic cardiovascular disease, moderate to severe hypertension, hyperthyroidism, and patients with severe anxiety, tension, agitation, severe

depression, anorexia nervosa, psychotic symptoms or suicidal tendency, and those with known drug dependence or alcohol abuse; those patients in the clinical setting with these comorbidities would not be prescribed lisdexamfetamine. Psychiatrists considering prescribing lisdexamfetamine would assess patients' comorbidities and concomitant medications before deciding whether it would be suitable for a particular patient with moderate to severe BED.

6.4. The role of lisdexamfetamine in the management of BED

The ACM noted that whilst the results of the studies were positive, there are biases to be considered such as that blinding may be ineffective due to the side effects of amphetamines making performance bias and detection bias more likely. The ACM also noted that the therapy was not compared to usual care. There was no consideration given to other therapies such as CBT as alternative or adjunctive therapies.

The sponsor indicated that the blinded trials within the BED development program utilised widely accepted methods for protecting the blind, and that a relative lack of familiarity with psychostimulants would have minimised the recognition of stimulant effects. The use of an observable primary endpoint was thought to also provide further protection against the introduction of subjective bias stemming from functional unblinding. The high placebo response rates observed in all of the blinded BED trials were thought to provide strong evidence that blinding was effective. That the clinical evaluator suggested placebo response as a possible reason for the fact that in Study 346, 68% of subjects who responded to lisdexamfetamine who were then randomised to placebo did not relapse, and that the proportions of subjects who did not complete the pivotal efficacy studies were nearly identical for both the placebo and lisdexamfetamine groups, suggested to the sponsor that the blind in efficacy assessments of lisdexamfetamine in BED was maintained throughout the studies.

Comment: This evaluator does believe that due to the side effects of stimulant medication, some unblinding would have occurred. It is noted however that the studies considered acceptable for ADHD were in the main double blind, placebo controlled trials; the few studies which included an active comparator utilised another stimulant medication. As it is likely that at least some patients who responded to lisdexamfetamine were aware that they were subsequently switched to placebo in Study 346, the fact that 68% of these subjects did not relapse strengthens the argument that 12 weeks of active lisdexamfetamine treatment may be sufficient.

Regarding the inclusion of a comparator, the sponsor noted that there were no approved pharmacological treatments for BED, and that the most recent NICE Clinical Practice Guidelines for Eating Disorders considered the evidence supporting efficacy of antidepressants and anticonvulsants in the treatment of BED to be weak. The sponsor suggested that non-pharmacologic treatments have limited accessibility, no widely accepted standard, and that some literature suggests they have limited efficacy (Peat et al, 2012). The lack of widespread availability of skilled clinicians and manualised behavioural therapies was thought to further limit the operational feasibility of conducting trials assessing lisdexamfetamine as an adjunctive therapy in BED.

Comment: While this evaluator believes it is possible to conduct clinical trials comparing lisdexamfetamine with psychotherapy such as CBT-Enhanced [4], such trials would not be without problems, including the almost impossible ability to blind the treatment. Issues such as patient preference can also threaten internal validity. [6] The sponsor indicated that the endpoint selection and design of the pivotal studies incorporated feedback from the US Food and Drug Administration.

The sponsor described how a dysfunction in DA and NE signalling (lisdexamfetamine increases the availability of both these neurotransmitters) appears to be associated with binge eating

behaviour, and several lines of scientific evidence (genetic, nonclinical and clinical) suggest that stimulants should be effective for the treatment of BED (Kessler et al, 2016).

As there are currently no medications in Australia approved for the treatment of BED, the sponsor indicated there was a significant unmet medical need in BED for effective and safe treatments. The sponsor indicated a recent analysis demonstrated the cost effectiveness of treatment of BED with lisdexamfetamine, given the benefits of treatment and the resulting increase in Quality Adjusted Life Years (Agh et al, 2016).

In the expert report, it was discussed that although psychiatrists are well trained in diagnosing eating disorders, few are trained in BED focused CBT or other psychotherapies. Some clinical psychologists have this training, but access to these highly specialised psychological services is limited by geography and cost. The authors knew of few clinical psychologists and no psychiatrists who run group treatments for BED.

In terms of pharmacological treatment for BED in Australia, Professors [information redacted] indicated that fluoxetine and topiramate are potentially being used off label, and that the RANZCP guidelines [4], which predate the publication of randomised controlled trials of lisdexamfetamine, refer to the use of topiramate and orlistat in obese patients with BED and consequential medical complications. Lisdexamfetamine is referred to as showing 'favourable results compared with placebo on remission, changes in BMI and binge eating' in the recent NICE guidelines.

For the various psychological, behavioural and pharmacological treatment approaches available, it was conceded that studies of the comparative and long term effectiveness are lacking. It was thought that psychiatrists are well placed to assess patients with BED and develop individual management plans, considering 'treatment availability, costs, adverse effects, patient preference, individual goals and patient specific factors, such as co-morbid depression or eating related obsessions and compulsions' (Brownley et al, 2016). Due to the fact that there are few trained practitioners in psychological therapies, the first line use with guided self-help of lisdexamfetamine as an alternative to an antidepressant in uncomplicated BED, and in BED complicated by obesity, as recently suggested by Professor James Mitchell, was discussed. It was thought by Professors [information redacted] that lisdexamfetamine would have a role as either initial treatment for those patients with uncomplicated BED, particularly if people are on waiting lists for psychological care, or as an adjunct to psychological care where psychotherapy alone cannot lead to a reduction in binge eating, particularly if there was a medical co-morbidity present (such as diabetes mellitus) prompting the need for more active care.

Comment: This evaluator believes that psychiatrists are well placed to consider whether lisdexamfetamine has a role in the treatment of moderate to severe BED for individual patients. Lisdexamfetamine may be appropriate when psychotherapy is unavailable, not-sufficiently effective or otherwise unsuitable. It is considered that the proposed indication does convey that management plans for BED ideally include psychotherapy.

6.5. Is there sufficient evidence to support the long term use of lisdexamfetamine in the management of BED?

The ACM agreed that there was not sufficient evidence to support long term use of lisdexamfetamine in the management of BED.

The sponsor indicated that the long-term efficacy of lisdexamfetamine for the treatment of moderate to severe BED is supported by the CGI-I and EDE-Q results from the 1 year open label Study 345, where improvement in the severity of illness and in the global and core eating disorder psychopathologies did not diminish with time in those who remained in the study. The fact that in the pivotal efficacy studies, the number of binge eating episodes per week declined

from baseline over the first 3 to 5 weeks of treatment and remained stable thereafter, suggested to the sponsor that the 12 week duration of these trials was sufficient to fully characterise the trajectory of treatment response. Maintenance of long term efficacy was further supported by the results of Study 346, in which subjects randomised to continue lisdexamfetamine were 8.7 times less likely to relapse than subjects who were randomised to placebo over 26 weeks. Language proposed in the Dosage and Administration section of the PI directs psychiatrists to assess ongoing treatment response and the risk/benefit of lisdexamfetamine therapy:

> *'In order to minimise exposure to cardiovascular risk in this population; the risk-benefit profile of the drug for the individual patient should be periodically re-evaluated. In clinical studies efficacy was studied for 12 weeks. The benefit of continuing treatment beyond this period should be regularly re-evaluated.'*

As outlined in the expert report, regarding BED, 'comparative effectiveness and long term studies are lacking'.

Comment: It is noted by this evaluator that the clinical trials described in the PI to support the ADHD indication were of no more than 8 weeks duration, with the maintenance of efficacy studies assessing relapse over a 6 week period (following a minimum of 6 months of documented lisdexamfetamine treatment).

Studies 345 and 346, which involved 52 and 38 weeks of active lisdexamfetamine treatment respectively, are thought by this evaluator to support the continued efficacy and safety of lisdexamfetamine in the treatment of moderate to severe BED in those patients who continued with lisdexamfetamine treatment. The clinical evaluator noted that treatment with lisdexamfetamine resulted in weight loss of about 5 kg (5.5% reduction in body weight) over 11 to 12 weeks and 8 kg (8.6% reduction in body weight) over 52 weeks, with the weight loss stabilising by about week 32 of treatment. This evaluator proposes additional language in the Indications (Section 7.1), Precautions (Section 7.2) and Dosage And Administration (Section 7.3) sections of the PI to indicate that a trial of withdrawal of lisdexamfetamine treatment should be undertaken after a period of 12 weeks of active treatment, to minimise exposure to cardiovascular risk. In the setting of long-term treatment, language in the PI directs psychiatrists to periodically assess the benefits and risks of lisdexamfetamine treatment on an ongoing basis. This should ensure that long term lisdexamfetamine treatment for individuals with BED is only undertaken in those patients who relapse upon lisdexamfetamine discontinuation and in whom the benefit-risk balance is considered favourable. The sponsor indicated that there was no evidence of an increased risk of serious cardiovascular events in BED patients being treated with lisdexamfetamine based on the cumulative review of post-marketing cases.

6.6. Should the initiation of and ongoing treatment with lisdexamfetamine for BED be restricted to a group of specialist medical practitioners, and if so which group?

The ACM agreed that should lisdexamfetamine be approved for the treatment of BED, its diagnosis and/or ongoing treatment be restricted to psychiatrists. The sponsor had no further comment in relation to this.

Comment: This evaluator agrees that the initiation of and ongoing treatment with lisdexamfetamine for moderate to severe BED should be restricted to psychiatrists. As the current term in the indication, 'specialists', is open to interpretation, this term has been amended to 'psychiatrists'.

6.7. Can the risk of misdiagnosis of general over eating as BED be appropriately managed and how would this be accomplished?

The ACM agreed with the Delegate that the risk of misdiagnosing BED and potential of abuse of lisdexamfetamine is high. The ACM noted that overeating is common, with obesity and overweight affecting over 50% of the Australian adult population, and that people who are desperate to lose weight may mimic symptoms of BED, potentially placing a high percentage of the population at risk of exposure to lisdexamfetamine as a weight loss agent.

The sponsor suggested that the risk of misdiagnosis of general over eating as BED is unlikely given key differentiating features present in BED but not in general over eating. Psychiatrists have expertise in the accurate diagnosis of BED and in distinguishing patients with BED from patients attempting to obtain a prescription for weight loss (or indeed for other reasons). Obese patients without BED would be treated by other clinicians with other pharmacological therapies and other treatment modalities such as bariatric surgery. The sponsor suggested the availability of these treatments should minimise any incentive to feign BED symptoms.

In the expert report, Professors [information redacted] outline that Australian psychiatrists are well trained in the assessment and diagnosis of eating disorders, with these disorders included amongst the Entrustable Professional Activities of the RANZCP's training program. Psychiatrists are extensively trained in undertaking clinical interviews, which are required for the diagnosis of eating disorders. During clinical interviews the nature and veracity of the presenting symptoms can be explored in-depth, and the presence of subtle psychological symptoms to confirm a diagnosis and factitious presentations can be detected. Obesity in the absence of BED is not core business for psychiatrists; those individuals seeking treatment for weight reduction would not be referred to psychiatrists and would not be able to self-refer.

Comment: The restriction of the indication to psychiatrists, proposed by the ACM and endorsed by this evaluator, should minimise the potential for this medication to be used for weight loss in the absence of BED.

6.8. Are the risks of abuse/misuse including intentionally increasing the dose to increase weight loss, addiction and diversion likely to be adequately managed by the mechanisms proposed by the sponsor?

The ACM indicated that the proposals of the sponsor to manage the risks of abuse/misuse including intentionally increasing the dose to increase weight loss, addiction and diversion were not going to be adequate. The ACM concluded that the evidence provided in the sponsor's submission did not satisfactorily establish the safety and efficacy of lisdexamfetamine capsules. The ACM also noted that the ongoing pharmaco-epidemiology study examining the incidence of major cardiovascular events in new users of lisdexamfetamine was restricted to patients with ADHD. This patient group is less likely to be obese and have pre-existing diagnosed or undiagnosed cardiovascular abnormalities. Thus the patient group most at risk of adverse cardiovascular outcomes from the use of lisdexamfetamine is not included in the current cardiovascular safety study.

The sponsor maintained that the risks associated with lisdexamfetamine therapy can be adequately managed through appropriate labelling, pharmacovigilance surveillance, the stringent control measures that are being applied to the prescribing of stimulants by local state and territory health authorities and by limiting the prescribing of lisdexamfetamine for BED to psychiatrists.

The sponsor suggested that the risks of intentional drug misuse, drug abuse and diversion could be reduced due to information such as warnings (that lisdexamfetamine is not indicated for

weight loss, and that the risk of abuse should be assessed initially and monitored during treatment) and contraindications in the product information, and restricting prescribing to psychiatrists. Off-label use would be monitored through the investigation of regional patterns including prescribing patterns among physicians and usage patterns among patients. Pharmacovigilance processes to monitor these risks were described in detail, and involve the intake of AE reports from all data sources, individual report characterisation and attribution analysis (including medical review) and aggregate case analysis and signal-detection activities. Additional measures to help ensure that the correct patients would receive lisdexamfetamine and use it appropriately include the proposal to implement educational materials for Australian Healthcare professionals reminding specialists to assess patients for the risk of abuse/misuse/diversion (both before and during treatment), the Drug Utilisation Study in Australia, and the stricter controls due to lisdexamfetamine's Schedule 8 status.

In terms of evidence supporting low diversion/misuse risk of lisdexamfetamine, the sponsor suggested that as the majority of subjects (> 97%) receiving lisdexamfetamine were compliant in Studies 208, 343, 344 and 345, misuse, abuse or diversion of lisdexamfetamine did not occur; however, these were highly controlled environments. Although a small but increased risk for substance abuse in individuals with BED was identified in a meta-analysis of published data (Calero-Elvira et al, 2009), post-marketing surveillance since the approval in the US of lisdexamfetamine for treatment of ADHD in 2007 and for BED in 2015 has revealed no increasing trends of lisdexamfetamine non-medical use or diversion compared to other stimulants, and data from the US National Survey on Drug Use and Health (Substance Abuse and Mental Health Services Administration; SAMHSA) indicate that lifetime prescription stimulant nonmedical use and diversion were not impacted by the lisdexamfetamine approvals. Prospective longitudinal studies have shown that stimulant treatment of ADHD, which shares with BED features of impulsivity and dopamine dysregulation, is associated with a reduced incidence of drug misuse and abuse (Shaw et al, 2012; Hammerness et al, 2013; Wilens et al, 2008; Biederman, 2003).

A cumulative search of Australian post-marketing data through to 30 June 2017 (cumulative patient exposure to lisdexamfetamine in Australia to 30 April 2017 was 18,884 patient years) identified 2 cases reporting 4 events of abuse/diversion, only 1 of which was considered serious.

Regarding cardiovascular risk, the sponsor indicated that the pharmaco-epidemiological study will collect some data on patients with a history of eating disorders, as there is some overlap between ADHD and BED, with a cross-sectional study estimating that the prevalence of ADHD in BED is 8.1%, versus 2.6% in the general population. The lisdexamfetamine product information contains contraindications in advanced arteriosclerosis, symptomatic cardiovascular disease including cardiac arrhythmia, ischemic heart disease, and moderate to severe hypertension, warnings for patients with structural heart defects, cardiac abnormalities, cardiomyopathy, arrhythmia, or coronary artery disease, and also states that blood pressure and cardiovascular status should be regularly reviewed. Ischemic cardiac events are monitored as a potential risk in the lisdexamfetamine risk management plan.

A broad search of the cumulative post-marketing data from all patients treated with lisdexamfetamine through to 30 June 2017 identified a total of 17 adverse event reports (11 serious and 6 non-serious) describing potential cardiovascular events in BED patients; global cumulative patient exposure through to 30 April 2017 was 7,740,107 patient years. The majority of these reports were either confounded by concomitant medications or medical history, expected events well-described in the product labelling, or lacking in sufficient detail to assess.

In the expert report, it was reiterated that in order to diagnose BED, psychiatrists will need to conduct in-depth interviews, in which the possibilities of factitious disorder and substance seeking would be explored. Good clinical practice involves developing a diagnostic formulation,

taking into account patients' personal, medical and psychiatric histories, before instituting treatment. Psychiatrists are medical practitioners and able to consider, monitor and manage in collaboration with family doctors and physicians, medical co-morbidities and complications.

Comment: This evaluator believes that the various measures described above would ensure help that the risks involved in the use of lisdexamfetamine are minimised. The proposal by the clinical and this evaluator to recommend the withdrawal of lisdexamfetamine treatment after 12 weeks should act to further reduce these risks.

7. Evaluator's assessment and recommendations

This evaluator agrees with the clinical evaluator's and the ACM's proposal that psychiatrists both initiate and manage lisdexamfetamine therapy in those with moderate to severe BED. The indication should specify 'psychiatrist' rather than 'specialist', a term which is open to interpretation.

Psychiatrists in Australia have ready access to guidelines and other resources which make clear that the first-line treatment for this disorder is psychological. However, there may be clinical situations where psychotherapy is not just unsuccessful or unavailable, but may not be the best first line choice for a particular patient. Psychiatrists consider guidelines, the safety, efficacy and availability of a particular treatment, and factors particular to the patient when formulating individual management plans. This evaluator has amended the wording in the '*need for comprehensive treatment programme*' section of the indication below to reflect that the inclusion of psychological therapy is optimal in the management of patients with BED. This evaluator believes the statement '*When remedial measures including psychotherapy are insufficient, the decision to prescribe stimulant medication will depend upon the physician's assessment of the chronicity and severity of the patient's symptoms*' implies that psychotherapy should be used first line if available and suitable.

This evaluator notes the concerns of the clinical evaluator, the Delegate and the ACM in relation to cardiovascular risk, and believes that the language proposed for inclusion in the Indications and Precautions sections below adequately conveys this risk to the prescriber. Although if approved, lisdexamfetamine would be the only medication indicated for the treatment of BED in Australia, it is believed that psychiatrists would consider all available therapies (psychological, pharmacological and others) when formulating a management plan for each patient, and would consider such issues as medical (including cardiovascular) and psychiatric (including substance use disorder histories) comorbidities and contraindications before selecting lisdexamfetamine. In recent years there has been an increased focus in psychiatry on monitoring patients' medical health, and psychiatrists, as medical practitioners, are well equipped to manage these risks, alone or in conjunction with physicians or general practitioners. The recommendation to withdraw treatment after 12 weeks should act to minimise these risks, as well as those of abuse and diversion out of the clinical setting.

In the treatment of psychiatric disorders, following a good response to a medication, it is standard to consider withdrawal of the medication. For example, after a favourable response in the treatment of a single major depressive episode, antidepressants are generally continued for 6 to 12 months before withdrawal.[7]. This evaluator believes that for lisdexamfetamine, a recommendation should be made to withdraw the medication after a period of 12 weeks, due to the results of the pivotal clinical trials and the maintenance of efficacy study. There may however be some clinical situations in which it may be appropriate to continue lisdexamfetamine treatment for a longer period, or reinstate it for a longer period following withdrawal after the initial 12 weeks of treatment. This evaluator has included statements in the proposed PI entries under Indications and Dosage and Administration to reflect this.

In summary, BED is a relatively recently recognised psychiatric disorder with significant medical and psychological comorbidities. The efficacy of lisdexamfetamine was demonstrated in the pivotal efficacy studies for a period of 12 weeks, and the results of Studies 345 and 346 are considered to be supportive of continued efficacy in those who continued treatment. The safety profile is considered to be consistent with that already known. The RANZCP guidelines for eating disorders[4], which are distributed to all Australian psychiatrists in the Australian and New Zealand Journal of Psychiatry and available on the College's website, indicate that first-line treatment for BED is psychological, and this evaluator believes that the proposed indication reflects this. The risks of abuse, misuse, dependence, or diversion for non-therapeutic uses, and the cardiovascular risks, with or independent of weight loss, are/will be prominently displayed in the PI. Restriction of the prescription of lisdexamfetamine for BED to psychiatrists should ensure that these risks are minimised. This evaluator does believe that lisdexamfetamine can be approved for the treatment of moderate to severe BED in adults, with amendments to the PI under INDICATIONS, PRECAUTIONS and DOSAGE AND ADMINISTRATION, as indicated below.

7.1. Proposed PI entry under INDICATIONS

Binge Eating Disorder (BED)

> *VYVANSE is indicated for the treatment of moderate to severe BED in adults. Treatment should be commenced ~~and managed~~ by a ~~specialist~~ psychiatrist.*
>
> *Need for comprehensive treatment programme: VYVANSE is indicated as ~~an integral~~ part of a total treatment program for BED that ~~may~~ optimally include~~s~~ other measures (nutritional, psychological, and medical) for patients with this ~~syndrome~~ disorder. When remedial measures including psychotherapy are insufficient, the decision to prescribe stimulant medication will depend upon the physician's assessment of the chronicity and severity of the patient's symptoms.*
>
> *Limitation of Use: VYVANSE is not indicated or recommended for weight loss. Use of other sympathomimetic drugs for weight loss has been associated with serious cardiovascular adverse events. The safety and effectiveness of VYVANSE for the treatment of obesity have not been established.*
>
> *Prescribers should consider that serious cardiovascular events have been reported with this class of sympathomimetic drugs. The BED clinical trials were not designed to assess cardiovascular safety. While there is an accumulation of safety data with VYVANSE use in the ADHD population, this is of limited relevance regarding cardiovascular risk in the BED population. Given the higher cardiovascular risk associated with obesity, the BED population may be at a higher risk (see PRECAUTIONS, Cardiovascular Disease and DOSAGE AND ADMINISTRATION).*
>
> *Long term use: There is some clinical data to suggest that a significant proportion of patients may not require continued treatment with lisdexamfetamine after an initial 12 weeks of treatment (see CLINICAL TRIALS and DOSAGE AND ADMINISTRATION). The physician who elects to use VYVANSE for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.*

7.2. Proposed PI entries under PRECAUTIONS

7.2.1. Under cardiovascular disease

This evaluator believes the following, which appears in the Canadian Product Monograph, should appear directly under the heading 'Cardiovascular Disease' in the precautions section:

> Serious cardiovascular events have been reported with the use of sympathomimetic drugs, including VYVANSE, in the ADHD population (see below). Given the higher

cardiovascular risk associated with obesity, the BED population may be at a higher risk. Prescribers should consider this potential risk when treating BED (see INDICATIONS and DOSAGE AND ADMINISTRATION).

Limited cardiovascular safety information is provided by the BED clinical trials, given the exclusion of higher risk patients (for example those with diabetes, moderate to severe hypertension and cardiovascular disease, and older than 55 years of age) combined with limited patient numbers and limited treatment duration.

As VYVANSE was not developed to the regulatory standard of a weight-loss drug, and is not indicated for weight loss, a post-approval cardiac safety assessment (for example, a dedicated cardiovascular outcome study) is not planned.

7.2.2. Under prescribing and dispensing

This evaluator recommends the following amendments to the statement proposed by the sponsor following the second round CER:

For treatment of BED, in clinical ~~studies~~ trials efficacy was studied for 12 weeks. A trial of withdrawal of treatment after a period of 12 weeks is therefore recommended to minimise cardiovascular risk in this population. The risk-benefit profile of continuing treatment beyond this period should be regularly re-evaluated.

7.2.3. Proposed PI entry under dosage and administration

The following PI entry under dosage and administration, Dosage, Treatment of BED is located in the annotated PI; the evaluator's comments appear in italics:

In order to minimise exposure to cardiovascular risk in this population, *VYVANSE should be prescribed for the shortest duration that is clinically indicated;* ~~the risk-benefit profile of the drug for the individual patient should be periodically re-evaluated~~.

In *the pivotal* clinical ~~studies~~ trials efficacy was studied for 12 weeks, *and there is some clinical data to suggest that a significant proportion of patients may not require continued treatment with lisdexamfetamine after the initial 12 weeks of treatment (see CLINICAL TRIALS, Adults with Binge Eating Disorder (BED), Maintenance of Efficacy Study). A trial of withdrawal of treatment after a period of 12 weeks is therefore recommended. If treatment with VYVANSE extends beyond 12 weeks,* the risk-benefit *profile* of continuing treatment ~~beyond this period~~ should be regularly re-evaluated.

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