



Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Lisdexamfetamine dimesilate

Proprietary Product Name: Vyvanse

Sponsor: Shire Australia Pty Ltd

May 2018

TGA Health Safety
Regulation

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Contents

Common abbreviations	5
I. Introduction to product submission	8
Submission details	8
Product background	9
Regulatory status	10
Product Information	10
II. Registration timeline	10
II. Quality findings	11
III. Nonclinical findings	11
Introduction	11
Pharmacology	12
Pharmacokinetics	13
Toxicology	13
Nonclinical summary and conclusions	15
IV. Clinical findings	17
Introduction	17
Pharmacokinetics	19
Pharmacodynamics	19
Dosage selection for the pivotal studies	19
Efficacy	20
Safety	21
First round benefit-risk assessment	24
First round recommendation regarding authorisation	28
Clinical questions and second round evaluation of clinical data submitted in response to questions	29
Second round benefit-risk assessment	29
Second round recommendation regarding authorisation	30
V. Pharmacovigilance findings	31
Summary	31
VI. Overall conclusion and risk/benefit assessment	34
Quality	34
Nonclinical	34
Clinical	34
Risk management plan	43
Risk-benefit analysis	44

Post ACM response from sponsor _____	54
VII. Clinical evaluation of supplementary information _____	73
Introduction _____	74
Clinical efficacy _____	75
Safety _____	76
Consideration of issues raised by the delegate _____	76
Supplementary clinical evaluator’s assessment and recommendations _____	84
VIII. Overall conclusion and risk/benefit assessment _____	85
Background _____	85
Risk benefit analysis _____	90
Outcome _____	96
Attachment 1. Product Information _____	96
Attachment 2. Extract from the Clinical Evaluation Report _____	97
Attachment 3. Extract from supplementary Clinical Evaluation Report _____	97

Common abbreviations

Abbreviation	Meaning
5-HT	Serotonin, 5-hydroxytryptamine
ACSA	Amphetamine Cessation Symptom Assessment
ADHD	Attention deficit hyperactivity disorder
AE	Adverse event
AEDs	Anti-epileptic drugs
ASA	Australian Specific Annex
BED	Binge eating disorder
BES	Binge eating scale
BMI	Body mass index
bpm	Beats per minute
CANTAB	Cambridge Neuropsychological Test Automated Battery
CGI-I	Clinical Global Impressions – Global Improvement
CGI-S	Clinical Global Impressions – Severity of Illness
CER	Clinical evaluation report
CI	Confidence interval
CNS	Central nervous system
C-SSRS	Columbia-Suicide Severity Rating Scale
CV	Cardiovascular
DA	Dopamine
DBP	Diastolic blood pressure
DLP	Data lock point
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders Fourth Edition
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

Abbreviation	Meaning
DUS	Drug Utilisation Study
ECG	Electrocardiogram
EDE-Q	Eating Disorder Examination-Questionnaire
EQ-5D-5L	EuroQol 5 Dimension 5 Level Questionnaire
ET	Early termination
EU	European Union
FAS	Full analysis set
GABA	Gamma-aminobutyric acid
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HbA1c	Haemoglobin A1c
ICD	International Classification of Diseases
ICH	International Conference on Harmonisation
LS	Least squares
MedDRA	Medical Dictionary for Regulatory Activities
MRHD	Maximum recommended human dose
msec	Millisecond
NE	Norepinephrine
NOAEL	No observed adverse effect level
OROS MPH	Osmotic controlled oral release delivery system methylphenidate
PD	Pharmacodynamics
PK	Pharmacokinetics
PO	Per oral, orally
PRUQ-BE	Patient Resource Utilisation Questionnaire for Binge Eating
RANZCP	Royal Australian and New Zealand College of Psychiatrists
RBBB	Right bundle branch block

Abbreviation	Meaning
RMP	Risk Management Plan
S8	Schedule 8
SAE	Serious adverse event
SAHOS	South Australian Health Omnibus Survey
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SCID-I	Structured Clinical Interview for DSM Axis I Disorders
SD	Standard deviation
SDS	Sheehan Disability Scale
sec	Second
SOC	System Organ Class
SPD489	Lisdexamfetamine (drug development name)
SSRI	Selective serotonin reuptake inhibitor
Study 208	SPD489-208
Study 343	SPD489-343
Study 344	SPD489-344
Study 345	SPD489-345
Study 346	SPD489-346
SUSMP	Standard for the Uniform Scheduling of Medicines and Poisons
TC	Total cholesterol
TEAE	Treatment emergent adverse event
US	United States
Y-BOCS	Yale-Brown Obsessive Compulsive Scale
Y-BOCS-BE	Yale-Brown Obsessive Compulsive Scale Modified for Binge Eating

I. Introduction to product submission

Submission details

<i>Type of submission:</i>	Major variation; new strength and extension of indications
<i>Decision:</i>	Approved
<i>Date of decision:</i>	22 January 2018
<i>Date of entry onto ARTG</i>	24 January 2018
<i>Active ingredient:</i>	Lisdexamfetamine dimesilate
<i>Product name:</i>	Vyvanse
<i>Sponsor's name and address:</i>	Shire Australia Pty Ltd PO Box 6240 North Ryde NSW 2113
<i>Dose form:</i>	Hard capsule
<i>Strengths:</i>	20 mg, 30 mg, 40 mg, 50 mg, 60 mg and 70 mg
<i>Container:</i>	Bottle
<i>Pack size:</i>	30 capsules
<i>Approved therapeutic use:</i>	<p><i>Binge Eating Disorder (BED):</i></p> <p><i>Vyvanse is indicated for the treatment of moderate to severe BED in adults when nonpharmacological treatment is unsuccessful or unavailable. Treatment should be commenced and managed by a psychiatrist.</i></p> <p><i>Need for comprehensive treatment programme:</i></p> <p><i>Vyvanse is indicated as part of a total treatment program for BED that optimally includes other measures (nutritional, psychological, and medical) for patients with this 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.</i></p> <p><i>Limitation of Use:</i></p> <p><i>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.</i></p> <p><i>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</i></p>

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 Sections 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Cardiovascular Disease and 4.2 DOSE AND METHOD OF ADMINISTRATION.

Long term use:

For BED the initial treatment period is 12 weeks. Patients should then be observed to assess whether further treatment with Vyvanse is required. Periodic re-evaluation of the usefulness of Vyvanse for the individual patient should be undertaken. See Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical Trials.

Route of administration: Oral

Dosage: 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. For further details see the Product Information.

ARTG numbers: 199227, 199226, 199228, 284020, 284021, 284019

Product background

This AusPAR describes the application by Shire Australia Pty Ltd (the sponsor) to register Vyvanse, lisdexamfetamine dimesilate 20 mg, 30 mg, 40 mg, 50 mg, 60 mg and 70 mg capsules for the following indication:

Vyvanse is indicated for the treatment of BED in adults.

Lisdexamfetamine was first approved in 2013 for treatment of attention deficit hyperactivity disorder (ADHD). Lisdexamfetamine is rapidly absorbed from the gastrointestinal tract and hydrolysed primarily to dexamphetamine, which is responsible for the drug's activity. It is thought to act by blocking the reuptake of noradrenaline and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space.

Binge eating disorder (BED) is defined according to Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5) as recurring episodes of eating significantly more food in a short period of time (for example 2 hours) than most people would eat under similar circumstances, with episodes marked by feelings of lack of control. The disorder is associated with marked distress and occurs on average at least once a week over 3 months. The condition also tends to have a long term remitting and relapsing course. Unlike those with bulimia nervosa or anorexia nervosa, people with BED will not regularly try to make up for the eating with compensatory behaviours such as vomiting or excessive exercise. This results in people with BED often being overweight or obese.

Psychotherapy is the current recommended first-line treatment. There are no medicines approved for treatment of BED in Australia. The sponsor reported that selective serotonin reuptake inhibitors (SSRIs), anti-epileptic drugs (AEDs) and ADHD medicines have been used in the treatment of BED.

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 22 July 2013 for:

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 patients 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 patients 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.'

At the time the TGA considered this application, a similar application (for the BED indication) had been approved in (Canada: approved 30 September 2016; USA: approved 30 January 2015).

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at < <https://www.tga.gov.au/product-information-pi> > .

II. Registration timeline

Table 1: Registration timeline for Submission PM-2016-01092-1-1

Description	Date
Submission dossier accepted and 1st round evaluation commenced	30 June 2016
First round evaluation completed	12 December 2016
Sponsor provides responses on questions raised in the First round evaluation	14 February 2017
Second round evaluation completed	20 March 2017
Delegate's overall risk-benefit assessment and request for Advisory Committee advice (ACM 3)	14 April 2017
Sponsor's pre-Advisory Committee meeting response	11 May 2017

Description	Date
Advisory Committee meeting (ACM 3)	2 June 2017
Sponsor's response to ACM resolution	9 August 2017
Supplementary clinical evaluation	30 October 2017
Delegate's overall risk-benefit assessment and request for Advisory Committee advice (ACM 6)	30 October 2017
Sponsor's pre-Advisory Committee meeting response	7 November 2017
Advisory Committee meeting (ACM 6)	30 November - 1 December 2017
Registration decision	22 January 2018
Entry onto ARTG	24 January 2018
Number of TGA working days from submission dossier acceptance to registration decision*	242

* Statutory timeframe 255 working days.

II. Quality findings

There was no requirement for a quality evaluation in a submission of this type.

III. Nonclinical findings

Introduction

Shire Australia Pty Limited (the sponsor) has applied to register a new indication for lisdexamfetamine dimesilate (LDX) (Vyvanse). Vyvanse is currently indicated for the treatment of ADHD. The proposed new indication is the treatment of BED in adults. The proposed dosing regimen for BED is oral administration of 30 mg once daily, to be adjusted in increments of 20 mg at about weekly intervals to achieve the recommended target dose of 50 or 70 mg/day (70 mg/day is the maximum recommended human dose (MRHD)). There is no specific duration of treatment recommended.

General comments

Amphetamine has been used clinically to treat a variety of conditions since the 1930s. There is a substantial amount of existing information relating to its pharmacology, pharmacokinetics and toxicology.

The nonclinical dossier of this application comprised nine new nonclinical studies on pharmacology (rat model) as it relates to BED and two repeat dose toxicity studies (in Beagle dog). Only these new studies were evaluated in this report. Only one repeat dose toxicity study was Good Laboratory Practice (GLP) compliant, and it was terminated early due to excess toxicity.

Pharmacology

Primary pharmacology

Nine *in vivo* pharmacology studies (8 studies and 1 which did not utilise LDX) were submitted in support of the BED indication. All nine studies were undertaken in the rat model (Wistar). The studies investigated the development of BED behaviour in rats, the effects of LDX on these BED behaviours, and postulated mechanisms of action for the triggering and treatment of BED.

It is noted that several of the mechanistic pharmacology studies included direct intracerebral catheterisation/injection of agonists or antagonists for the monitoring of neurotransmitter activity. This is a limitation to the extrapolation of study findings given the potential effect of such a profound surgical procedure. Irrespective of this, the studies did contain appropriate control groups where deemed necessary.

In vitro

No studies were provided.

In vivo

The efficacy of LDX in moderating BED was assessed in rat neurobehavioural models. The main objectives of the studies involved investigating the potential for LDX to attenuate compulsive, impulsive and perseverative behaviours of rats that had acquired binge eating tendencies.

Doses of LDX in rats ranged from 0 to 1.5 mg/kg per oral (PO). The investigators found that LDX (d-amphetamine) was demonstrated as capable of attenuating bingeing (in this particular study model, on chocolate), with varying degrees of dose response effect on the consumption of normal chow. The studies overall indicated that BED chocolate consumption was reduced with doses of 0.3 mg/kg PO or greater. Effects on normal chow consumption (as reductions during the BED phase and over 24 hours) were varied, but related to and generally occurred at higher doses of LDX (for example > 0.8 mg/kg PO). In most cases, water intake and bodyweight (over the test period) were not affected. Thus, there was some evidence that in this animal model, an optimal dose of LDX could preferentially reduce BED chocolate consumption whilst maintaining regular food consumption.

The mechanism of action of LDX in attenuating BED has not been conclusively elucidated from this series of experiments. There was evidence from the rat studies that BED could reduce the number of dopamine D₁ receptors and increase the number of μ -opioid receptors in the striatum, and increase hypothalamic dopamine and serotonin (5-HT) turnover, while LDX could increase dopamine efflux in the dorsal striatum and nucleus accumbens. The reduction in binge eating by LDX could be attenuated by prazosin, suggesting involvement of noradrenaline via central α_1 -adrenoceptors. The findings also suggest a role for altered gamma-aminobutyric acid (GABA) neurotransmission in the frontal cortex and nucleus accumbens in mediating impulsive behaviours characteristic of BED.

These types of neuropharmacological experiments can be difficult to design and interpret, especially when investigating potential dysfunctions in linked neurotransmitter roles involved in the regulation of behaviour such as appetite, satiety, motivation, reward, liking, wanting and impulsivity (as characteristic of BED). The nonclinical data offer some support for the use of LDX for BED, although clearly, the outcome of the clinical assessment will be paramount.

From these pharmacology studies, the investigators conclude that the absence of any new safety/adverse outcome data, in addition to the known clinical data from the original

ADHD registration application (Submission PM-2012-01494-3-1), support the safe use of LDX in the treatment of BED.

Secondary pharmacodynamics and safety pharmacology

There were no new secondary pharmacodynamics or safety pharmacology studies submitted.

Pharmacokinetics

There were no new pharmacokinetic studies submitted.

Pharmacokinetic drug interactions

There were no new drug interaction studies submitted.

Toxicology

Acute toxicity

There were no new acute toxicity studies submitted.

Repeat-dose toxicity

Two studies investigating the toxicity of repeated doses of LDX were submitted; a 4 week and a 39 week study in Beagle dogs. The 39 week study was stopped on Day 23 due to excess toxicity seen in the higher dose groups.

In the 4 week study, Beagle dogs were administered 0, 3, 6, or 8 mg/kg/d PO. There were no unscheduled deaths, and all treatment groups in the study exhibited clinical signs consistent with the known pharmacological response of amphetamines in dogs. Clinical signs were observed each day of the test period and resolved overnight. Effects were dose related with the severity and duration increased at the higher doses of 6 and 8 mg/kg/day. No, no observed adverse effect level (NOAEL) was determined from this study as clinical signs were observed at all doses.

In the 39 week study, Beagle dogs were initially administered 0, 1, 3, or 10 mg/kg/d PO. Adverse effects seen at 10 mg/kg/day and included exhaustion, dehydration, and decreased food consumption, lasting up to 16 h; these animals were given a 'dose holiday' and reduced to 5 mg/kg/d. However, 5 mg/kg/d also caused similar effects for up to 12 h. In addition to stereotypic amphetamine-type effects seen in the 3 and 1 mg/kg/d groups, the study was terminated on Day 23. No NOAEL was determined from this study as clinical signs were observed at all doses.

The investigators proposed these observations to be due to an apparent difference in sensitivity between the animals in this study compared to animals receiving similar doses in previous studies with LDX. It is noted that similar clinical observations were seen in the higher doses of the 4 week study, but of relatively less severity and duration. Of particular significance in the new studies is that that no unexpected signs of toxicity were observed; all observed effects are consistent with those of amphetamine. In effect, the two new dog repeat dose toxicity studies therefore provide no new information.

Given NOAEL was identified in the new toxicology studies, there is some reliance on the existing clinical data package for the approved ADHD indication, which is of equivalent dosing and unspecified duration. The existing package for ADHD was reviewed for repeat dose toxicity in the dog model. Findings from the ADHD submission included:

- Beagle dogs were administered oral doses from 3 to 12 mg/kg bodyweight (bw)/d for 4 weeks (Study D01366M-SPD489), from 2 to 12 mg/kg bw/d for 26 weeks (Study 01363M-SPD489), and at doses of 3 and 10 mg/kg/day PO in a 2 week study in juvenile Beagle dogs (Study D01363M-SPD489). There were signs of overstimulation at all doses, and no NOAEL was determined.
- Maximum doses in repeat dose toxicity studies were limited by body weight losses/reductions in body weight gains and clinical signs. Clinical signs were considered to reflect exaggerated pharmacological effects and included increased activity and behavioural changes. No target organ toxicity was revealed.
- There were no treatment-related mortalities in dogs. Clinical signs were observed in almost all toxicity studies, in all species tested and in both sexes. Clinical signs were broadly consistent with effects that could be ascribed to d-amphetamine and are considered exaggerated pharmacological effects. The main clinical sign, increased activity, was seen in all dose groups in all repeat dose toxicity studies in both rats and dogs.
- Decreased body weight gain, and at higher doses, body weight loss, were consistent findings in both sexes, being observed in all repeat dose studies, and were dose limiting. Decreased body weight gain was associated with reductions in food consumption in some, but not all, instances, with hyperactivity likely contributing. In the 4 week dog study, they were observed at the 6 mg/kg/day (exposure ratio 0.9 and 7 for d-amphetamine and LDX, respectively). The anorectic effect of amphetamines is well known clinically.

The clinical signs observed in the two new dog studies are therefore consistent with those of the initial submission for the ADHD indication, at similar doses and study duration. As there were no nonclinical objections to registration for the ADHD indication, it is concluded that there are no nonclinical objections to extension to BED (notwithstanding clinical evaluation of the human BED data package).

Major toxicities

There were no new, previously unidentified toxicity findings from the updated rat and dog data. All observed toxicities are previously seen and/or expected from the pharmacological activity of an amphetamine type substance.

Genotoxicity

There were no new genotoxicity studies submitted.

Carcinogenicity

There were no new carcinogenicity studies submitted.

Reproductive toxicity

There were no new reproductive toxicity studies submitted.

Pregnancy classification

There are no changes proposed for the pregnancy classification of lisdexamfetamine as it relates to BED.

Local tolerance

Local tolerance studies are not relevant to lisdexamfetamine as it is administered in oral formulations.

Immunotoxicity

There were no new immunotoxicity studies submitted.

Phototoxicity

There were no new phototoxicity studies submitted.

Metabolites

There were no new metabolite studies submitted.

Impurities

There were no new studies submitted relating to impurities associated with lisdexamfetamine (as Vyvanse).

Paediatric use

There were no new nonclinical studies submitted that extend to paediatric use.

Comments on the nonclinical safety specification of the risk management plan

The Nonclinical part of the Safety Specification in the Risk Management Plan (RMP) contains no nonclinical information relevant to this extension of indications.

Nonclinical summary and conclusions**Summary**

- Amphetamine has been used clinically to treat a variety of conditions since the 1930s. There is a substantial amount of existing information relating to its pharmacology, pharmacokinetics and toxicology. The nonclinical component of this application comprised 9 new nonclinical studies on pharmacology (rat model) as it relates to BED and 2 repeat dose toxicity studies (in Beagle dog; 4 week and 39 week repeat dose).
- Nine in vivo pharmacology studies, undertaken in the rat model, were submitted in support of the BED indication. The studies investigated the development of BED behaviour in rats, the effects of LDX on these behaviours, and postulated mechanisms of action for the triggering and treatment of BED. The main objectives involved investigating the potential for LDX to attenuate compulsive, impulsive and perseverative behaviours of rats with acquired binge eating tendencies, with a dose range of 0 to 1.5 mg/kg PO. The studies found LDX capable of attenuating bingeing (in this particular model, on chocolate), with varying degrees of dose response effect on the consumption of normal chow. The studies overall indicated that BED chocolate consumption was reduced with doses of ≥ 0.3 mg/kg PO. Effects on normal chow consumption were varied, but related to and generally occurring at higher doses of LDX (for example, > 0.8 mg/kg PO).
- The mechanism of action of LDX in attenuating BED was not conclusively demonstrated. In the rat BED model, there was evidence that BED was linked with a decrease central dopamine D_1 and an increase μ -opioid receptors, and an increase dopamine and 5-HT turnover. LDX may attenuate BED via actions in dopamine, noradrenaline, and GABA pathways in various brain regions.

- Two studies investigated the toxicity of repeated doses of LDX; a 4 week and a 39 week study (Beagle dogs). In the 4 week study, animals were administered 3, 6, or 8 mg/kg/d PO. There were no unscheduled deaths, and all treatment groups in the study exhibited clinical signs consistent with the known pharmacological effects of amphetamines in dogs. Effects were dose related with the severity and duration increased at the higher doses. In the 39 week study, animals were initially administered 1, 3, or 10 mg/kg/d PO. Adverse effects at 10 mg/kg/day included exhaustion, dehydration, and reduced food consumption, lasting up to 16 h. A reduced dose of 5 mg/kg/d also caused similar effects for up to 12 h, and as stereotypic amphetamine type symptoms were also seen in the 3 and 1 mg/kg/d groups, the study was terminated (Day 23). No NOAEL was determined from either study as clinical signs were observed at all doses.
- There is some reliance on the existing toxicology data for the approved ADHD indication, which is of equivalent dosing and unspecified duration. From the nonclinical evaluation for the ADHD indication, it was reported that signs of overstimulation were observed in all repeat dose studies (at all doses); no NOAEL was determined in these studies either. Maximum doses in the repeat dose toxicity studies were limited by body weight losses/reductions in body weight gains and clinical signs (including increased activity and behavioural changes), and no target organ toxicity was revealed. The clinical signs observed in the two new dog studies are therefore consistent with those of the initial submission for the ADHD indication, at similar doses and study duration. As there were no nonclinical objections to registration for the ADHD indication, it remains that there are no nonclinical objections to extension to BED (notwithstanding clinical evaluation of the human BED data package).

Conclusions and recommendation

- The mechanism of action of LDX in attenuating BED has not been fully elucidated. In the rat BED model, BED was associated with changes in the number of central dopamine D₁ and μ -opioid receptors, and in dopamine and 5-HT turnover, and the effect of LDX in BED may involve dopamine, noradrenaline, and GABA in particular brain regions. There was also some evidence that LDX could reduce BED chocolate consumption while maintaining regular food consumption.
- No NOAEL was determined in either repeat dose study as clinical signs were observed at all doses. There were no unscheduled deaths, and all treatment groups exhibited clinical signs consistent with the known pharmacological effects of amphetamines in dogs, which were dose related and with severity and duration increased at the higher doses. The 39 week study was terminated prematurely due to excess toxicity.
- This submission relies on the existing toxicology data for the approved ADHD indication, in which it was reported that signs of overstimulation were observed in all repeat dose studies at all doses (no NOAEL determined). The clinical signs observed in the two new dog studies are therefore consistent with those of the initial submission for the ADHD indication (in terms of dose range and study duration).
- As with the submission to register LDX for ADHD, there are no nonclinical objections to the extension of indications to BED.
- There are no recommended changes to the draft PI document from a nonclinical perspective.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Information on the condition being treated

Binge eating disorder (BED) is defined according to the DSM-5 as recurring episodes of eating significantly more food in a short period of time (for example 2 hours) than most people would eat under similar circumstances, with episodes marked by feelings of lack of control. The disorder is associated with marked distress and occurs on average at least once a week over 3 months. The condition also tends to have a long term remitting and relapsing course. Unlike those with bulimia nervosa or anorexia nervosa, people with BED will not regularly try to make up for the eating with compensatory behaviours such as vomiting or excessive exercise. This results in people with BED often being overweight or obese.

BED was approved for inclusion in the DSM-5 as its own category of eating disorder, while in Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV) it was not a recognised disorder (though it was described in the appendix) and was diagnosable using the category of 'Eating disorder not otherwise specified'.

There are notable differences between BED and the common problem of overeating. BED is much less common, more severe and is associated with psychological problems. The long term effects of BED relate to the comorbidities of excess weight (for example hypertension, coronary artery disease, diabetes, arthritis, and obstructive sleep apnoea) as well as psychiatric comorbidities such as depression, anxiety and substance abuse.

Current treatment options

The current treatment goals are multifaceted and aimed at reducing the following: binge eating episodes; excessive weight if overweight; excessive concerns with body image; and psychiatric comorbidity. The standard first line therapy is psychotherapy (such as cognitive behaviour therapy) and a meta-analysis of 6 randomised trials reported a large positive effect of this therapy.¹ Other therapy options are self-help treatment and behavioural weight loss treatment and these are often combined with psychotherapy.

Pharmacotherapy is generally recommended only as second line therapy as it is regarded as less effective than psychotherapy. There is, however, a lack of head to head comparisons of pharmacotherapy and psychotherapy and there may be a place for pharmacotherapy in patients who decline, or do not have access to, psychotherapy.

Medications which have been assessed in the treatment of BED include selective serotonin reuptake inhibitors (SSRIs) (for example citalopram, fluoxetine, sertraline and fluvoxamine), antiepileptics (for example topiramate and zonisamide) and medications used for ADHD (for example atomoxetine and the proposed lisdexamfetamine).

In Australia, there are currently no products approved for the treatment of BED. Lisdexamfetamine was approved by the FDA in 2015 for treatment of moderate to severe BED and is the only medication approved for treatment of the condition.

¹ Vocks S et al., (2010) Meta-analysis of effectiveness of psychological and pharmacological treatments for binge eating disorder. *Int J Eat Disord.* 2010; 43: 205.

Clinical rationale

The sponsor states in the clinical overview that:

'Lisdexamfetamine (SPD489) is thought to treat the symptoms of ADHD through a mechanism of action that is presumed to be related to the blockade of dopamine and norepinephrine 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 dopamine (DA) and/or norepinephrine (NE) neurotransmission may reduce pathological overeating (for example binge eating) in both animals and humans.'

It then goes on to state that:

'Stimulants such as SPD489 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 one placebo controlled study of BED in adults'.²

Guidance

There was no pre-submission advice provided to the sponsor by the TGA.

Contents of the clinical dossier

The dossier contained five clinical studies relating to the clinical development of lisdexamfetamine (drug development name: SPD489) in BED, as well as four clinical studies in ADHD. No new pharmacology data were submitted.

The five studies for the BED indication were:

- Study SPD489-208 (208); a Phase II, dose finding study.
- Studies SPD489-343 (343) and SPD489-344 (344); both Phase III, efficacy and safety studies with the same design.
- Study SPD489-345 (345); an open label, 52 week extension study.
- Study SPD489-346 (346); a randomised, controlled withdrawal study.

There were four clinical studies in ADHD:

- Study SPD489-325 (325); an evaluation of a morning dose of SPD489.
- Study SPD489-404 (404); an open label, 2 year safety study of SPD489 in children and adolescents 6 to 17 years.
- Study SPD489-405 (405); a comparison with osmotic controlled release oral delivery system methylphenidate (OROS-MPH) in adolescents (dose optimised).
- Study SPD489-406; a comparison with OROS-MPH in adolescents (forced titration).

Studies SPD489-208, 343, 344, 345, and 346 will be hereafter referred to as Studies 208, 343, 344, 345, and 346.

A Clinical Overview for BED; a Clinical Overview for the ADHD additional data; a Summary of Clinical Efficacy in BED; a Summary of Clinical Safety in BED; a list of literature references; and study synopses were also included.

² McElroy, et al. (2007) Atomoxetine in the treatment of binge eating disorder: a randomized placebo controlled trial. *J Clin Psychiatry*. 2007; 68: 390-398.

Paediatric data

All studies in BED were conducted in adults 18 to 55 years of age.

The included studies in ADHD were conducted in children aged 6 to 17 years.

Good clinical practice

The sponsor stated in the clinical overviews that all studies were conducted in accordance with International Conference on Harmonisation (ICH) and Good Clinical Practice (GCP) guidelines, as well as local regulatory and ethical requirements.

Pharmacokinetics**Studies providing pharmacokinetic data**

There were no pharmacokinetic (PK) studies submitted in the dossier.

For details of the evaluator's PK summary, please see Attachment 2.

Evaluator's conclusions on pharmacokinetics

No new PK data were submitted.

There is reduced amphetamine clearance in patients with severe renal impairment.

Drug interactions due to effects on hepatic enzymes are not anticipated.

The PK in adults has been established and the data are sufficient for application to the BED population.

Pharmacodynamics**Studies providing pharmacodynamic data**

There were no pharmacodynamic studies submitted in the dossier.

Evaluator's conclusions on pharmacodynamics

There are no new pharmacodynamic data.

The pharmacodynamic mechanism leading to the effect of lisdexamfetamine (SPD489) on BED is uncertain.

Dosage selection for the pivotal studies

The dossier included one dose finding study which assessed doses of 30 mg, 50 mg and 70 mg once daily. The higher doses of 50 mg and 70 mg demonstrated a significant difference to placebo on the chosen endpoint of log transformed number of binge days per week. There was no significant improvement over placebo for 30 mg dose. There was a suggestion of a dose response however no interdose comparisons were undertaken. The sponsor chose 30 mg as a titration dose for the Phase III studies with 50 mg and 70 mg as the target doses. This is acceptable and is the same as the approved dosage range for ADHD.

Efficacy

Studies providing efficacy data

There were 5 clinical studies in the dossier relating to the BED indication. Studies 343 and 344 were pivotal, Phase III, efficacy and safety studies and had an identical design. Study 208 was a Phase II dose finding study. These three studies had treatment durations of 11 to 12 weeks. Study 345 was a one year safety and tolerability extension study for subjects who had completed Studies 343, 344 or 208. There were minimal efficacy data in this study. Study 346 was a randomised, controlled withdrawal study and provided data on efficacy maintenance and relapse risk.

For full details of the evaluation of efficacy please see Attachment 2.

Evaluator's conclusions on efficacy (BED)

There were five clinical studies submitted with efficacy data to support the BED indication and the two pivotal trials were moderate in size and included 773 subjects.

The population assessed were those with moderate to severe BED (on average 4 to 5 binge days per week) and this needs to be reflected in the indication which currently covers all BED patients.

Only adults 18 to 55 years were included in the development and this also should be reflected in labelling.

The clinical trial population were largely obese, White females in the US and the sponsor is to comment on the applicability of this to the Australian population.

The study population were on the whole naïve to any prior treatment for their BED. Given psychotherapy is the recommended initial therapy for BED, an assessment of efficacy in subjects who had failed psychotherapy would have been useful.

The primary efficacy endpoint was based on binge days rather than binge episodes and this is sensible as it could be difficult discerning the end of a binge episode and the start of another episode.

Treatment with lisdexamfetamine for 12 weeks was found to be superior to placebo in both pivotal efficacy studies with an improvement over placebo of approximately 1.5 binge days per week (95% confidence interval (CI): -1.8,-1.3).

Subjects with BED did have a notable placebo response with a reduction of about 2.4 binge days per week.

Efficacy data were robust and were supported by sensitivity and secondary endpoint analyses.

The most clinically relevant data were the response rates, and the 4 week cessation rate was notably higher with lisdexamfetamine than placebo (36 to 40% versus 13 to 14%).

Lisdexamfetamine resulted in an improvement on Clinical Global Impressions – Global Improvement (CGI-I) as well as a reduction in bodyweight of 5 to 6% over 12 weeks (which did not occur on placebo despite a reduction in binge eating days).

Given the weight reduction in the lisdexamfetamine group, it is possible that the effect on BED is mediated through its appetite suppression activity.

There were several issues at sites relating to GCP and other concerns; however inclusion or exclusion of subjects from these sites produced similar results.

Efficacy was maintained over the 26 week randomised withdrawal period in those who were initial treatment responders and there was a significantly lower relapse rate in those

continuing on lisdexamfetamine (4%, versus 32% for the placebo group). Nevertheless, the majority of subjects who responded to lisdexamfetamine and then ceased active treatment after 12 weeks (placebo group) did not relapse (68%). This suggests that 12 weeks may be sufficient treatment duration for the majority of patients.

Subgroups using combined data from Studies 343 and 344 found consistent effects across the groups apart from in non-US subjects where numbers were low.

The dose of 30 mg per day was not efficacious and should only be used for dose titration in first week of treatment.

Open label data were provided for up to one year duration and while the rate of subjects who remain in the improved CGI category was high (90%), only about 60% of subjects completed the one year of therapy. The evaluator concludes that long term efficacy remains to be fully established and that there are only clear efficacy data for treatment up to 12 weeks duration.

The clinical evaluator also made conclusion on other efficacy studies in ADHD, however as these were not directly related to the new indication this has not been included in the AusPAR. Please see Attachment 2 for details.

Safety

Studies providing safety data

Pivotal and/or main efficacy studies

For the BED indication, the pivotal studies were Studies 343 and 344. Treatment duration was 12 weeks. Safety data in these studies included: adverse events (AE) and serious adverse events (SAEs); vital signs (blood pressure using an automated cuff); waist circumference; weight; physical examination; clinical laboratory measurements (biochemistry, haematology, urinalysis, urine drug screens, pregnancy tests); electrocardiograms (ECGs) with central reading; Columbia Suicide Severity Rating Scale (C-SSRS);³ and Amphetamine Cessation Symptom Assessment (ACSA).

Other studies

The safety data listed above (apart from the ACSA) were also collected in the short term Phase II Study 208, the placebo controlled, randomised withdrawal Study 346 and the 52 week open label extension Study 345. The ACSA was also collected in Study SPD489-346.

Safety analysis was conducted on randomised or enrolled subjects who had received at least one dose of study medication and who had a post-baseline safety assessment. Safety data from the three short term, placebo controlled studies (Studies 208, 343 and 344) were pooled into the integrated safety database. There was also a safety pool of all five BED studies.

Of the four studies in ADHD, safety data from the new Studies 404, 405 and 406 were evaluated as some changes in relation to ADHD safety have been proposed for the PI. In the Clinical Overview, data from the ADHD Integrated Safety Database was presented due to the inclusion of data from the three new studies.

³ The C-SSRS is semi-structured questionnaire administered by a clinician trained by the sponsor or designee. It assesses suicidal ideation and behaviour.

Patient exposure

In the three short term placebo controlled studies (safety analysis set), there were 434 subjects exposed to placebo and 568 to lisdexamfetamine (all doses) with 502 exposed to doses of 50 to 70 mg per day (see Table 10, Attachment 2). The mean duration of exposure was 73.1 and 73.7 days in the lisdexamfetamine and placebo groups, respectively. In Study 208, the treatment duration was 11 weeks while it was 12 weeks in Studies 343 and 344. The total person-time of exposure to lisdexamfetamine was 41,652 days.

Overall, in the clinical development program for BED there were 1,244 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 and a total person-time exposure of 263,996 days (see Table 11, Attachment 2).

Safety issues with the potential for major regulatory impact

For the full evaluation of safety information please see Attachment 2.

Post marketing data

It was reported that, as of 31 January 2015, the total cumulative exposure to lisdexamfetamine was 5.49 million person years for the treatment of ADHD. The Summary of Clinical Safety did not contain any further post marketing safety data. No PSURs were included in the dossier.

Evaluator's conclusions on safety***BED***

For the BED indication, which consisted of 5 clinical trials, there were 1,244 subjects exposed to lisdexamfetamine with a mean duration of 212 days at an average daily dose of 57.5 mg. There were 380 subjects with ≥ 361 days of exposure and a total person-time exposure of 263,996 days. In the three short term placebo controlled studies there were 502 subjects exposed to 50 or 70 mg per day with mean duration of 73 days.

Treatment emergent adverse events (TEAE) were frequent (in the short term studies, lisdexamfetamine versus placebo: 82% versus 55%) and were generally treatment related (70.5% versus 33.6%). The most common treatment related events were dry mouth, insomnia, decreased appetite, headache, nausea and irritability.

Events tended to occur early in treatment and there was some evidence of resolution while on treatment.

Severe TEAEs occurred in 5.8% of lisdexamfetamine treated patients compared to 3.4% in the placebo group and were most commonly decreased appetite, dry mouth, headache and insomnia.

There was one death in the BED program in a male subject 9 days after the last study visit. The cause of death was methamphetamine and amphetamine toxicity. While the substance abuse became apparent after his death, it is unclear whether there was any triggering role from the lisdexamfetamine treatment.

There was also a death of a neonate with congenital abnormalities who had been exposed to lisdexamfetamine for 41 days. There were no other congenital abnormalities reported in the other pregnancies in the program. Nonetheless, the sponsor has been asked to comment on pregnancy and fetal outcome data associated with lisdexamfetamine exposure.

While the overall rate of AEs is high, the rate of SAEs was relatively low at 2.3% in the overall population. In the short term studies, the serious adverse event (SAE) rate was slightly higher with lisdexamfetamine than placebo (1.5% versus 0.9%). There were 4 SAEs of cholecystitis (0.4%). The BED population which is typically obese females would be at risk of gall bladder disease, however it is unclear whether there is an association with treatment and this should be monitored. There were also 2 SAEs of syncope (compared to one in the placebo group) both of which led to treatment discontinuation. The sponsor has been asked to comment on these two risks and why they are not included in the PI.

While study discontinuation rates were high (49% of the overall population and 21% in the short term studies), the reported rate of discontinuation due to an AE was lower (4.4% versus 2.1% in the lisdexamfetamine and placebo groups, respectively in the short term studies). The notable events leading to discontinuation were feeling jittery, irritability and syncope.

Laboratory findings on the whole were unremarkable and changes in lipids (total cholesterol (TC) and triglyceride (TG)) were minimal.

Treatment with lisdexamfetamine resulted in weight loss of about 5 kg (5.5% reduction in body weight) over the 11 to 12 weeks and 8 kg (8.6% reduction in body weight) over 52 weeks. The weight loss stabilised by about Week 32 of treatment. Interestingly, despite a reduction in binge eating, there was little weight reduction in placebo treated subjects.

Consistent with what is known, subjects treated with lisdexamfetamine had a small increase in systolic blood pressure (SBP) and diastolic blood pressure (DBP) of 1 to 3 mmHg and an increase in heart rate of 5 to 7 beats per minute (bpm). The ECG findings were not remarkable and the rate of cardiovascular (CV) events was low. While this is encouraging, CV risks may not have been detected due to insufficient treatment duration, inadequate sample size and careful trial population selection.

Psychiatric events were more common with lisdexamfetamine than placebo, although events, typically insomnia, irritability and affect lability, were not serious. Suicidal ideation and behaviour was infrequent and no higher than with placebo.

There was no evidence of treatment abuse in the data supplied however this does not remove the reality of this risk. A quoted report on this could not be located in the dossier and this has been queried.

Treatment withdrawal symptoms, as assessed by the ACSA questionnaire, were not a significant issue and TEAEs of withdrawal syndrome were only reported in 0.2%.

Safety data assessment by subgroups of age, obesity status, gender and race was hampered by low numbers of males and non-Whites although no major signals were evident.

No post marketing data were supplied.

Overall, safety data in subjects with BED were generally consistent with that reported for the ADHD indication and with what is known for stimulants. Data on pregnancy, cholecystitis and syncope need further elucidation. While cardiovascular event risk and risk of treatment abuse were not evident in the clinical program, they still cannot be ruled out.

ADHD

Safety data subjects with ADHD aged 6 to 17 years were included in the dossier. The 2 year extension study included 314 subjects with a mean exposure duration of 555 days and 96 subjects had ≥ 24 months exposure to lisdexamfetamine.

The rate of treatment related TEAEs was high at 73.9% and the most frequent events were decreased appetite (49.4%), weight decreased (18.2%), insomnia (13.1%), initial insomnia (8.9%) and irritability (8.6%). Tic was reported in 5.1%. Most events were mild (35.7%) or moderate (42.4%) in severity, with severe TEAEs occurring in 11.8% of subjects.

The SAE rate in long term study was 8.9% and the most frequent event was syncope (1.9%) which was required to be reported as an SAE. In all syncope cases treatment was continued. There was one treatment related right bundle branch block (RBBB) and T wave inversion in a subject with a subdural haematoma.

Discontinuation rate due to an AE in the long term ADHD study was reasonably frequent at 12.4% and the main reasons were decreased appetite, drug ineffective, irritability, depressed mood, insomnia and tic.

The rate of a positive response on the C-SSRS was 2.2% and there were two (0.6%) suicide attempts. Aggression related AEs were reported in 5.4% of subjects.

An increase in heart rate of about 7 bpm and increase in SBP and DPB of about 3 mmHg were reported.

The concern that lisdexamfetamine could decrease growth was confirmed as the average age and sex matched weight percentile declined from 65% to 48% over the 2 years of the long term study. This risk has been added to the PI.

There was no effect on sexual maturation as measured by Tanner scale. Cambridge Neuropsychological Test Automated Battery (CANTAB) assessment of cognitive safety did not show an adverse impact of treatment although the lack of a control group made interpretation difficult.

Following the inclusion of the three latest ADHD studies in the integrated safety database, the sponsor reported that there has been a change incidence of 13 adverse drug reaction terms. These changes are shown in Table 23, Attachment 2.

It is unclear why tabulated data on the incidence of adverse drug reactions has not been included in the PI for ADHD (nor proposed for BED). This has been queried.

First round benefit-risk assessment

First round assessment of benefits

Table 2, shown below, summarises the assessment of benefits associated with lisdexamfetamine for the given indication at the first round.

Table 2: Assessment of benefits and uncertainties

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.

Indication – Binge Eating Disorder	
Benefits	Strengths and Uncertainties
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 Yale-Brown Obsessive Compulsive Scale Modified for Binge Eating (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 lisdexamfetamine 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 1,244 subjects with 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 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.	TEAEs 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.

First round assessment of risks

Table 3, shown below summarises the assessment of risks associated with lisdexamfetamine for the given indication at the first round.

Table 3: Assessment of risks and uncertainties

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 SAE 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 to 2 mmHg and an increase in heart rate of 5 to 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 to the nature of the drug, it is an evident possibility.
Growth retardation in children with ADHD	The 2 year ADHD study confirmed reduction in growth of children.

First round assessment of benefit-risk balance

The clinical development program for binge eating disorder produced robust efficacy results compared to placebo. The trial populations were required to have BED (DSM-IV-TR diagnosis;⁴ with Clinical Global Impressions – Severity of Illness (CGI-S) score ≥ 4) of at least moderate severity as defined by at least 3 binge days per week in the 2 weeks prior to randomisation. The proposed indication is for ‘adults with BED’. This is not appropriate given the population studied and treatment needs to be limited to those with moderate to severe BED.

The safety of lisdexamfetamine in the BED population was consistent with what is already known for the product and risks have been assessed through to 1 year of treatment. There is a possible risk of cholecystitis, although there are insufficient data to confirm the association. This potential risk should be monitored.

One of the main safety issues is that of the longer term cardiovascular risk. This is a concern given the history of amphetamine based weight loss products. Had the product been developed for weight loss, there would have been a requirement for a cardiovascular outcome study. This requirement was sidestepped due to the development occurring in BED. Lisdexamfetamine results in a small increase in blood pressure together with increase heart rate and the BED population is obese and cardiovascular events are feasible. While no cardiovascular risk was evident in the clinical program, the sample may have been too small, the trial duration too short and the population carefully selected. Given these issues, a number of measures need to be put in place to manage the potential cardiovascular risk. These include avoidance of the product in those with high cardiovascular risk, careful blood pressure and cardiovascular monitoring and treatment of hypertension.

The evaluator has not been shown any convincing argument for the need to continue the treatment long term. In fact, in the withdrawal study the relapse rate in the placebo group was not 100% but only 32% indicating that 68% of subjects did not relapse. While this may partly be a placebo response, there is also the possibility that the initial 12 weeks treatment had a training effect and further treatment may not be necessary.

The presented data provide sufficient evidence of efficacy over 12 weeks treatment. However, the lack of evidence for long-term efficacy and the absence of longer term cardiovascular outcome data, lead the evaluator to recommend that treatment with lisdexamfetamine in BED should be limited to a maximum duration of 12 weeks. As lisdexamfetamine is an amphetamine stimulant, there is a real risk of treatment abuse, dependency and diversion out of the clinical setting. Also, given the positive data on weight loss, there could well be off label use in this indication. There is a widespread issue of overeating and obesity in our community and coupled with this is the ever-present desire for pharmacological solutions. The availability of lisdexamfetamine for binge eating disorder poses a broader issue as it could lead to a perceived normalisation of the use of amphetamines as appetite suppressants. This public health risk is obviously difficult to quantify but deserves consideration.

The recommended first line treatment for BED is psychotherapy; however this was used in less than 3% of the pivotal efficacy population. Unfortunately, there are no efficacy data for patients who have failed psychotherapy and this is a limitation of the clinical development program. Given the risks of lisdexamfetamine treatment to the patient and the community in general, the evaluator believes that the most prudent course of action would be to limit its use to second line therapy and that it is available for first line therapy only if there is no possible access to psychotherapy.

⁴ DSM-IV-TR: Diagnostic and Statistical Manual of Mental Disorders Fourth Edition –Text Revision

Labelling must be very clear that the product not be used for weight loss, and it is recommended the indication includes wording such as that in the US label:

'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 [see Warnings and Precautions].'

There should also be very tight controls on the use of the drug and it is recommended that treatment should only be initiated and managed by specialist psychiatrists. This is similar to ADHD where the PI states that treatment should be commenced by a specialist.

In summary, lisdexamfetamine was found to be an efficacious treatment for BED with a short term safety profile that, despite high adverse reaction rates, appears tolerable. There is an evident clinical place for a product to treat BED as there are no currently approved drug therapies in Australia for the condition and patients may not all have access to recommended psychotherapy. On the other hand, there are numerous serious risks largely due to the nature of this amphetamine product. These risks include off label use for weight loss, abuse, dependency, diversion out of the clinical setting, normalising amphetamine use as an appetite suppressant, lack of firm efficacy data beyond 12 weeks and the absence of longer term cardiovascular outcome data. Given these issues, the evaluator concludes that under the proposed usage the benefit-risk balance is negative.

ADHD data were submitted to support changes to the product information. These new data showed similar efficacy between lisdexamfetamine and osmotic controlled oral release delivery system methylphenidate (OROS MPH). Safety data with treatment up to two years duration showed a reduction in growth which has been covered adequately in the proposed PI changes.

First round recommendation regarding authorisation

It is currently not recommended to authorise Vyvanse in the proposed indication of *'the treatment of BED in adults'*. 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. Consideration should be given to the following recommendations:

- The indication should limit treatment to adults with moderate to severe BED.
- Treatment should be a second line therapy after failed psychotherapy. It is recommended that it is used as first line only in those who do not have access to psychotherapy. The indication should include a warning that the treatment is not for weight loss and also included the risk of serious cardiovascular adverse events associated with sympathomimetic drugs for weight loss.
- Treatment should only be initiated and managed by specialist psychiatrists.
- In the absence of further longer term efficacy, safety and cardiovascular outcome data, treatment duration should be limited to a maximum of 12 weeks.
- Changes to the PI and CMI outlined need to be addressed.
- Questions raised (see Clinical questions, Attachment 2) need to be satisfactorily addressed.

It is recommended that the changes to the PI in relation to the ADHD indication be approved subject to satisfactory responses to the comments.

Clinical questions and second round evaluation of clinical data submitted in response to questions

For details of the questions raised by the evaluator, the sponsor's responses and the evaluation of these responses, please see Attachment 2.

Second round benefit-risk assessment

Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of lisdexamfetamine in the proposed usage are unchanged from those identified in the first round assessment of benefits.

Second round assessment of risks

After consideration of the responses to clinical questions, the risks of lisdexamfetamine in the proposed usage are unchanged from those identified in the first round assessment of risks.

Second round assessment of benefit-risk balance

In response to the first round evaluation, the sponsor has altered the indication. As recommended, the indication now states that treatment should be limited to adults with moderate to severe BED. In addition, warnings that treatment is not for weight loss and the risk of serious cardiovascular events have been added. The need for a comprehensive treatment program has also been added. These are all appropriate changes.

After the first round evaluation, it was recommended that treatment with lisdexamfetamine for BED should be a second line option. This was due to the inherent risks of the product to the patient and the community as well as treatment guideline recommendations. The Royal Australian and New Zealand College of Psychiatrists (RANZCP) clinical practice guidelines for the treatment of eating disorders clearly state that the '*first-line treatment for bulimia nervosa and binge eating disorder in adults is an individual psychological therapy*'.⁵ The evaluator notes that the efficacy data on lisdexamfetamine used as first line therapy from the clinical development program is positive, that head to head comparisons of pharmacotherapy and psychotherapy are lacking, and that the guidelines may have been published prior to the availability of lisdexamfetamine in the US as a treatment for BED. Nonetheless, the recommended prudent course of action is to use the product in those who have had a limited or unsuccessful response to psychotherapy or in those for whom psychotherapy options are not available. In all situations pharmacological treatment should remain just one component of therapy and this has been addressed in the revised indication. It is noted that there are some recommended changes to the proposed wording for this.

After the first round evaluation, it was also recommended to limit treatment duration to 12 weeks. The sponsor however states that treatment duration would be best left to physician discretion. The evaluator maintains, given the lack of longer term efficacy data, the positive findings after 12 weeks treatment, the lack of cardiovascular outcome data and the inherent risks of the amphetamine based product that treatment duration should still be for a maximum of 12 weeks.

⁵ Hay P et al. 2014 Royal Australian and New Zealand College of Psychiatrists Clinical practice guidelines for the treatment of eating disorders. *Australian & New Zealand Journal of Psychiatry*. 2014; 48: 977-1008.

The sponsor has agreed to manage and monitor the risk of off label use for weight loss by having the product available only through specialists, by including label warnings and by including BED in the Drug Utilisation Study. As BED treatment is recommended for a maximum of 12 weeks, it is appropriate for specialists to not only initiate but also manage therapy.

Other changes to the PI and CMI and the clinical questions directed to the sponsor (see Attachment 2) have been satisfactorily addressed. The PI still needs to include the risks of peripheral vasculopathy and syncope and the RMP should monitor cholecystitis, syncope and pregnancy exposure.

As previously stated, there should be tight controls on the availability of the drug.

In summary, there are still two main issues which need to be addressed. Firstly the recommendation that treatment duration should be limited to 12 weeks. Secondly, that lisdexamfetamine use in BED should be only for those patients who have had unsatisfactory response to psychotherapy or who have limited access to psychotherapy. Pharmacological therapy should always be part of an integrated, multipronged treatment strategy. Until these issues are resolved, the evaluator concludes that, under the proposed usage, the benefit-risk balance is negative.

Second round recommendation regarding authorisation

It is not recommended to approve Vyvanse (lisdexamfetamine) for 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.

The reasons for this are as follows:

- 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.
- 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.
- There remain some changes to the PI and CMI which need to be addressed.

Should the sponsor implement the recommended change to the indication regarding second line use, limit the treatment duration to 12 weeks, and satisfactorily address the further comments on the draft PI and CMI then Vyvanse (lisdexamfetamine) could be approved. The proposed modified indication is:

Binge Eating Disorder (BED)

Vyvanse is indicated for the treatment of moderate to severe BED in adults when psychotherapy is unsuccessful or unavailable. Treatment should be commenced and managed by a specialist.

Need for comprehensive treatment programme: Vyvanse is indicated as one 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.

There are no changes to the recommendations relating to the ADHD indication and changes to the PI in relation to this are satisfactory.

V. Pharmacovigilance findings

Summary

- The sponsor has applied to extend the indications of lisdexamfetamine dimesilate (LDX; Vyvanse) to include treatment of BED in adults. Vyvanse is currently approved for the treatment of ADHD in children and adults, with daily oral treatment of 30 to 70 mg (starting dose 30 mg capsule per day, titrated in 20 mg intervals to a maximum recommended dose of 70 mg per day). The current submission seeks to extend the indications to include treatment of BED in adults.
- The most recently evaluated AU-RMP was version 1.0 (dated 14 June 2012; data lock point (DLP) 29 April 2011). AU-RMP version 2.0 was submitted to the TGA on 4 June 2015 which included results from Study SPD489-404 (AU-RMP version 2.0 dated 20 May 2015, DLP 22 April 2015). In support of the extension of indications to include BED, the sponsor has submitted AU-RMP version 3.0 (dated 24 March 2016; DLP 8 October 2015). AU-RMP version 3.1 (dated 7 February 2017; DLP 8 October 2015) was submitted in sponsor's post-first round response (dated 8 February 2017).
- The proposed Summary of Safety Concerns and their associated risk monitoring and mitigation strategies are summarised below in Table 4.

Table 4: Summary of Safety Concerns and their associated risk monitoring and mitigation strategies

Summary of safety concerns		Pharmacovigilance ⁶		Risk Minimisation ⁷	
		Routine	Additional	Routine	Additional
Important identified risks	Cardiomyopathy	ü	ü*	ü	ü
	Increased blood pressure	ü	ü*	ü	ü
	Growth retardation and developmental delay in children and adolescents	ü	-	ü	ü
	Intentional drug misuse, abuse and diversion	ü	-	ü	ü
Important potential risks	Ischaemic cardiac events	ü	ü*	ü	ü
	Sudden death	ü	ü*	ü	ü
	Syncope	ü	ü*	ü	ü
	Cerebrovascular disorders (ischaemic and haemorrhagic stroke)	ü	ü*	ü	ü
Missing information	Safety in pregnant women	ü	-	ü	-
	Off-label use	ü	ü	ü	ü
	Safety in patients with hepatic impairment	ü	-	ü	ü

*From mandated EU Study SPD489-825; the TGA considers this study as relevant additional pharmacovigilance for cardiovascular outcomes.

- There is an ongoing Drug Utilisation Study (DUS) to monitor off label use of lisdexamfetamine; the outcomes of this DUS are to be reportedly annually for 5 years. The first reports have been submitted to the TGA in February 2015 and February 2016. The third year report (version 1.0, dated 26 January 2017) was included in the sponsor's response of 8 February 2017. The sponsor has notified the TGA that the BED indication will be included in the DUS.
- There is an ongoing pharmacovigilance activity mandated in the EU which is comprised of a pharmaco-epidemiology study examining the incidence of major cardiovascular events in new users of lisdexamfetamine for ADHD (final study report expected in 2020).

⁶ Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

⁷ Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.

- There is additional risk minimisation proposed for the use of lisdexamfetamine in the form of web based educational tools for prescribers. The aim of the online educational tools is 'to enable healthcare professionals in the appropriate selection of patients and prescription of LDX for the treatment of patients with ADHD.' The online education also includes a downloadable leaflet for the patients (and carers/guardians). The website is found at <http://www.ldxguide.com/au> and has been active ('approved') since March 2014. A review of the website reveals that it is focused on the ADHD cohort. The sponsor has clarified that the educational tools are for prescribers only. The sponsor has also advised that the BED cohort will be incorporated, and healthcare professionals advised of the amended educational materials.

New and outstanding recommendations in the second round evaluation

The recommendations made in the first round evaluation, along with consideration of the sponsor's response, were summarised (in the second round report).

From the review of the sponsor's response (dated 8 February 2017), there is commitment by the sponsor to provide the TGA with amended educational materials and outcomes from ongoing/planned pharmacovigilance activities.

However, it is considered that some issues remain from the first round evaluation that require further clarification and/or commitment from the sponsor. There also remain issues for final determination by the Delegate:

- *Recommendation 1:* Should the Delegate request the inclusion of cholecystitis and events related to gall bladder disease as safety concerns, the sponsor should nominate pharmacovigilance and risk minimisation and update the RMP/Australian Specific Annex (ASA), PI and CMI accordingly.
- *Recommendation 2:* The sponsor has committed to providing an updated DUS protocol to the TGA that outlines analyses of BED patients. It is recommended that this protocol be provided to the TGA prior to registration of this indication.
- *Recommendation 3:* It appears from the third year DUS report that the sponsor still intends to conclude the DUS in 2018, 5 years following launch of Vyvanse for ADHD. The sponsor should include in the revised DUS protocol a proposal to extend the DUS to monitor use of Vyvanse following approval of the BED indication.
- *Recommendation 4:* It remains from clinical evaluation that a precaution for peripheral vasculopathy should be included in the PI. With the addition of a Precaution in the PI, the Summary of Safety Concerns should be updated to reflect 'peripheral vasculopathy' as an identified safety concern.
- *Recommendation 5:* In addition to revising the current approach to risk minimisation, the sponsor should provide a new proposal for monitoring the effectiveness of the risk minimisation that demonstrates appropriate reach, acceptability and ease of use for prescribers, and important outcomes measured in the DUS such as off label use.

Wording for conditions of registration

Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.

The suggested wording is:

The AU-RMP (version 3.1, dated 7 February 2017, data lock point 8 October 2015), to be revised to the satisfaction of the TGA, must be implemented (see outstanding issues above).

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations from the Delegate's overview for ACM 3 June 2017.

Quality

There was no requirement for a quality evaluation in a submission of this type.

Nonclinical

The nonclinical evaluator noted that amphetamine has been used clinically to treat a variety of conditions since the 1930s. There is a substantial amount of existing information relating to its pharmacology, pharmacokinetics and toxicology. The nonclinical dossier of this application comprised 9 new nonclinical studies on pharmacology (rat model) as it relates to BED and 2 repeat dose toxicity studies (in Beagle dog; 4 week and 39 week repeat dose).

The mechanism of action of lisdexamfetamine in attenuating BED was not conclusively demonstrated. In the rat BED model, there was evidence that BED was linked with a decrease in central dopamine D₁ and an increase in μ -opioid receptors, and an increase dopamine and 5-HT turnover. Lisdexamfetamine may attenuate BED via actions in dopamine, noradrenaline, and GABA pathways in various brain regions.

The nonclinical evaluator noted that there is some reliance on the existing toxicology data for the approved ADHD indication, which is of equivalent dosing and unspecified duration. From the nonclinical evaluation for the ADHD indication, it was reported that signs of overstimulation were observed in all repeat dose studies (at all doses); no NOAEL was determined in these studies. Maximum doses in the repeat dose toxicity studies were limited by body weight losses/reductions in body weight gains and clinical signs (including increased activity and behavioural changes), and no target organ toxicity was revealed. The clinical signs observed in the two new dog studies are therefore consistent with those of the initial submission for the ADHD indication, at similar doses and study duration.

The nonclinical evaluator stated that as there were no nonclinical objections to registration for the ADHD indication, it remains that there are no nonclinical objections to extension to BED (notwithstanding clinical evaluation of the human BED data package).

Clinical

Pharmacology

No pharmacology studies to support the proposed extension of indications were submitted. The sponsor opined that stimulants such as dexamfetamine might relieve binge eating in BED by stabilising a deficient dopamine reward system via blockade of dopamine reuptake. Noradrenaline blockade also appears to be a potentially effective therapy for eating disorders.

Efficacy

Five studies assessed efficacy and/ or safety of lisdexamfetamine in the treatment of BED. Of these, Studies 343 and 344 were pivotal and had the same design. Study 208 was a Phase II dose finding study; Study 345 was a one year safety and tolerability extension study for subjects who had completed Studies 208, 343 or 344. Study 346 was a randomised, withdrawal study and provided data on efficacy maintenance and relapse risk.

Studies 343 and 344

Studies 343 and 344 were multicentre, randomised, placebo controlled, double blind, parallel group, dose optimisation studies which evaluated the efficacy and safety of lisdexamfetamine in adults (18 to 55 years) with moderate to severe BED. Study centres were located in the EU and the USA.

These studies consisted of a 2 to 4 week screening period, a 4 week dose optimisation period, an 8 week dose maintenance period, and a follow up visit 1 week after the last visit. The 4 week dose optimisation period and the 8 week dose maintenance period comprised the 12 week, double blind treatment phase of the studies.

The primary objective was to demonstrate efficacy compared to placebo at Visit 8 (at 11 to 12 weeks of treatment) as measured by the number of binge eating days per week. The primary efficacy endpoint was the change from Baseline to Visit 8 in the number of binge eating days per week (Week 11 to 12). Baseline was the weekly average of the number of binge days per week for the 14 days prior to the baseline visit (Visit 0).

Key secondary endpoints were:

- CGI-I dichotomised (improved versus not improved).
- 4 week cessation from binge eating behaviour during the 28 days preceding Visit 8/Early termination (ET).
- Percent change from Baseline in body weight.
- Change from baseline in the Yale-Brown Obsessive Compulsive Scale Binge Eating (Y-BOCS-BE) modified version which measures obsessiveness and compulsiveness of binge eating. The Y-BOCS-BE measures the obsession of binge eating thoughts and compulsiveness of binge eating behaviours. The scale is a clinician rated, 10 item scale, with each item rated from 0 (no symptoms) to 4 (extreme symptoms). The scale includes questions about the amount of time the subject spends on obsessions, how much impairment or distress they experience, and how much resistance and control they have over these thoughts. As well, the same types of questions are asked about compulsions. A total score of 0 to 7 is subclinical; 8 to 15 is mild; 16 to 23 is moderate; 24 to 31 is severe; and 32 to 40 is extreme.
- Change from Baseline in TG.

In order to maintain study wide Type I error control, the key secondary endpoints were tested in a hierarchical testing procedure in the order shown above. There was no adjustment for multiplicity for other efficacy endpoints.

Other assessments included:

- total cholesterol;
- Haemoglobin A1c (HbA1c);
- Eating Inventory which is a self-reported 51 item questionnaire which covers cognitive restraint, disinhibition and hunger;

- Binge Eating Scale (BES) which is a 16 item self-reported questionnaire assessing control over eating behaviour;
- Frontal Systems Behaviour Scale (self-rated scale);
- Quality of life (EuroQol 5 dimension 5 level questionnaire (EQ-5D-5L));
- Functional impairment using the Sheehan Disability Scale (SDS); and
- Health outcomes patient resource utilisation questionnaire for binge eating (PRUQ-BED) a system that measures 5 dimensions of health, including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is represented by a single item with 5 levels of responses. Days lost and Days unproductive were measured. These were number of days in the last week which were missed in school or work or when normal daily responsibilities were not carried out due to symptoms and the number of days underproductive in the last week in which the subject felt so impaired by symptoms that productivity was reduced.

Subjects were required to meet with following DSM-IV-TR⁸ criteria for a diagnosis of BED:

- Recurrent episodes of binge eating. An episode of binge eating was characterised by both of the following: eating, in a discrete period of time (for example, within a 2 hour period) an amount of food that is definitely larger than most people would eat in a similar period of time under similar conditions, and a sense of lack of control over the eating (for example, a feeling that one cannot stop eating or control what or how much one is eating).
- The binge eating episodes were associated with at least 3 of the following: eating much more rapidly than normal; eating until uncomfortably full; eating large amounts of food when not feeling physically hungry; eating alone because of being embarrassed by how much one is eating; feeling disgusted with oneself, depressed, or feeling very guilty after overeating.
- Marked distress regarding binge eating.
- The binge eating occurred, on average, at least 2 days a week for 6 months.

Additionally the BED was of at least moderate severity with subjects reporting at least 3 binge eating days per week for the 14 days prior to the baseline visit (Visit 0) as documented in the subject's binge diary. A binge day is a day during which at least 1 binge eating episode occurs.

The principal investigator or a sub-investigator who was experienced in psychiatric evaluations determined a diagnosis of BED based on the DSM-IV-TR; the SCID-I Eating Disorders Module H;⁹ review of the Eating Disorder Examination-Questionnaire (EDE-Q); and comorbid psychiatric diagnoses based on the MINI-Plus. The psychiatric evaluations were carried out by a clinician or trained mental health professional with experience using these instruments and who was qualified to establish a psychiatric diagnosis. This included physicians, nurse practitioners, or licensed psychologists. Individuals performing these interviews were pre-approved by the sponsor or designee.

Exclusion criteria of note were:

- A current diagnosis of bulimia nervosa or anorexia nervosa
- Psychotherapy (for example, supportive psychotherapy, cognitive behaviour therapy, interpersonal therapy) or weight loss support (for example, Weight Watchers) for BED that began within the 3 months prior to the screening visit (Visit -1).

⁸ DSM-IV-TR = Diagnostic and Statistical Manual of Mental Disorders Fourth Edition –Text Revision

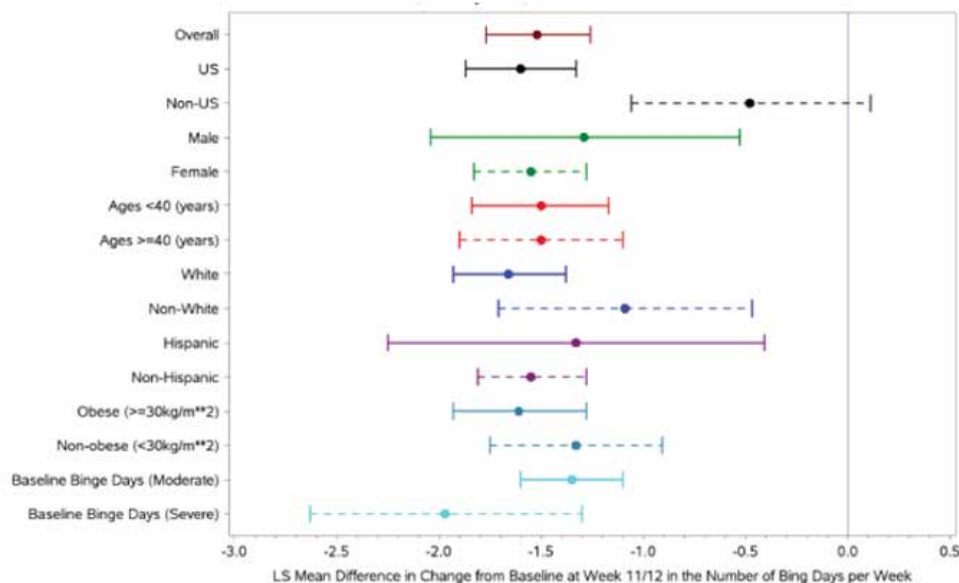
⁹ SCID-I: Structured Clinical Interview for DSM Axis I disorders

- Use of psychostimulants to facilitate fasting or dieting as part of their BED within the 6 months prior to the screening visit.
- Current comorbid Axis I or Axis II psychiatric disorder that was either controlled with medications prohibited in this study or was uncontrolled and associated with significant symptoms.
- Concurrent chronic or acute illness, disability or other condition that might confound the results of safety assessments or that might increase risk to the subject.
- History of seizures, tic disorder, serious neurological disease, cardiovascular disease, or cerebrovascular disease.

During the 4 week dose optimisation period, subjects commenced on lisdexamfetamine 30 mg per day and after one week were titrated to 50 mg per day. A further increase to 70 mg per day was allowed at the end of Week 2 or 3 if indicated and treatment tolerated.

Combined results for the primary efficacy endpoint by subgroups including by country (USA/non-USA), sex, age (< 40 years/≥ 40 years), body mass index (BMI) (< 30/≥ 30) and number of binge eating days per week (moderate/severe) from the 2 pivotal studies is displayed in Figure 1. Results across these subgroups were consistent and showed a reduction in days in which binge eating occurred associated with lisdexamfetamine.

Figure 1: Combined data from Studies 343 and 344. LS mean difference (95% CI) in change from Baseline at Weeks 11 and 12 in number of binge days per week presented by subgroup for the combined Phase III studies (Full analysis set)



CI=confidence interval; LS=least squares; US=United States

Note: A 95% CI that falls left of 0 indicates a greater mean improvement for SPD489 subjects compared to placebo subjects. A 95% CI that crosses zero indicates similarity between treatment groups.

Results by study are summarised below:

In both studies subjects were > 85% women, mostly white with mean age 38.1 years in Study 343 and 37.9 years in Study 344. Mean BMI was 33.45 in Study 343 and 33.52 in Study 344. There were 9 to 10% of subjects in each study with BMI < 25. In Study 343 mean age at BED diagnosis was 36.1 years and in Study 344 mean age at diagnosis of BED was 37.1 years, in both studies indicating fairly recent diagnosis for the majority of subjects. In both studies over 95% of subjects in both treatment groups had not received past psychotherapy for BED.

In Study 343, of the 642 subjects screened 383 were randomised to treatment, 191 were randomised to placebo and 192 to lisdexamfetamine. 374 (97.6%) of randomised subjects were included in the analysis of efficacy with 315 (80.7%) of randomised subjects completing the study and included in the analysis of the primary endpoint. The most frequent reasons for non-completion were loss of follow up and withdrawal by subjects. At Baseline the mean number of binge eating days per week was 4.60 in the placebo group and 4.79 in the dexamfetamine group. At Visit 8 (Weeks 11 and 12) mean binge eating days per week was reduced to 2.22 in the placebo group and 0.78 in the lisdexamfetamine group. The least squares (LS) mean difference in reduction in binge eating days per week was -1.35 (95% CI -1.70, -1.01; $p < 0.001$).

In Study 344 of 700 subjects screened 390 were randomised to treatment, 195 to placebo and 195 to lisdexamfetamine. 350 (89.7%) of randomised subjects were included in the analysis of efficacy with 287 (73.6) of randomised subjects completing the study and included in the analysis of the primary endpoint. The most frequent reasons for non-completion were loss of follow-up and withdrawal by subjects. At baseline the mean number of binge eating days per week was 4.82 in the placebo group and 4.66 in the dexamfetamine group. At Visit 8 (Weeks 11 and 12) mean binge eating days per week was reduced to 2.57 in the placebo group and 0.77 in the lisdexamfetamine group. The LS mean difference in reduction in binge eating days per week was -1.66 (95% CI -2.04, -1.28; $p < 0.001$).

In both studies the key secondary endpoints were similarly statistically significant in both studies. The change in binge eating was apparent from the first week of blinded study treatment. Of particular interest, over the 12 weeks of the study subjects given lisdexamfetamine lost a mean of 6.25% body weight compared to 0.11% for placebo in Study 343 and 5.57% body weight compared to 0.15% for placebo in Study 344.

Study 346

Study 346 was a multicentre, double blind, placebo controlled, randomised withdrawal study of lisdexamfetamine in adults with moderate to severe BED to evaluate maintenance of efficacy. The study had a 4 week screening phase, a 12 week open label treatment phase (4 weeks dose optimisation and 8 weeks dose maintenance), a 26 week double blind treatment withdrawal phase and a 1 week follow up period. The primary efficacy endpoint was defined as the time (in days) from randomisation to relapse. Relapse was defined as ≥ 2 binge days each week for 2 consecutive weeks (14 days) prior to the visit and a ≥ 2 point increase in CGI-S score relative to the score at the randomised withdrawal baseline visit. Relapse status was assessed by the investigator at each visit during the double blind treatment phase.

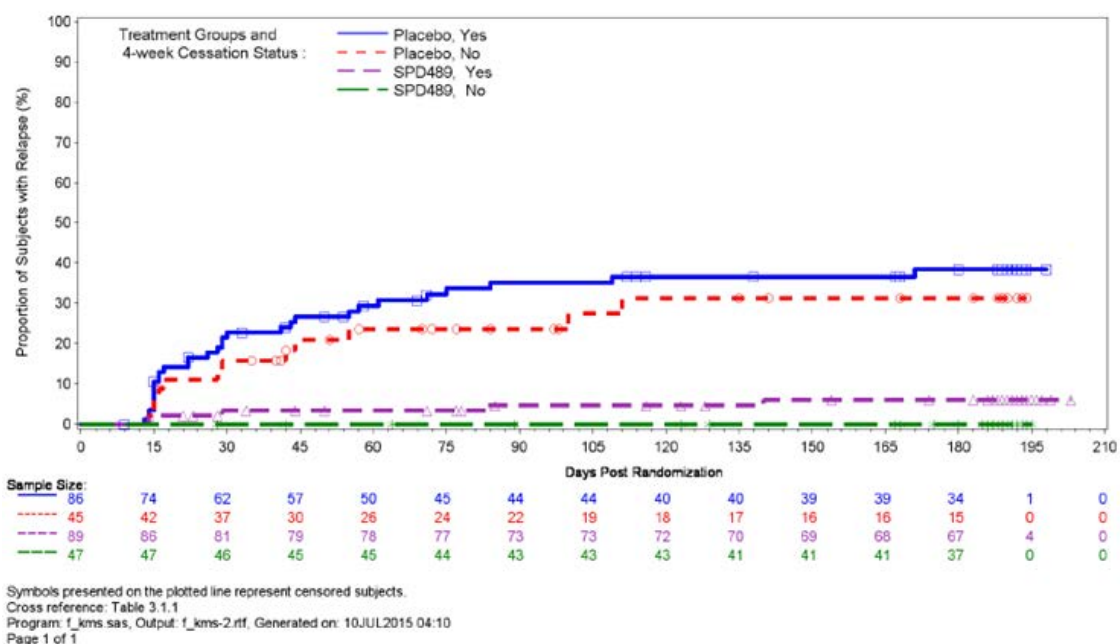
Inclusion and exclusion criteria and dose optimisation were similar to that of the pivotal studies. A total of 639 subjects were screened with 418 enrolled in the open label phase of the study. Of these 275 (65.8%) of randomised subjects completed the open label phase and were eligible for randomisation to the double blind phase. Of these, 137 subjects were randomised to lisdexamfetamine and 138 to placebo. A total of 152 out of 275 (55.3%) subjects completed the randomised withdrawal phase.

Demographic characteristics of study subjects were similar to those of subjects in the pivotal studies. Mean age for randomised subjects was 38.7 years; over 85% were female and most were white. Mean BMI was 33.86 with 7.4% of subjects having BMI < 25 at randomisation. Mean binge eating days per week was 4.78 across the randomised groups. As in the pivotal studies, few subjects had received prior therapy for BED. Of the 411 subjects in the Safety analysis set, 16 (3.9%) had received any lifetime pharmacotherapy for BED. Similarly, of the 270 subjects in the randomised Safety analysis set, 2 (1.5%) of subjects given lisdexamfetamine and 6 (4.5%) of subjects given placebo

had received any lifetime pharmacotherapy for BED. Two subjects were receiving current psychotherapy for BED at the time of informed consent.

Of the 267 subjects in the Full analysis set evaluated for the primary efficacy endpoint, 136 received lisdexamfetamine and 131 received placebo. 5 (3.7%) subjects given lisdexamfetamine and 42 (32.1%) subjects given placebo had an observed relapse. As neither treatment group had over 50% of subjects experiencing relapse during the 26 week randomised withdrawal phase, the median time to relapse was not calculable. Figure 2 (see below) shows the Kaplan-Meier survival plot of time to relapse presented by 4 week cessation status (full analysis set). Of particular note at the end of the 24 week period of the 267 subjects initially randomised at Day 180 only 49 out of 131 subjects randomised to placebo and 104 out of 136 randomised to lisdexamfetamine were available for assessment of relapse at the end of the assessment period.

Figure 2: Study 346 Kaplan-Meier survival plot of time to relapse presented by 4 week cessation status (Full analysis set)



Note: Time to relapse is based on date of randomization.

Study 345

Study 345 was primarily a longer term safety study however it provided data on persistence of efficacy in study subjects who continued treatment for up to 12 months. Of the 604 subjects enrolled in this extension study, 369 completed 12 months of open label treatment, with either 50 mg or 70 mg lisdexamfetamine. No overall reduction in the initial effect of lisdexamfetamine on binge eating days was seen in subjects who completed the study, suggesting that for that group tolerance did not occur.

Mean (standard deviation (SD)) changes from Baseline over time in body weight were observed at all study visits reaching a decrease of approximately 8 kg decrease at Week 32 (Visit 11) and remaining essentially stable after thereafter. The maximum mean decrease from Baseline was 8.21 kg (8.67%) at Week 44 (Visit 14). There were 387 subjects with body weight data at this visit. For the 369 subjects with body weight data at Week 52 (Visit 16), the mean (SD) decrease from Baseline was 8.20 (7.926) kg, an 8.64% decrease from baseline. A weight decrease of at least 10% from Baseline was observed in 273 (45.7%) of subjects.

Safety

The clinical evaluation report evaluates safety data from studies in ADHD and BED separately. Safety data relating to 3 studies of lisdexamfetamine in the treatment of ADHD will be considered separately and does not require the advice of the ACM.

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 (see Table 5, below).

Table 5: Investigational product exposure in the short term, placebo controlled studies (Safety analysis set)

Exposure Variable	Statistic	SPD489-208				SPD489-343/-344		SPD489-208/-343/-344		
		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	NA	NA	NA	NA	NA	109 (29.2)	NA	NA	NA
	70 mg/day	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

In the BED studies the most frequent System Organ Classes (SOC) for AE 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 6, below). 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 6: Treatment emergent AEs occurring in ≥ 5 of subjects in the short term, placebo controlled studies by preferred term (Safety analysis set)

Preferred term	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 (%)
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.

No new safety issues were apparent from these studies. Cardiovascular and psychiatric AEs 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 week 11 to 12) and a smaller increase was also noted in the placebo group (1 to 3 bpm) (see Figure 3, below). 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 7, below. A SBP of ≥ 140 mmHg and an increase of > 10 mmHg from Baseline on 2 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 heart rate of 6.6 bpm.

Figure 3: Mean (SD) change from Baseline in pulse rate by visit for the short term, placebo controlled studies (Safety analysis set)

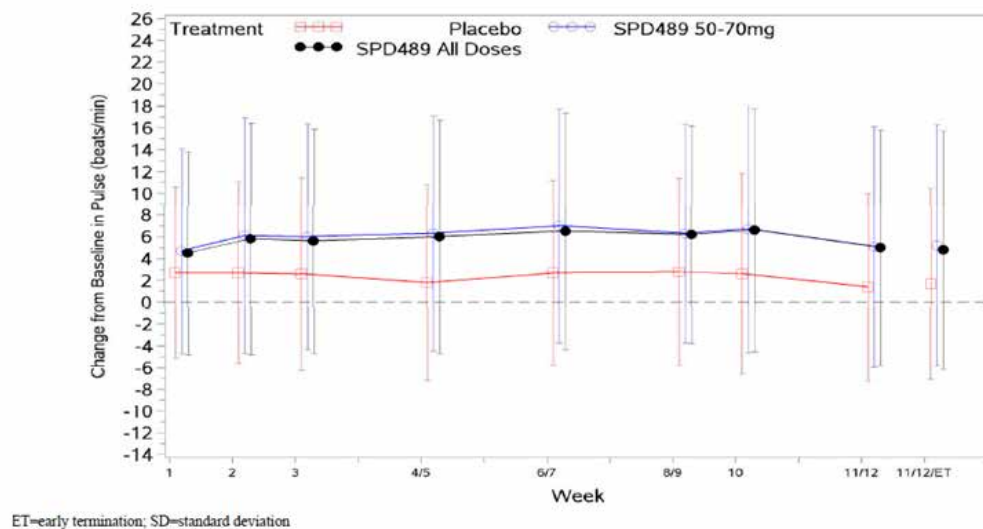


Table 7: Potentially clinical important vital signs values in the short term, placebo controlled studies (Safety analysis set)

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

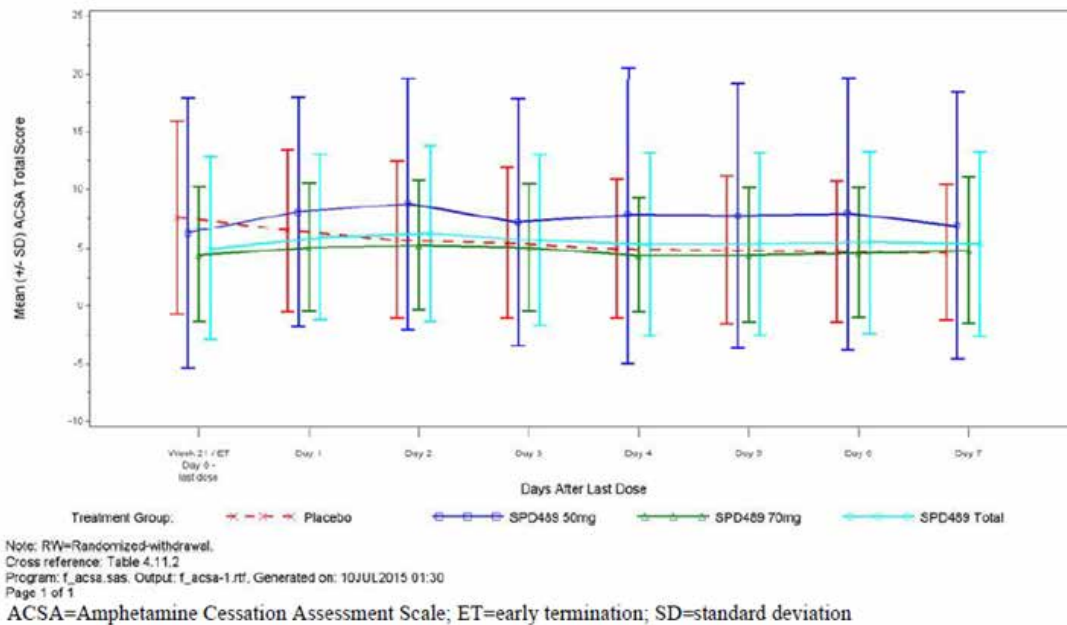
Note: Percentages are based on all Safety Analysis Set subjects with a baseline and at least 1 postbaseline assessment.

The most frequently reported psychiatric AEs 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 2 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 1 extra capsule was taken; in one case, 1 extra capsule was taken on 2 days and in the last case, ≤ 3 capsules were taken (precise number unknown). There were 2 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 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 4 (see below) shows ACSA scores by dose in the 7 day period following the last dose of study drug for all BED studies.

Figure 4: Mean (\pm 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)



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 was included in the clinical data. 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.

Risk management plan

The RMP evaluator has noted that in support of the extension of indications to include BED, the sponsor has submitted AU-RMP version 3.0 (dated 24 March 2016; DLP 8 October 2015). AU-RMP version 3.1 (dated 7 February 2017; DLP 8 October 2015) was submitted in the sponsor's response for the second round evaluation (dated 8 February 2017).

There is an ongoing DUS to monitor off label use of lisdexamfetamine; the outcomes of this DUS are to be reportedly annually for 5 years. The first reports have been submitted to the TGA in February 2015 and February 2016. The third year report (version 1.0, dated 26 January 2017) was included in the response of 8 February 2017. The sponsor has notified the TGA that the BED indication will be included in the DUS. There is an ongoing pharmacovigilance activity mandated in the EU which is comprised of a

pharmaco-epidemiology study examining the incidence of major cardiovascular events in new users of lisdexamfetamine for ADHD (final study report expected in 2020).

There is additional risk minimisation proposed for the use of lisdexamfetamine in the form of web based educational tools for prescribers. The aim of the online educational tools is 'to enable healthcare professionals in the appropriate selection of patients and prescription of lisdexamfetamine for the treatment of patients with ADHD.' The online education also includes a downloadable leaflet for the patients (and carers/guardians).

The website is found at <http://www.idxguide.com/au> and has been active ('approved') since March 2014. A review of the website reveals that it is focused on the ADHD cohort. The sponsor has clarified that the educational tools are for prescribers only. The sponsor has also advised that the BED cohort will be incorporated, and healthcare professionals advised of the amended educational materials.

If the extension to the indications to include BED is approved the RMP evaluator has recommended the following condition of registration:

The AU-RMP (version 3.1, dated 7 February 2017, data lock point 8 October 2015), to be revised to the satisfaction of the TGA, must be implemented.

Risk-benefit analysis

In the design of the pivotal studies there was a presumption that a reduction in the number of days each week in which a subject reported binge eating is an appropriate primary measure of efficacy of treatment for BED. Binge eating disorder is a psychiatric disorder. The measure of efficacy was a short term, frequency based, self-reported outcome measure of a symptom of BED. It was also subjective, being based on each subject's perception of whether they were overeating during a time period in each day. The EDE-Q6 questionnaire and the YBOCS-BE respectively, used in the diagnosis of BED in the pivotal studies were provided. Total food intake, except by the proxy of change in body weight, was not assessed. The sponsor is requested to justify the choice of primary efficacy measure in the pivotal studies.

Study subjects were not assessed for underlying psychosocial issues which may be contributing to BED nor was any attempt made to identify or manage these issues in the studies. Psychological and psychiatric assessments were intended to identify inclusion and exclusion criteria. It is also notable that prior to study entry over 95% of subjects enrolled in both the pivotal studies had not received prior psychotherapy for BED. Additionally for the majority of patients the diagnosis of BED appears to have been very recent though this is not specifically identified in the study reports. It was strongly suggested by the mean age of subjects at study entry and mean age at diagnosis. The sponsor is requested to clarify the proportion of study subjects in the pivotal studies who were diagnosed with BED during the screening period for these studies. The available data suggests that for a substantial proportion of study subjects the diagnosis and duration of BED were established by subject history obtained during the study screening period and had not previously been noted in the subject's medical history.

Binge eating disorder is a chronic condition which varies in severity over time. The pivotal studies were short term, with only 8 weeks of stable treatment. The randomised withdrawal study was limited by the low rate of observed relapse in the placebo group during the 24 week double blind assessment period and by the low rate of study completion. The result strongly suggests that continued treatment beyond 8 weeks is not required for the control of a primary symptom of BED (that is over eating in episodes) for the majority of patients. It is clear though that with continued use of dexamfetamine at the doses proposed there is substantial and clinically meaningful weight loss for the majority of individuals. However, lisdexamfetamine is not being proposed as an aid to weight loss.

It is proposed as a treatment for a psychiatric condition that has an association with overweight and obesity.

The extent of tolerance and dependence with long term use has not been adequately explored however, if managed as with ADHD the risks most likely would be similar. Likewise the risks of misuse and over-use may also be similar, though a larger population would potentially be exposed. Given the nature of BED many overweight individuals are likely to meet the current diagnostic criteria for BED from time to time.

Delegate's considerations

- The diagnosis of BED is based on subjective reporting of over eating (please see BED diagnostic criteria and diagnostic questionnaire). There was no objective assessment of the amount of food consumed in reported binge eating episodes. Thus the risk of diagnosis of BED to a person who, while consuming average amounts of food, makes a subjective assessment of episodic over eating appears to be very high.
- In the pivotal studies the diagnosis of BED appears to have been established at study screening for most subjects. It was not an established diagnosis. Most subjects in the pivotal studies had not received prior treatment for BED and did not receive psychotherapy for BED either prior to study participation or during the study. It is therefore not possible to determine whether psychotherapy (the current recommended treatment) would be more effective than lisdexamfetamine or whether a combination of psychotherapy and lisdexamfetamine would be more effective than lisdexamfetamine alone in reducing BED.
- For the majority of subjects in the pivotal studies reported BED did not recur during the post study observation period, suggesting this may be a temporary or episodically manifested disorder for the majority of study subjects.
- The selection of reduction in the number of binge eating days per week as the primary measure of efficacy in the management of BED has not been adequately justified.
- In the randomised withdrawal study the majority of subjects were not identified as relapsing in the 24 weeks after an 8 week open label course of lisdexamfetamine. Use of lisdexamfetamine as symptomatic treatment for BED beyond 8 weeks is not supported by that study.
- It is not known whether the reduction in BED symptoms was due to general reduction in appetite alone (a known effect of amphetamines) or whether some other action was also occurring.
- Given the highly subjective criteria for diagnosis of BED the extension of use of lisdexamfetamine as an aid to weight loss for individuals who have no psychiatric disorder seems very likely. The sponsor is asked to consider how this risk may be minimised.
- Given the history of amphetamine use and misuse for weight loss and associated addiction and other safety issues associated with intentional overuse the sponsor is requested to advise the TGA on how this could be minimised should lisdexamfetamine be made available as a treatment for BED.

Proposed action

The Delegate was not in a position to say, at this time, that the application to extend the indications for Vyvanse (lisdexamfetamine) as proposed by the sponsor should be approved for registration.

Request for ACM advice

The committee is requested to provide advice on the following specific issues:

1. Clarity on the acceptance of BED as a distinct psychiatric condition in Australia rather than a symptom of another underlying psychiatric condition is requested.
2. Is the committee satisfied that the selection of days of binge eating per week, as determined in the pivotal studies is an appropriate primary efficacy measure for a treatment of BED?
3. Does the committee consider that subject selection for the pivotal studies was appropriate to support the current proposed BED indication for lisdexamfetamine?
4. Does the committee consider there is a role for lisdexamfetamine in the management of BED? If so what is that role?
5. Does the committee consider that there is sufficient evidence to support long term use of lisdexamfetamine in the management of BED?
6. If lisdexamfetamine were to be approved for treatment of BED should the diagnosis and/or ongoing treatment, be restricted to a group of specialist medical practitioners? If so, which group?
7. Does the committee consider that the risk of misdiagnosis of general over eating as BED can be appropriately managed? If so, how would this be accomplished?¹⁰
8. Does the committee consider that proposals to manage the risks of abuse/misuse including intentional increase in dose to increase weight loss, addiction and diversion are likely to be adequately managed by the mechanisms proposed by the sponsor?

The committee is (also) requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Response from sponsor

The sponsor is seeking to extend the indication for Vyvanse for treatment of BED in Australia. Vyvanse has received marketing approval for BED in the US and Canada.

Sponsor's comments on the pre-ACM Delegate's overview

The sponsor's response is provided below on some of the matters that the Delegate has asked the ACM for advice on:

Issue 1

'Clarity on the acceptance of BED as a distinct psychiatric condition in Australia rather than a symptom of another underlying psychiatric condition is requested.'

As mentioned in sponsor's response to clinical questions; Question 8 (See Attachment 2) demographic information on people with eating disorders has been collected for a number of years in the annual South Australian Health Omnibus Survey (SAHOS) sponsored by the South Australian Health Commission. These are sequential cross sectional interview based surveys and samples were selected from both metropolitan and rural 'collectors' districts' used by the Australian Bureau of Statistics.

The combined data from the 2008 and 2009 survey have been used in a study to estimate the prevalence of BED after the revision of DSM-IV-TR to DSM-5 in 2013. In this study,

¹⁰ Please see the BED diagnostic criteria in Attachment 2 and EDE-Q 6.0 in Attachment 3.

BED was defined as participants with weekly objective large binge eating episodes without weekly purging and BMI \geq 18 (that is DMS-5 criteria A, D and E).^{11,12}

RANZCP clinical practice guidelines for the treatment of eating disorders makes a mention of BED in the aforementioned publication.¹³

A report published by Deloitte Access Economics (commissioned by the Butterfly Foundation);¹⁴ examined the economic and social costs of eating disorders in Australia. According to estimates in this report, in 2012 there were 913,986 people in Australia with eating disorders, or approximately 4% of the population. Of these, 3% have anorexia nervosa, 12% bulimia nervosa, 47% BED, and 38% other eating disorders.

A summary of evidence for best treatment options for BED by Stephen Touyz (Professor of Clinical Psychology and Clinical Professor in Psychiatry, University of Sydney. Executive Chair: Centre for Eating and Dieting Disorders; Editor; Journal of Eating Disorders) was provided by the sponsor.¹⁵ His Australian team recently assessed the time trends in recurrent binge eating prevalence and its burden correlates over the 18 years inclusive of 1998 to 2015 by means of 6 sequential cross sectional surveys of the South Australian adult population (15 + years).¹⁶ These surveys were conducted in 1998, 2005, 2008, 2009, 2014, and 2015. The prevalence of binge eating increased linearly over time such that compared to 1998 (2.7% and 1.1%) the odds of reporting weekly and twice weekly episodes of binge eating were 6 fold higher in 2015 (13.0% and 5.3%). In those individuals with both obesity and comorbid binge eating, there was a 5.6 fold increase from 1995 to 2015.¹⁷

Issue 2

Is the committee satisfied that the selection of days of binge eating per week, as determined in the pivotal studies is an appropriate primary efficacy measure for a treatment of BED?

Overall, across the 5 studies in the BED clinical development program, efficacy assessments were chosen to comprehensively evaluate the effect of lisdexamfetamine treatment on the behavioural and psychopathological signs and symptoms of BED. Specifically, BED symptom reduction (measured by changes in number of binge eating days per week), binge related global functioning (measured by changes in CGI-S) and improvement (measured by changes CGI-I), reduction in binge related psychopathology (measured by the Y-BOCS-BE total score) specific eating disorder psychopathology (measured by the EDE-Q total score and subscale scores) have been assessed.

As diagnosis of BED is characterised by 2 binge eating days per week for 6 months, the selection of days of binge eating per week best reflects the measure associated with the symptom criteria of the diagnosis. In Study 208 (the pilot study), the primary efficacy endpoint of binge days per week with log transformation was selected due to its sensitivity in the detection of treatment effects based on available published literature.²

¹¹ Hay PJ et al 2008. Eating Disorder Behaviours Are Increasing: Findings from Two Sequential Community Surveys in South Australia *PLoS ONE* 2008; 3(2): e1541. doi:10.137

¹² Hay PJ et al 2015. Prevalence and sociodemographic correlates of DSM-5 eating disorders in the Australian population. *Journal of Eating Disorders* 2015; 3: 19

¹³ Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the treatment of eating disorders (Available at: <https://www.ranzcp.org/Files/Resources/Publications/CPG/Clinician/Eating-Disorders-CPG.aspx>).

¹⁴ https://www.deloitteaccesseconomics.com.au/uploads/File/Butterfly_Report_Paying%20the%20Price_online.pdf

¹⁵ Touyz 2017, a letter in the sponsor's response to issues raised dated 18 January 2017.

¹⁶ Mitchison D et al 2017. How abnormal is binge eating? 18-Year time trends in population prevalence and burden. *Acta Psychiatrica Scandinavica* 2017; 137: 147-155

¹⁷ Da Luz FQ et al 2017 Prevalence of obesity and comorbid eating disorder behaviors in South Australia from 1995 to 2015. *International Journal of Obesity* 2017; 41: 1148-1153

Additionally, several secondary efficacy endpoints (for example, CGI-I, 1 week and 4 week remission (referred to as cessation of binge eating behaviour), binge episodes per week, and weekly response status) were selected to provide a better understanding of the effects of pharmacological intervention in subjects with BED.

For the primary efficacy endpoint in the two pivotal Phase III studies (Studies 343 and 344), change from Baseline to end of study in binge days per week was used. The measurement focused on the core features of the disorder as defined in the DSM-IV-TR, providing a clinically meaningful endpoint that is consistent with how the disorder is diagnosed, sensitive to treatment effect and easily interpreted by clinicians. Both log and non-log transformed data provided consistent results in Study 208.

For the above reasons and consistency, this primary efficacy endpoint was maintained throughout the clinical development program studying Vyvanse as a treatment for BED.

Issue 3

Does the committee consider that subject selection for the pivotal studies was appropriate to support the current proposed BED indication for lisdexamfetamine?

Inclusion/exclusion criterion for the clinical program used the criteria for BED as defined in the DSM-IV. BED was formally added as a free standing diagnosis under the DSM-5 which was published during the clinical program for BED (see below).

In the past 20 years there have been over 1,000 research papers published that support the idea that BED is a specific diagnostic criteria that has validity and consistency. The population in the clinical development program reflects the diagnosis criteria.

The key diagnostic features of BED are:

- Recurrent and persistent episodes of binge eating
- Binge eating episodes are associated with 3 (or more) of the following:
 - Eating much more rapidly than normal
 - Eating until feeling uncomfortably full
 - Eating large amounts of food when not feeling physically hungry
 - Eating alone because of being embarrassed by how much one is eating
 - Feeling disgusted with oneself, depressed, or very guilty after overeating
- Marked distress regarding binge eating
- Absence of regular compensatory behaviours (such as purging).

Issue 4

Does the committee consider there is a role for lisdexamfetamine in the management of BED? If so what is that role?

Treatment goals for patients with BED include abstinence from binge eating, improved psychological functioning, and appropriate weight regulation in overweight patients.¹⁸ Because of the limited effectiveness of current treatments to achieve these goals, there is significant unmet medical need in effectively treating the multiple aspects of BED and there are no approved pharmacological agents indicated for BED in Australia. It is thought that 47% of all eating disorders in Australia are BED.¹⁴

¹⁸ Peat C. M et al, 2012 Binge Eating Disorder. Evidence based treatments Alone or combined, pharmacotherapy and CBT can reduce bingeing, psychopathology. *Current Psychiatry* 2012; 11: 33-39

Cognitive behavioural therapy and interpersonal psychotherapy can be effective in reducing bingeing; however some patients do not respond;^{19,20} and psychotherapy also appears to have minimal effect on weight regulation.²⁰ The general availability of specialised psychotherapy is also limited. Most patients who suffer from BED may have already tried non-psychotherapeutic methods including non-approved products and diet to control their eating before they present to a medical professional. In addition to psychotherapy there are very few medications with indications specific for this particular eating disorder.

Several medications classes have been studied and some have been used off label to treat BED, such as SSRIs and AEDs. In general, these medications either have limited overall effectiveness and/or are associated with problematic adverse effects.

While the neurobiology of BED remains poorly understood, a dysfunction in dopamine and norepinephrine (noradrenaline) signalling appears to be associated with binge eating behaviour, and several lines of scientific evidence (genetic, nonclinical, and clinical) suggest that a stimulant would be an effective therapy for BED. Stimulant medications increase the availability of both of these neurotransmitters and, therefore, might be expected to reduce BED symptoms. Further support for the potential utility of stimulants for the treatment of BED is the research indicating that BED and ADHD may share common neurobiological bases.

Importantly, BED is often comorbid with ADHD.^{21,22} ADHD neurobiology is also characterised by abnormalities in the dopaminergic signalling, and impulsivity and reward systems similar to those observed with BED. In summary, there is a significant scientific basis to support evaluation of Vyvanse as a treatment in BED.

Overall, there is significant unmet medical need in BED for effective treatments that safely reduce binge eating and lead to improvement in binge related psychopathology. Thus the role for lisdexamfetamine is as another tool to psychotherapy in the management of BED.

Issue 5

Does the committee consider that there is sufficient evidence to support long term use of lisdexamfetamine in the management of BED?

BED can be a chronic condition that requires a comprehensive treatment program. Lisdexamfetamine has been studied as a treatment for BED in a clinical program that included one 12 month extension study and one 38 week maintenance of efficacy study (both provided either as part of the original new drug submission or included in the response to the Notice of Deficiency). Study 346 provides valuable information with regards to the extent of benefit that remains beyond the end of the treatment period evaluated in the pivotal studies, that is, 12 weeks. Most patients that relapsed did so within 30 days after discontinuation of the initial 12 week treatment period. While some patients can be treated for a shorter period (for example, 12 weeks) and do not relapse (68% of subjects randomised to placebo had not relapsed at the end of the 26 week randomised withdrawal period), other patients may need ongoing treatment. Whether to continue treatment with Vyvanse for periods longer than 12 weeks for BED must be

¹⁹ Berkman N et al., (2006) Evidence Report/Technology Assessment Number 135 Management of Eating Disorders Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services AHRQ Publication No. 06-E010 April 2006

²⁰ Wifley D et al., (2002). A Randomized Comparison of Group Cognitive-Behavioural Therapy and Group Interpersonal Psychotherapy for the Treatment of Overweight Individuals With Binge-Eating Disorder. *Arch Gen Psychiatry*. 2002;59:713-721

²¹ Hudson J et al., (2007). The Prevalence and Correlates of Eating Disorders in the National Comorbidity Survey Replication. *Biol Psychiatry* 2007;61:348-358

²² Surman, C et al., (2006). Association between attention-deficit/hyperactivity disorder and bulimia nervosa: analysis of 4 case control studies. *J Clin Psychiatry* 2006; 67: 351-354

determined for individual patients. Ongoing treatment with lisdexamfetamine has demonstrated continuous benefit for patients as observed in the open label study, suggesting that those that need longer treatment would also benefit.

The sponsor recommends that the specialist is best suited to decide whether further long term treatment beyond 12 weeks would be appropriate. It is noted that 60% of patients do not relapse.

Taking a conservative approach and weighing the benefit risk of treatment for individual patients; the sponsor has proposed the following as an appropriate recommendation for treatment duration under Dosage and Administration section:

'In order to minimise exposure to cardiovascular risk in this population; the risk-benefit 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.'

This recommendation is also proposed in the Precaution section under the subheading Prescribing and Dispensing.

Issue 6

If lisdexamfetamine were to be approved for treatment of BED should the diagnosis and/ or ongoing treatment be restricted to a group of specialist medical practitioners? If so, which group?

As noted BED is a complex disorder and requires a multiple disciplinary set of experts. Local regulation concerning the prescribing of lisdexamfetamine in Australia would generally guide use towards specialists and those generally familiar with the specific medical need for patients with BED. No additional restrictions are needed or recommended.

Issue 7

Does the Committee consider that the risk of misdiagnosis of general over eating as BED can be appropriately managed? If so, how would this be accomplished?²³
(please see the BED diagnostic criteria in Attachment 2 and EDE-Q 6.0 in Attachment 3)

Similar to enrolling in the clinical program, subjects should be diagnosed with BED per the DSM-5. In the clinical study program, subjects met the DSM-IV-TR criteria for a diagnosis of BED. As part of this diagnosis, general over eating was excluded.

While there are certain habits and behaviours that overlap between the conditions of BED and overeating, the two are very different and should be correctly diagnosed by a professional therapist or doctor. BED is a separate entity and diagnosable eating disorder, not just an occasional happening or symptom.

Binge eating is a different experience. Binge eating is overeating, but key to the binge eating definition is that binge eaters experience a loss of control. Once the binge eater begins eating, they feel they cannot stop eating even if they are uncomfortably full. Whereas overeating might be caused by feeling good, binge eating is often driven by poor body image, low self-esteem, trauma, or body image issues. Binge eating is also typically associated with consuming a larger amount of food than others would consider reasonable in a short period of time, even when not hungry. Eating more rapidly than normal eating until uncomfortably full. Eating alone and being embarrassed about eating behaviour and hiding food. Men and women who struggle with binge eating eat in isolation to conceal the

²³ Please see the BED diagnostic criteria in Attachment 2 and EDE-Q 6.0 in Attachment 3.

behaviour. While overeating may occur periodically in a person without this disorder, an individual with BED also experiences significant emotional and physical distress.

The DSM-5 criteria, which are very specific and part of the diagnosis, excludes overeating. BED is a debilitating disease and can lead to fatal episodes. More often, the immediate symptoms of a binge episode cause physical distress to the patients. Most patients who suffer from BED may have already tried non-psychotherapeutic methods to control their eating before they present to a medical professional.

An 8 to 12 week treatment of BED using medication with or without other therapies provides a positive outcome in more than 60% of patients, in that the patient recognises there is a lowering in the number of BED episodes in each week. In addition many patients have comorbidity (obesity, diabetes, and etcetera), alleviating BED can also allow treatment of other illnesses.

Issue 8

Does the committee consider that proposals to manage the risks of abuse/misuse including intentional increase in dose to increase weight loss, addiction and diversion are likely to be adequately managed by the mechanisms proposed by the sponsor?

Vyvanse is a prescription only medication, which would be prescribed to patients diagnosed with BED exclusively by healthcare professionals.

Vyvanse is not indicated/ recommended for use as a weight loss medication. As such, this statement has been proposed for inclusion as a warning, in the PI, to warn against such use.

In a previous response to the TGA, the sponsor reported that from a cumulative review of all Vyvanse cases reported up to 25 January 2017, only 32 reports were found to contain weight loss indication. Given approximately 7 million patient years of exposure to Vyvanse, the reporting rate of off label use for weight loss was considered to be very low.

The maximum therapeutic dose proposed for the treatment of BED is 70 mg/day. As a prescription only medication, the healthcare professional (specialist) would be expected to titrate to the most appropriate dose for each patient, and maintain such dose for the treatment duration. If the patient were to increase their dose, there would likely be a request to refill the prescription earlier than the expected period, which should raise concerns with the prescribing specialist.

Concerning potential for abuse/misuse/diversion, three single dose, abuse potential studies have shown that Vyvanse has a significantly low potential for abuse and misuse. Vyvanse (lisdexamfetamine) is a pharmacologically inactive pro-drug. The gradual bioconversion from pro-drug to dexamfetamine in red blood cells makes it impossible for abusers to attain the desired effect of a rise in plasma levels which many dexamfetamine abusers desire.

Although very low, the potential for abuse, misuse or diversion for non-therapeutic purposes however, cannot be ignored. As such, the sponsor has proposed to include in the PI, a warning about such and advice to prescribers to assess the risk of abuse prior to prescribing and to monitor these signs during treatment.

In addition, the sponsor has also proposed to implement educational materials for Australian healthcare professionals, highlighting these risks and as a reminder to the specialists to assess patients for the risk of abuse/misuse/diversion, both before initiation and during treatment with Vyvanse.

Furthermore, the sponsor has proposed a Drug Utilisation Study (DUS) in Australia, as part of measures to monitor and manage these risks. The DUS proposes to collect and analyse data on how drug is prescribed and used. The study will provide data on an annual basis, for 3 years in Australia, to evaluate drug utilisation with a special interest in BED,

and to monitor off-label use of Vyvanse. This study will characterise the patients who are prescribed Vyvanse, focusing on the indication for use, the age of patients being prescribed the drug to ensure it is being prescribed within the product information, and describe the pattern of use amongst physicians in Australia. In addition to this, the study will monitor how effective other measures which will be/are being used to minimise the risk of abuse/misuse.

Advisory Committee Considerations (ACM meeting June 2017)

The Advisory Committee on Medicines (ACM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, agreed with the Delegate and considered Vyvanse capsules containing 30 mg, 50 mg, and 70 mg of lisdexamfetamine dimesilate to have an overall negative benefit-risk profile for the indication:

Binge Eating Disorder (BED):

Vyvanse is indicated for the treatment of moderate to severe BED in adults when nonpharmacological treatment is unsuccessful or unavailable. Treatment should be commenced and managed by a specialist.

Need for comprehensive treatment programme: Vyvanse is indicated as one 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.

Initially the proposed additional indication was:

Binge Eating Disorder (BED):

Vyvanse is indicated for the treatment of BED in adults.

In making this recommendation the ACM was of the view that:

- the pivotal studies were short term whereas the condition BED is a long term condition. Long term efficacy of lisdexamfetamine in the treatment of BED was not demonstrated.
- the primary efficacy measure in the pivotal studies was a frequency based and self-reported behavioural outcome measure. While noting it is subjective the ACM accepts use of this outcome measure as an appropriate primary efficacy parameter.
- 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 on prohibited medication or 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.
- appropriate safety studies including to assess cardiovascular safety in patients with BED have not been carried out.

- there was insufficient evidence to demonstrate that lisdexamfetamine is better than available treatments for BED; the sponsor has not compared lisdexamfetamine with a currently approved or recommended treatment for BED in an appropriately designed clinical trial.
- at most, with further study data, lisdexamfetamine could be assessed as a possible third line therapy for BED.

Specific advice

The ACM advised the following in response to the Delegate's specific questions on the submission:

1. *Clarity on the acceptance of BED as a distinct psychiatric condition in Australia rather than a symptom of another underlying psychiatric condition is requested.*

The ACM noted that BED is recognised as a distinct condition by International Classification of Diseases (ICD); ICD 10 (F50.81) in October 2016 with specific DSM diagnostic criteria (DSM-5 (307.51)).

The ACM also noted that the diagnostic criteria rely on subjective measures as is normal in psychiatry, as subjectivity does not undermine the diagnostic classification but may reduce the reliability of individual diagnosis.

2. *Is the committee satisfied that the selection of days of binge eating per week, as determined in the pivotal studies is an appropriate primary efficacy measure for a treatment of Binge Eating Disorder (BED)?*

The ACM noted 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. Questionnaires contained 300 to 400 questions but included few directly relevant to the criteria. The ACM agreed 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.

3. *Does the committee consider that subject selection for the pivotal studies was appropriate to support the current proposed BED indication for lisdexamfetamine?*

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 safety of lisdexamfetamine were it to be used in the general BED patient population.

4. *Does the committee consider there is a role for lisdexamfetamine in the management of BED? If so what is that role?*

The ACM noted that there was a need to assess the strength of the evidence. Whilst the results of the studies are positive, there are biases to be considered such as that the 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.

5. *Does the committee consider that there is sufficient evidence to support 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.

6. *If lisdexamfetamine were to be approved for treatment of BED should the diagnosis and/or ongoing treatment be restricted to a group of specialist medical practitioners? 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.

7. *Does the committee consider that the risk of misdiagnosis of general over eating as BED can be appropriately managed? If so, how would this be accomplished (please see the BED diagnostic criteria and EDE-Q 6.0).*

ACM agreed that the risk of misdiagnosing BED and potential of abuse of lisdexamfetamine is high. ACM noted that overeating is common, with obesity and overweight affecting over 50% of the Australian adult population.

ACM also noted 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.

8. *Does the committee consider that proposals to manage the risks of abuse/ misuse including intentional increase in dose to increase weight loss, addiction and diversion are likely to be adequately managed by the mechanisms proposed by the sponsor?*

The ACM agreed that the proposals to manage the risks of abuse/ misuse including intentional increase in dose to increase weight loss, addiction and diversion are not going to be adequately managed by the mechanisms proposed by the sponsor.

The ACM concluded that the evidence provided in the sponsor's submission did not satisfactorily establish the safety and efficacy of Vyvanse capsules containing 30 mg, 50 mg, and 70 mg of lisdexamfetamine dimesilate.

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 use of lisdexamfetamine is not included in the current cardiovascular safety study.

Post ACM response from sponsor

The sponsor requested a mutual stop clock to allow time to respond to issues raised by the ACM. The sponsor provided a response dated 8 August 2017 together with two reports from Australian clinical experts in the field.

Introduction

The TGA Delegate and ACM have evaluated the sponsor's application for extending indication of lisdexamfetamine (Vyvanse) to include treatment of BED. The sponsor wishes to thank the TGA and ACM for their comments and provides responses addressing each point herein to assist the TGA Delegate in further considering the application. To help address concerns raised by the ACM regarding current practice for the diagnosis and treatment of BED in Australia, a summary, prepared by [information redacted] is also included. Professors [information redacted] are leading experts in the treatment of BED and their summary provides important context regarding the current standard of practice in Australia for diagnosis and treatment of BED.

Executive summary

BED is characterised by recurrent binge eating episodes without the purging behaviours that characterise bulimia nervosa. It is the most common eating disorder and was recognised as a specific diagnostic eating disorder in the DSM-5. BED is associated with significant psychiatric comorbidity and disability; among patients with eating disorders. Women with BED have been observed to have the highest rates of psychiatric comorbidity, with up to 70% of patients meeting DSM-5 criteria for at least one additional psychiatric disorder (typically major depression).²⁴ Currently, there are no approved medications in Australia for treatment of BED, and there is significant unmet medical need in BED for effective treatments that safely reduce binge eating and lead to improvement in binge related psychopathology.

Across the 5 studies in the sponsor's BED clinical development program, efficacy assessments were chosen to comprehensively evaluate the effect of lisdexamfetamine treatment on the behavioural and psychopathological signs and symptoms of BED. Endpoint selection and design of the pivotal studies incorporated feedback from the FDA. The pivotal studies provided robust evidence of the efficacy of lisdexamfetamine in the treatment of adults with BED. The long term efficacy of lisdexamfetamine for the treatment of moderate to severe BED is also supported by the CGI-I and the EDE-Q results from the 1 year open label safety study, and the maintenance of efficacy is supported by results that demonstrated that the initial efficacy of lisdexamfetamine seen after 12 weeks of open label treatment was maintained over the subsequent 26 week double blind, randomised withdrawal phase for the majority of subjects.

The BED clinical development program enrolled subjects with moderate to severe BED and was designed to evaluate lisdexamfetamine in the treatment of patients with moderate to severe BED. The design also took into account the well-established safety profile of the drug and class, as observed in ADHD, and the need to remove factors that could confound the assessment of efficacy and safety. Results of the clinical program are thus applicable to the BED population as defined in the proposed Australian PI. In the BED clinical program mean body weight decreased over time in the treatment group, and remained essentially stable after 32 weeks. A similar pattern of results was seen for BMI and waist circumference.

While weight control is an important aspect of management of BED patients,²⁵ overall the weight loss observed in the BED program was modest relative to typical weight loss goals in the treatment of obesity;²⁶ and results from a rodent model of BED provided strong evidence that the primarily pharmacological action of lisdexamfetamine is on cognitive impulsivity rather than appetite suppression leading to weight loss (nonclinical Study R6847M-SHP489). Importantly the proposed Australian PI clearly indicates in the Limitation of Use that lisdexamfetamine is not indicated for weight loss.

Across studies, the TEAE profile of lisdexamfetamine was generally similar for obese and non-obese lisdexamfetamine treated subjects and was consistent with the TEAE profile observed in ADHD. For the 38 week maintenance of efficacy Study 346 and the 1 year Study 345, vital sign trends were similar to those seen in the pivotal Studies 343 and 344. Based on the cumulative review of the post-marketing cases reported in BED, there was no evidence of an increased risk of serious cardiovascular events in BED patients being treated with lisdexamfetamine. The totality of the data indicates that the safety profile of lisdexamfetamine in BED is generally consistent with the established safety profile of lisdexamfetamine in ADHD. A Supplemental New Drug Application (sNDA) supporting

²⁴ Ulfvebrand S et al 2015 Psychiatric comorbidity in women and men with eating disorders results from a large clinical database *Psychiatry Research* 2015; 230: 294-299

²⁵ Crow S. Treatment of Binge Eating Disorder. *Current Treatment Options in Psychiatry* 2014; 1: 307-314

²⁶ Mordes JP et al Medications for weight loss. *Curr Opin Endocrinol Diabetes Obes* 2015; 22: 91-97

BED was approved by the FDA Division of Psychiatry under priority review in January 2015. Based on the data generated in the BED program, the FDA concluded that the existing cardiovascular language in the labelling was adequate. Shire proposes to implement the same labelling language to the Australian PI, including a clear limit of use statement that the lisdexamfetamine is not indicated for weight loss.

In conclusion, a favourable benefit-risk profile is associated with the use of lisdexamfetamine for the treatment of moderate to severe BED in adults. Robust efficacy with an acceptable safety profile has been demonstrated in each of the studies in the BED Clinical Development Program. The adults enrolled in these studies are generally representative of the adult population as defined in the proposed Australian PI and likely to be treated with lisdexamfetamine for the symptoms of BED. The risk associated with lisdexamfetamine therapy can be adequately managed through appropriate labelling, pharmacovigilance surveillance, and 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 specialists. Professors [information redacted] conclude in their report that lisdexamfetamine would be the first pharmacologic agent approved in Australia for the treatment of BED and could have a role either as initial treatment for uncomplicated BED or as an adjunct to psychological treatment. They further observe that restriction of prescription of lisdexamfetamine for BED in Australia to psychiatrists will ensure that misuse of lisdexamfetamine is minimised as core training for these specialists includes specific training on differential diagnosis and management of BED.

Clinical program for BED

On 1 June 2016, the sponsor submitted an application to extend the indication of lisdexamfetamine capsules to treat BED in adults 18 to 55 years of age. The initial application, presented the BED development program experience derived from 5 clinical studies:

- Study SPD489-208: Phase II dose finding study
- Study SPD489-343 and SPD489-344: Pivotal Phase III studies
- Study SPD489-345: Phase III open label safety study
- Study SPD489-346: Phase III, double blind, placebo controlled, randomised-withdrawal study
- Study 208 was a dose finding study that included an 11 week placebo controlled, double blind treatment period. During the 3 week forced dose titration period, subjects were titrated to the dose to which they were randomised. Subjects were maintained on their randomised dose for the subsequent 8 week dose maintenance period.
- Studies 343 and 344 were identical double blind, placebo controlled studies that each included a 12 week treatment period. Both studies included a 4 week dose optimisation period followed by an 8 week dose maintenance period. Both studies assessed efficacy (based on impact of treatment on psychiatric and medical aspects of BED) and safety.
- Study 345 was an open label safety study with a 52 week treatment period. This study enrolled subjects who completed 1 of the 3 placebo controlled Studies 208, 343, or 344. It included a 4 week dose optimisation period and a 48 week maintenance period. During the maintenance period, the investigator could make dose adjustments if necessary based upon the occurrence of TEAEs and the investigator's overall impression of clinical response to the investigational product.

- Study 346 was a placebo controlled, randomised withdrawal study assessing maintenance of efficacy. The study consisted of 12 weeks of open label treatment followed by a 26 week double blind, placebo controlled, randomised withdrawal period. Following completion of the 12 week open label treatment phase, subjects were assessed for response (defined as ≤ 1 binge day per week for the 4 consecutive weeks [28 days] prior to the randomised withdrawal baseline visit and CGI S score of ≥ 2). Subjects meeting both criteria were considered responders and were eligible to enter the 26 week double blind randomised-withdrawal phase. These subjects were randomised to receive either lisdexamfetamine at the dose established during the open label treatment phase or placebo. Subjects not meeting these criteria were discontinued from the study.

Pivotal Studies 343 and 344 were identically designed, double blind, placebo controlled studies in adults ages 18 to 55 with moderate to severe BED and demonstrated the efficacy of lisdexamfetamine in treating BED. Both studies met their primary efficacy endpoint in reducing binge eating days/week and found statistically and clinically significant improvement in global binge related symptoms, distress and function (CGI-I), greater 4 week cessation from binge eating, and improvement on binge eating obsession and compulsion total score (Y-BOCS-BE). Change from Baseline in weight was observed as a secondary/medical endpoint or a safety endpoint in these studies. The primary endpoint and majority of secondary endpoints related to bingeing and related psychopathology.

Sponsor's response to concerns of the TGA delegate and the ACM

The ACM advised the following in response to the Delegate's specific questions on the submission:

Issue 1

Clarity on the acceptance of BED as a distinct psychiatric condition in Australia rather than a symptom of another underlying psychiatric condition is requested.

The ACM noted that BED is recognised as a distinct condition by ICD 10 (F50.81) in October 2016 with specific DSM diagnostic criteria (DSM-5 (307.51)).

The ACM also noted that the diagnostic criteria rely on subjective measures as is normal in psychiatry, as subjectivity does not undermine the diagnostic classification but may reduce the reliability of individual diagnosis.

Sponsor's response

Local data indicate that the clinical approach to BED in Australia aligns with ICD-10 and 11 and DSM-IV and DSM-5 in recognising BED as a distinct disease, with specific diagnostic criteria, disease course, and treatment recommendations.²⁷ Further, public recognition of BED as a significant source of social and personal burden in Australia is growing. A 2012 assessment of the social and economic cost of eating disorders in Australia estimated the total cost of eating disorders in Australia to be \$69.7 billion per annum, including healthcare costs, costs related to loss of productivity, and costs of informal care (www.thebutterflyfoundation.org.au). A more recent survey in Australia confirmed that, among Eating Disorders, mental health related quality of life is poorest for those with BED.²⁸ BED prevalence estimates in Australia are similar to those reported globally and are summarised in the accompanying report from Professors [information redacted].

²⁷ Hay P et al., (2014) Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the treatment of eating disorders. *Australian & New Zealand Journal of Psychiatry*. 2014; 48: 977-1008.

²⁸ Hay P et al., (2017) Burden and health-related quality of life of eating disorders, including Avoidant/Restrictive Food Intake Disorder (ARFID), in the Australian population. *Journal of Eating Disorders*. 2017; 5: 21.

Evidence supporting the reliability of individual diagnosis of BED has come from formal assessment of the validity and test-retest reliability of diagnostic criteria for BED. This has demonstrated that DSM criteria identify a group of patients whose symptoms are distinct from those of patients with other eating disorders. Further, substantial interrater reliability between clinicians and research assessors has been shown for both DSM-IV (84% agreement) and DSM-5 (83% agreement) criteria.²⁹ These observations support high reliability of the individual diagnosis of BED.

Thus, although diagnostic evaluation of BED includes evaluation of information reported by the patient which can be subjective (for example, current and prior distress), validity and reliability of the diagnosis have been shown to be high.

Issue 2

Is the committee satisfied that the selection of days of binge eating per week, as determined in the pivotal studies is an appropriate primary efficacy measure for a treatment of Binge Eating Disorder (BED)?

The ACM noted 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. Questionnaires contained 300 to 400 questions but included few directly relevant to the criteria. ACM agreed 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.

Sponsor's response

The primary endpoint, the number of binge eating days per week, was selected as this is a core symptom by which BED is diagnosed.³⁰ This endpoint is the basis for the DSM-5 severity criteria, has been shown to be highly clinically relevant (correlated with psychopathology;³¹ and has been used most widely in formal assessments of the efficacy of both behavioural and pharmacologic treatments of BED.³² Further, on the relative value of different outcomes, Section 8.4.6 of the United Kingdom's National Institute for Clinical Excellence (NICE) 2017 Eating Disorders guidelines state: *'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.'*³³

The endpoints included in the BED development program sought to measure a range of core and comorbid symptoms commonly associated with BED. To minimise the risk of Type I error (false positive or rejecting the null hypothesis of no difference between treatment conditions when it is in fact true), a hierarchical testing procedure was used in the comparisons between the lisdexamfetamine and the placebo groups on the primary and key secondary efficacy endpoints. This hierarchical testing procedure was pre-specified in the Statistical Analysis Plan (SAP), which was finalised before the studies were unblinded and data were analysed. Testing was conducted in the following order in both pivotal Studies 343 and 344:

²⁹ Thomas JJ et al. (2014) Do DSM-5 Eating Disorder Criteria Overpathologize Normative Eating Patterns among Individuals with Obesity? *Journal of Obesity* 2014; Volume 2014, Article ID 320803

³⁰ Guerdjikova A I et al, 2017 Binge Eating Disorder *Psychiatr Clin N Am* 2017

³¹ Gianini L et al, 2017 Mild, moderate, meaningful? Examining the psychological and functioning correlates of DSM-5 eating disorder severity specifiers. *Int J of Eat Disord* 2017; 2017; 1-11

³² Peat C M et al, 2017 Comparative Effectiveness of Treatments for Binge-Eating Disorder: Systematic Review and Network Meta-Analysis. *Eur. Eat. Disorders Rev.* 2017; Published online in Wiley Online Library (wileyonlinelibrary.com) DOI: 10.1002/erv.2517

³³ <https://www.nice.org.uk/guidance/ng69/evidence/fullguideline-pdf-161214767896>

1. Change from Baseline in the number of binge eating days per week (primary efficacy endpoint)
2. CGI-I score
3. Proportion of subjects with 4 week binge eating cessation
4. Percent change from Baseline in body weight
5. Change from Baseline in Y-BOCS-BE total score
 - a. The Y-BOCS-BE includes question about the amount of time the subject spends on obsessions and compulsions, how much impairment or distress they experience, and how much control they have over these thoughts or behaviours.
6. Change from Baseline in triglycerides (TG)
7. Change from Baseline in total cholesterol (TC)
8. Change from Baseline in HbA1c.

A later test was reported as statistically significant only if all earlier tests were also statistically significant at the 2-sided 0.05 level. This approach is widely accepted as a robust method for controlling Type I error. With the exception of HbA1c, all of the above endpoints showed significant improvement with lisdexamfetamine treatment relative to placebo.

Additional secondary and exploratory endpoints that showed significant improvement with treatment with lisdexamfetamine compared to placebo included:

- The Cognitive Restraint of Eating score of the Eating Inventory
- The Emotionally Based Disinhibition of Eating Score of the Eating Inventory
- The Perceived Hunger Score of the Eating Inventory
- The Binge Eating Scale (BES)
 - The BES assesses behavioural, affective, and attitudinal components of the subjective experience of binge eating; measuring degree of control.
- The Sheehan Disability Scale (SDS) global impairment score
 - The SDS measures the extent to which a patient's illness has impacted their work, social life, family life and home responsibilities.

Taken as a whole these data provide robust evidence of the efficacy of lisdexamfetamine across a range of BED symptom domains including core symptoms directly relevant to the BED diagnosis and common comorbid symptoms of BED. This efficacy was demonstrated using a rigorous and disciplined statistical testing procedure that adhered to accepted standards of practice for minimising Type I error and bias, such as that which would result from testing of multiple efficacy endpoint assessments and selective reporting of only positive results. Indeed both the TGA's clinical evaluator and the ACM found the results of the pivotal studies to be positive. The clinical evaluator stated in the CER; 'Efficacy data were robust and were supported by sensitivity and secondary endpoint analyses'.

Issue 3

Does the committee consider that subject selection for the pivotal studies was appropriate to support the current proposed BED indication for lisdexamfetamine?

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 Shire 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 safety of lisdexamfetamine were it to be used in the general BED patient population.

Sponsor's response

Sites and investigators selected for participation in Shire studies within the lisdexamfetamine BED program were identified, evaluated and selected if they were part of or lead of a team that diagnosed and treated BED patients using current standards of care, including pharmacological and nonpharmacological 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 inclusion and exclusion criteria used across the five BED studies were developed to allow for a generalisability of results from the clinical studies to the intended BED population.

All studies enrolled male and non-pregnant female subjects with a diagnosis of BED who were 18 to 55 years of age at the time of consent. Subjects entering Study 208 were required to have a BMI of ≥ 25 to ≤ 45 kg/m². For all subsequent studies, a BMI criterion of ≥ 18 to ≤ 45 kg/m² was used. These demographic inclusion criteria were chosen to ensure that subjects included in these studies reflected the typical demographic features of patients with BED (for example: young to middle aged adults with elevated BMI.³⁴ To maintain consistency in subject selection, all five of the BED studies used DSM-IV-TR BED diagnostic criteria.

Binge eating disorder severity was primarily determined by the number of binge days per week. Subjects enrolled across all five studies had BED of at least moderate severity, defined as 3 or more days per week for 2 consecutive weeks. Studies 343 and 344 also required a CGI-S score of ≥ 4 .

Key safety related exclusion criteria in the BED clinical trials reflected either 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 central nervous system, blood pressure or heart rate; abnormal thyroid function). Importantly, 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.

Of subjects receiving lisdexamfetamine in Studies 208, 343, and 344, 57.7%, 47.4%, and 49.2% met BMI criteria for obesity (BMI ≥ 30 to < 40), respectively, while 19.9%, 19.8%, and 19.9% met BMI criteria for morbid obesity (BMI ≥ 40). Thus, the majority of subjects receiving lisdexamfetamine in these studies were obese or morbidly obese, consistent with the broader BED population.

Together, these data provide strong evidence to support that subjects included in the BED program were representative of the BED population for whom lisdexamfetamine treatment would be prescribed under the proposed label.

³⁴ Cossrow N et al, 2016. Estimating the Prevalence of Binge Eating Disorder in a Community Sample From the United States: Comparing DSM-IV-TR and DSM-5 Criteria *J Clin Psychiatry* 2016; 77: 8

Issue 4

Does the Committee consider there is a role for lisdexamfetamine in the management of BED? If so what is that role?

ACM noted that there was a need to assess the strength of the evidence. Whilst the results of the studies are positive, there are biases to be considered such as that the blinding may be ineffective due to the side effects of amphetamines making performance bias and detection bias more likely.

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.

Sponsor's response

Blinded trials within the BED development program utilised widely accepted methods for protecting the blind, including matching placebo and identical procedures for all randomised subjects, who were randomised after an evaluation determined that they met study inclusion/exclusion criteria. Sites and Shire did not have access to the treatment codes. Sites participating in the BED clinical trials did not have extensive prior experience with psychostimulants and patients with a history of psychostimulant use within 6 months of screening were excluded. This relative lack of familiarity with psychostimulants would have minimised recognition of stimulant effects. Thus, these trials employed rigorous methods to ensure fidelity of the blind in study design, conduct and analysis for demonstration of efficacy and safety in clinical trials.

The use of an observable primary endpoint (number of binge episodes per week) provided further protection against the introduction of subjective bias stemming from functional unblinding.³⁵ The high placebo response rates observed in all of the blinded BED trials (for example 4 week remission rates ranged from 13.1 to 20.3% in the placebo arms for Studies 208, 343, and 344) provides strong evidence that blinding was effective. In Study 346 (randomised withdrawal study), the majority of subjects who responded to lisdexamfetamine who were then randomised to placebo did not relapse (68%). As noted in the TGA's clinical evaluation report, this low rate of relapse among subjects randomised to placebo may reflect both persistence of efficacy as well as placebo response. In addition, the proportion of subjects who did not complete the study was nearly identical for both placebo and lisdexamfetamine groups in both Study 343 (18% for both groups) and Study 344 (25% for both groups). Thus, the totality of the data suggests that the blind in efficacy assessments of lisdexamfetamine in BED was maintained throughout the studies.

Regarding the inclusion of a comparator or other therapies such as CBT as alternative or adjunctive therapies; treatment goals for patients with BED include abstinence from binge eating, improved psychological functioning, and appropriate weight regulation in overweight patients.³⁶ Although a reference treatment may be included in clinical trials to (for example, for assessment of assay sensitivity), there are no approved pharmacological treatments for BED. In addition, non-pharmacologic treatments, such as CBT and interpersonal psychotherapy, have limited accessibility, have no widely accepted standard, and, literature suggests, have limited efficacy.³⁶

For example, while CBT can be effective in reducing bingeing, some patients do not respond.³⁶ Psychotherapy also appears to have minimal efficacy.³⁷ As noted by Professors [information redacted] in the attached report, the general availability of specialised

³⁵ Day S J and Altman D G. 2000 Statistics Notes Blinding in clinical trials and other studies *BMJ* 2000; 321: 19-26

³⁶ Peat C. M et al, 2012 Binge Eating Disorder. Evidence based treatments Alone or combined, pharmacotherapy and CBT can reduce bingeing, psychopathology. *Current Psychiatry* 2012; 11: 33-39

³⁷ Hay PPJ et al 2009 Psychological treatments for bulimia nervosa and bingeing (Review) *Cochrane Database of Systematic Reviews* 2009, 4; Art. No.: CD000562.

psychotherapy and behavioural therapy is also limited. Lack of widespread availability of skilled clinicians and manualised behavioural therapies further limits the operational feasibility of conducting trials assessing lisdexamfetamine as an adjunctive therapy in BED.

Several medication classes have been studied and some have been used off label to treat BED, such as SSRIs and anticonvulsant medications. 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.³⁸ In addition, these medications can be associated with problematic adverse effects.

In the context of the above factors, the focus of the clinical program for BED at Shire was to assess the safety and efficacy of lisdexamfetamine in the treatment of BED.

While the neurobiology of BED remains poorly understood, a dysfunction in dopamine and norepinephrine (noradrenaline) signalling 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.³⁸ Lisdexamfetamine increases the availability of both of these neurotransmitters and, therefore, its efficacy in BED is expected based upon the most current neurobiological understanding of BED.

There are no currently approved medications in Australia indicated for treatment of BED. Overall, there is significant unmet medical need in BED for effective treatments that safely reduce binge eating and lead to improvement in binge related psychopathology. Evidence supporting the efficacy of lisdexamfetamine as a treatment for moderate to severe BED is robust, demonstrating broad efficacy observed across core and comorbid symptoms commonly associated with BED,³⁹ a conclusion also drawn by the TGA clinical evaluator. A recent analysis showed that treatment of BED with lisdexamfetamine is cost effective, given the benefits of treatment and the resulting increase in Quality Adjusted Life Years.³⁹ The clinical trials providing evidence supporting the use of lisdexamfetamine in the treatment of BED were rigorously conducted following established and accepted standards for maintenance of the study blind.

Issue 5

Does the Committee consider that there is sufficient evidence to support 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.

Sponsor's response

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 safety study (Study 345). For subjects who remained in this study, improvement in the severity of illness (as measured by the CGI-I) and improvement in the global and core eating disorder psychopathologies (as measured by the EDE-Q) did not diminish with time. In pivotal Study 343 and 344, the number of binge eating episodes per week declined from baseline over the first 3 to 5 weeks of treatment and remained stable thereafter, suggesting that the 12 week duration of these trials was sufficient to fully characterise the trajectory of treatment response.

Maintenance of long term efficacy is further supported by results for the primary efficacy endpoint in Study 346. In this study, subjects randomised to continue lisdexamfetamine

³⁸ Kessler R M et al, 2016. The neurobiological basis of binge eating disorder. *Neuroscience and Biobehavioral Reviews* 2016; 63: 223–238

³⁹ Agh T et al, 2016. The Cost Effectiveness of Lisdexamfetamine Dimesylate for the Treatment of Binge Eating Disorder in the USA. *Clin Drug Investig* 2016 (online article) DOI 10.1007/s40261-016-0381-3

were 8.7 times less likely to relapse than subjects who were randomised to placebo, strongly demonstrating that the initial efficacy of lisdexamfetamine seen after 12 weeks of open label treatment is maintained over a subsequent 26 week treatment period.

Concern was raised in the TGA's CER that only 60% of subjects entering the open label safety study (Study 345) completed 1 year of treatment. However, data from this study together with that from Study 346 support long-term efficacy of lisdexamfetamine in BED. Furthermore, language is included in the Dosage and Administration section on BED in the proposed Australian PI that instructs physicians to assess ongoing treatment response and risk/benefit of lisdexamfetamine therapy as follows:

'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.'

Issue 6

If lisdexamfetamine were to be approved for treatment of BED should the diagnosis and/ or ongoing treatment be restricted to a group of specialist medical practitioners? 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.

Sponsor's response

No further comment.

Issue 7

Does the Committee consider that the risk of misdiagnosis of general over eating as BED can be appropriately managed? If so, how would this be accomplished? (please see the BED diagnostic criteria in Attachment 2 and EDE-Q 6.0 in Attachment 3).

The ACM agreed that the risk of misdiagnosing BED and potential of abuse of lisdexamfetamine is high. ACM noted that overeating is common, with obesity and overweight affecting over 50% of the Australian adult population.

The ACM also noted 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.

Sponsor's response

Shire acknowledges the concerns raised by the ACM, but believes 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. These features include:

- Loss of control and inability to stop eating even when uncomfortably full
- Consuming a larger amount of food than others would consider reasonable in a short period of time even when not hungry
- Eating more rapidly than normal
- Eating until uncomfortably full
- Eating alone and being embarrassed about eating behaviour and hiding food
- Significant emotional and physical distress associated with overeating.

Most importantly, prescription of lisdexamfetamine for BED will be restricted to psychiatrists, who have expertise in appropriate diagnosis of BED and in distinguishing patients with BED from patients attempting to obtain a prescription for weight loss. In the

Australian clinical practice setting, the Expert Statement by Professors [information redacted] (provided below) confirms that Australian psychiatrists are trained in performing assessment and able to make accurate diagnosis of BED. A key feature that distinguishes patients with BED from obese individuals without BED is the significant, impairing levels of shame and emotional distress that these patients experience. These symptoms tend to prompt referral of these patients to psychiatrists. In contrast, obese patients without BED, can be treated by other clinicians with the use of pharmacological therapies such as phentermine, and orlistat in Australia as well as other treatment modalities such as bariatric surgery. Availability of these treatments should minimise any incentive to feign BED symptoms in order to secure lisdexamfetamine from Australian psychiatrists who, as Professors [information redacted] have attested, are expertly trained to evaluate and diagnose BED.

Issue 8

Does the committee consider that proposals to manage the risks of abuse/ misuse including intentional increase in dose to increase weight loss, addiction and diversion are likely to be adequately managed by the mechanisms proposed by the sponsor?

The ACM agreed that the proposals to manage the risks of abuse/ misuse including intentional increase in dose to increase weight loss, addiction and diversion are not going to be adequately managed by the mechanisms proposed by the Shire.

The ACM concluded that the evidence provided in the Shire's submission did not satisfactorily establish the safety and efficacy of lisdexamfetamine capsules containing 30 mg, 50 mg, and 70 mg of lisdexamfetamine dimesilate.

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 relative to patients with BED. Thus the patient group most at risk of adverse cardiovascular outcomes from use of lisdexamfetamine is not included in the current cardiovascular safety study.

Sponsor's response

Monitoring for intentional drug misuse, drug abuse and diversion: Intentional drug misuse, drug abuse and diversion are monitored as identified risks through pharmacovigilance processes described below. Proposed labelling should help to exclude at risk patients from receiving therapy. Off-label use is monitored through investigation of regional prescribing patterns including prescribing patterns among physicians and usage patterns among patients. Restricting prescribing to psychiatrists should further reduce the risk of successful diversion, as these specialists typically receive specific training in the recognition and management of substance abuse.

The sponsor has a single Global Drug Safety (GDS) department supporting all Shire products with a designated Qualified Person for Pharmacovigilance. Pharmacovigilance (PV) practices are governed by a global set of standard operating procedures and are used in the training of all GDS personnel worldwide. GDS Safety Surveillance performs ongoing signal detection, safety monitoring, and evaluations for all Shire products. Adverse events from all data sources are routinely reviewed and evaluated to identify potential safety signals for investigational and marketed products following a standardised procedure. These activities begin with the intake of an AE report, proceed with individual report characterisation and attribution analysis, including medical review, and conclude with aggregate case analysis and signal detection activities.

All post-marketing and serious clinical trial reports are entered into the Shire Global Safety System. Safety information is entered and coded by trained GDS personnel and is checked by an independent reviewer for accuracy. Medical assessment of all SAEs is done

by the product assigned GDS physician. All reports meeting requirements for expedited reporting are submitted to Regulatory Authorities. Aggregate reports (for example, Periodic Safety Update Reports) are prepared, medically reviewed, and submitted to the respective Regulatory Authorities.

The GDS physician is responsible for the review of all individual safety reports. A signal detection review is performed on a monthly basis. Two external data sources, the FDA's Adverse Event Reporting System (AERS) database and Vigibase are data mined on a quarterly basis to identify potential signals. The continuous monitoring of safety data from clinical trials is performed within the sponsor's clinical research department and from nonclinical sources within the sponsor's preclinical research department.

Results of the signal detection process are presented to a product specific Safety Review Team (SRT). The product specific SRT is a group of experts from various fields within the sponsor's company, co-chaired by the responsible product physicians from GDS and clinical development. The SRT is responsible for review of all safety signals encompassing nonclinical trials, clinical trials, and post-marketing reports. Potential risks are identified and characterised and targeted active data collection is coordinated on potential risks. The SRT determines whether changes to the safety profile of products have occurred and develops risk-management strategies. In addition, the SRT is responsible for immediately escalating any potential issues negatively impacting the benefit/risk balance to the Executive Safety Review Committee. Safety Review Team meets regularly, with the frequency dependent on the lifecycle stage of the product. Ad hoc meetings are held, as needed.

Additional measures to ensure that the correct patients are receiving lisdexamfetamine and that they are using it appropriately include:

- Warning, in the PI, that lisdexamfetamine is not indicated for weight loss to place emphasis on the psychiatric aspects of the disorder and clearly indicate that the drug was not developed and should not be used for weight loss.
- Inclusion of a warning in the product information advising prescribers to assess for the risk of abuse prior to prescribing and to monitor these signs during treatment.
- 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 with lisdexamfetamine).
- Drug Utilization Study in Australia.
- Controlled drug status: Medicines listed as Schedule 8 (S8) in the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) are subject to stricter control than Schedule 4 (S4) prescription only medicines. State based legal obligations require documentation of prescribing, secure storage, dispensing and destruction of these medicines. Prescribers can prescribe S8 psychostimulant medicine to a patient only upon obtaining an authority to prescribe from state health authority. lisdexamfetamine being one such medicine is already subject to these strict controls when prescribed for use in patients with ADHD and, based on the discussions Shire has had with state health authorities, similar controls will be applicable for use of lisdexamfetamine in patients with BED once approved by the TGA.

Evidence supporting low diversion/misuse risk of lisdexamfetamine capsules: Data related to adherence and drug accountability were collected in Studies 208, 343, 344 and 345. Per the Statistical Analysis Plan for these studies, % compliance was defined as the total number of capsules taken x 100/total days of dosing, where the total number of capsules taken was calculated as the total number of capsules dispensed minus the total number of capsules returned for each subject. Subjects who had taken 80 to 120% of prescribed investigational product were defined as compliant. In Studies 208, 343, 344, and 345, the

majority (> 97%) of subjects receiving lisdexamfetamine were compliant, suggesting that misuse, abuse or diversion of lisdexamfetamine did not occur in these studies.

Meta-analysis of published data on substance abuse among patients with eating disorders has identified a small but increased risk for substance abuse in individuals with BED.⁴⁰ However, since the approval in the US of lisdexamfetamine for treatment of ADHD in 2007 and for BED in 2015, post-marketing surveillance has revealed no increasing trends of lisdexamfetamine nonmedical use or diversion compared to other stimulants. In fact, data from 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 was not impacted by the lisdexamfetamine approvals. Consistent with this trend, prospective longitudinal studies have shown that stimulant treatment of ADHD, a disorder that shares with BED the features of impulsivity and dopamine dysregulation, is associated with reduced incidence of drug misuse and abuse.^{41,42,43,44}

A cumulative search of Australian post-marketing data through to 30 June 2017 of the sponsor's Global Safety System (GSS) identified 2 Australian post-marketing cases reporting 4 events associated with abuse/diversion of lisdexamfetamine. The following search strategy with Medical Dictionary for Regulatory Activities (MedDRA) version 20.0 was used: Drug abuse and dependence SMQ (narrow); Drug diversion PT; Product tampering PT; Suspected product tampering PT. The reported events were as follows: Drug diversion; Intentional overdose; Intentional product misuse; Product tampering. Cumulatively through to 30 April 2017, the patient exposure to lisdexamfetamine in Australia was 18,884 Patient Years. Consequently, the 2 cases report isolated events and therefore no significant new safety information has been identified in Australia.

The first case (considered serious) concerned a 16 year old female patient who experienced drug diversion, described as 'bought 5 capsules of lisdexamfetamine from a friend at school', and took all 5 capsules at once in an intentional overdose. The second case (considered non-serious) reported a male patient of unknown age who believed that his roommate was removing powder from the lisdexamfetamine capsules and switching them with another powder.

Additional Information Regarding Cardiovascular Safety of lisdexamfetamine: With respect to the pharmaco-epidemiological study it should be pointed out that there is some overlap between ADHD and BED. A cross-sectional study estimated that the prevalence of ADHD in BED is 8.1% versus 2.6% in the general population. Therefore, while not specifically designed to evaluate patients with BED, the study will collect data about which patients have a history of eating disorders.⁴⁵ Lisdexamfetamine is labelled with a contraindication in advanced arteriosclerosis, symptomatic cardiovascular disease including cardiac arrhythmia, ischemic heart disease, and moderate to severe hypertension. In addition it contains a cardiovascular warning for patients with structural heart defects, cardiac

⁴⁰ Calero-Elvira A et al., (2009) Meta-Analysis on Drugs in People with Eating Disorders *Eur. Eat. Disorders Rev.* 2009; 17: 243-259

⁴¹ Shaw M et al., (2012) A systematic review and analysis of long-term outcomes in attention deficit hyperactivity disorder: effects of treatment and non-treatment. *BMC Medicine* 2012; 10:99.

⁴² Hammerness P et al., (2013) Do Stimulants Reduce the Risk for Cigarette Smoking in Youth with Attention-Deficit Hyperactivity Disorder? A Prospective, Long-Term, Open-Label Study of Extended-Release Methylphenidate. *J Pediatr* 2012;

⁴³ Wilens T et al., (2008) Effect of Prior Stimulant Treatment for Attention-Deficit/Hyperactivity Disorder on Subsequent Risk for Cigarette Smoking and Alcohol and Drug Use Disorders in Adolescents. *Arch Pediatr Adolesc Med.* 2008; 162: 916-921

⁴⁴ Biederman, J. (2003) Pharmacotherapy for Attention-Deficit/Hyperactivity Disorder (ADHD) Decreases the Risk for Substance Abuse: Findings from a Longitudinal Follow-Up of Youths With and Without ADHD. *J. Clin Psychiatry* 2003; 64: S 3-8

⁴⁵ Svedlund N et al., (2017) Symptoms of Attention Deficit Hyperactivity Disorder (ADHD) among adult eating disorder patients. *BMC Psychiatry* 2017; 17: 19

abnormalities, cardiomyopathy, arrhythmia, or coronary artery disease. The labelling also states that blood pressure and cardiovascular status should be regularly reviewed. Ischemic cardiac events are monitored as a potential risk in the lisdexamfetamine RMP.

A broad search of the cumulative post-marketing data from all patients treated with lisdexamfetamine through 30 June 2017 identified a total of 17 adverse event (AE) reports describing potential cardiovascular events in BED patients. Global cumulative patient exposure through to 30 April 2017 was 7,740,107 patient years.

The search consisted of MedDRA 20.0 preferred terms including the following SOCs and SMQs:

- Cardiac disorders SOC
- Ischaemic Heart Disease SMQ Narrow
- Cardiomyopathy SMQ Broad
- Central Nervous System Haemorrhagic and Cerebrovascular Condition SMQ Narrow
- Cardiac failure SMQ Narrow
- Cardiac Arrhythmias SMQ Narrow.

Of the 17 reports, 11 were serious and 6 were non-serious. One serious AE report included an ischemic stroke secondary to spontaneous vertebral artery dissection in a 42 year old obese female previously treated with lisdexamfetamine for BED. The patient had a medical history significant for alcohol use and increased blood pressure. The patient commenced treatment with lisdexamfetamine 30 mg (frequency unknown) as part of an open label portion of a clinical trial (Study 346) for BED. On Day 8 of treatment the dose was increased to 50 mg (unknown frequency). Approximately 3 months later, the patient was randomised to lisdexamfetamine or placebo and the last dose was taken was approximately 2 months later. The patient stopped the study medication due to headaches and elevated blood pressure. Approximately 1 month following withdrawal from the study (and the last dose of the study medication), the patient woke up with a mild headache. A few hours later she experienced slurred speech, loss of balance, right facial droop with numbness and weakness intermittently to the right side of her body and difficulty swallowing. The patient visited the emergency room where alteplase and apixaban were started. A computed tomography angiogram revealed stenosis 50% with dissection at V3, V4 segment of the right vertebral artery, and a magnetic resonance imaging of the brain revealed a diffusion weighted imaging of hyperintensity in the right lateral medulla. The patient was diagnosed with spontaneous vertebral artery dissection (right V3 and V4) and acute ischemic stroke secondary to a vertebral artery dissection.

Vertebral artery dissection is most commonly associated with trauma and/or genetic connective tissue disorders;⁴⁶ however hypertension is also a risk factor. Given this patient's pre-existing hypertension and the fact that study drug had been discontinued 1 month prior to the vertebral artery dissection event, this event and the related stroke were considered unlikely to be related to lisdexamfetamine.

In the remaining 10 SAEs, based upon BMI the majority of patients would have been considered obese or morbidly obese. In 3 weight and BMI was unknown, one had a BMI between 20 and 30, 3 had a BMI between 30 and 40, and 3 had a BMI greater than 40. In one the AE of atrial fibrillation was considered unlikely to be related to lisdexamfetamine. Relatedness of a second event of arrhythmia could not be determined due to insufficient information. 5 events (tachycardia, palpitations, 3 reports of chest pain or discomfort) were considered expected events for lisdexamfetamine. One event of decreased blood pressure and one event of irregular heart rate were considered possibly related to

⁴⁶ Ortiz J and Ruland, S. 2015 Cervicocerebral artery dissection. *Curr Opin Cardiol* 2015; 30: 603–610

lisdexamfetamine. Of 2 reports of syncope, relatedness of 1 report could not be determined due to multiple confounding concomitant medications, while the second was considered possibly related to lisdexamfetamine.

There were 7 non-SAEs reported in 6 patients that included palpitations (4 events), dyspnoea (2 events), and heart rate increased (1 event).

Overall based on the cumulative review of the 17 relevant post-marketing AE reports for BED, the majority were either confounded by concomitant medications or medical history, expected events well described in the product labelling, or lacking in sufficient detail to assess. As a result of this review the benefit risk profile of lisdexamfetamine was considered to remain favourable.

The sponsor proposes to add a Limitation of Use statement in the Indications section of labelling to address the fact that lisdexamfetamine has not been evaluated and is not recommended for weight loss or to treat obesity. The following statement is proposed for the Australian PI:

'lisdexamfetamine 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 lisdexamfetamine for the treatment of obesity have not been established'.

Concluding remarks

The accessibility to high quality psychological therapy is limited in Australia for patients with BED according to the Expert Statement by Professors [information redacted] and this limitation is also acknowledged by the TGA clinical evaluator.

The medical need for pharmacological treatments for BED, in addition to psychotherapy, is evident from RANZCP clinical practice guidelines for the treatment of eating disorder despite none of the recommended drug therapies being used have been subject to rigorous regulatory review and approval by the TGA for the indication.

The efficacy of lisdexamfetamine in reducing binge eating behaviour and associated psychopathology has been demonstrated in double blind randomised placebo controlled studies and longer-term supportive studies. The safety profile of lisdexamfetamine in BED is consistent with that established in ADHD and this observation is supported by a review of the post-marketing safety data which includes those derived from markets in which lisdexamfetamine is approved for BED.

The profile of patients with BED that can be treated with lisdexamfetamine have been further refined and the recommended duration of treatment has now been included in the proposed Australian PI to address concerns raised by the TGA and ACM.

lisdexamfetamine, if approved by the TGA, will only be prescribed by psychiatrists who are well versed in making accurate assessment and diagnosis of BED and thus minimizing the potential for overweight patients feigning BED to obtain lisdexamfetamine for weight loss.

Only psychiatrists authorised by State/Territory health authorities will be able to prescribe lisdexamfetamine (a controlled drug) and they will be required to submit periodic reports containing information on prescribed doses and quantities for monitoring purposes. In the community, pharmacists will only dispense lisdexamfetamine upon receipt of a prescription signed by an authorised psychiatrist. These control measures provide a high degree of safeguard against abuse/misuse of lisdexamfetamine.

Shire strongly considers that the clinical benefit to patients with BED in having access to lisdexamfetamine outweighs the potential risk of abuse/misuse, and the overall benefit/risk balance is positive when lisdexamfetamine is used according to the proposed PI supported by implementation of the proposed RMP.

Summary of current practice for the diagnosis and treatment of BED in Australia, prepared by two Australian clinical experts

Report dated 21 July 2017. Note, names of clinical experts have been redacted.

Report prepared at the request of the sponsor to experts to provide a summary to address the following queries from Australian context:

Question 1

How familiar Australian specialists are in diagnosing/identifying a patient with BED and what measures if any, can be taken to avert risk of misdiagnosis of BED?

Expert's response

Australian clinical psychologists and psychiatrists are well trained in both the assessment and diagnosis of eating disorders. Whilst screening questionnaires are useful in detecting the possible presence of an eating disorder, a diagnosis can only be confirmed on careful clinical interview. Psychiatrists are extensively trained in undertaking such clinical interviews and are both well versed in detecting the presence of subtle psychological symptoms to confirm a diagnosis and to distinguish these from nonclinical behaviours or emotional states for example, to distinguish grief from depression and to detect factitious presentations where the person is consciously creating false symptoms.

People with BED need to fulfil several diagnostic criteria such as loss of control and marked distress as well as other diagnostic qualifiers for binge eating as in the DSM-5 criteria (APA, 2013). Psychiatrists are trained to inquire not only into the veracity of the presenting symptoms but into the nature of the binge eating episodes as well. Further, eating disorders comprise core training and are included amongst Entrustable Professional Activities of the RANZCP training program.

BED is core business for Australian psychiatrists as it is now included as a distinct psychiatric diagnosis in DSM-5 (APA, 2013). On the other hand, the management of obesity is not core business for psychiatrists and those individuals seeking treatment for weight reduction are not referred to psychiatrists and would not be able to self-refer.

Australian psychiatrists under the auspices of the RANZCP have taken the lead in producing bi-national guidelines for eating disorders which have been actively presented and discussed at major psychiatric meetings such as the 2015 RANZCP Congress in Brisbane.⁴⁷ The RANZCP has been at the forefront of disseminating new evidence based treatments for eating disorders. This is not only through the publication of updated clinical practice guidelines in an open access format but also their but also by dissemination in consumer accessible formats and dissemination to the profession with a binational webinar in 2014. See:

- www.ranzcp.org/Files/Resources/Publications/CPG/Clinician/Eating-Disorders-CPG.aspx; Information for the public
- <https://www.yourhealthinmind.org/mental-illnesses-disorders/eating-disorders>
- 'Eating disorders and related exam content'
<https://www.ranzcp.org/Publications/Presentations/Webinars.aspx>).

Question 2

What is the disease burden and clinical consequences of BED in Australian patients?

⁴⁷ Malhi G et al., 2015 The 2014 RANZCP Clinical Practice Guideline Project and CPG for Eating Disorders. Australian and New Zealand Journal of Psychiatry 2015; 49(S1): 29-31

Expert's response

BED is not just a psychiatric disorder but has metabolic consequences and/or secondary complications. It is gaining recognition as a serious public health problem.⁴⁸ Australian researchers have been at the forefront of investigating the population prevalence of BED in Australia as well as the burden and health related quality of life as well as the socioeconomic correlates of eating disorders. 4 of the most recently published papers in 2017 include the following:

- Mulders-Jones B et al., (2017) Socioeconomic Correlates of Eating Disorder Symptoms in an Australian Population-Based Sample. *PloS one* 12.1 (2017): e0170603.
- Mitchison D et al., (2017) How abnormal is binge eating? 18 Year time trends in population prevalence and burden. *Acta Psychiatrica Scandinavica*. 2017 Apr 16. (Online early view).
- Hay P et al., (2017) Burden and health-related quality of life of eating disorders, including Avoidant/Restrictive Food Intake Disorder (ARFID), in the Australian population. *Journal of Eating Disorders*. Jul 3; 5(1):21.
- Linardon J. Correlates of the over-evaluation of weight and shape in binge eating disorder and mixed eating disorder samples: A meta-analytic review. *Eat Disord*. 2017 May-Jun; 25(3):183-198.

Hay et al. (2017) reported that the 3 month prevalence of BED (using criteria of recurrent binge eating with marked distress) in Australians is 1.5% (95% CI 1.1 to 2.0). This is much lower than Unspecified Feeding or Eating Disorder (UFED) prevalence of 10.4% (95% CI 0.9 to 11.5) where the majority of individuals with UFED were characterised by having recurrent binge eating with little or no distress. Eating disorders were represented throughout all sociodemographic groups and those with BED had a mean weight (BMI, kg/m²) in the obese range. Mental health related quality of life (HRQoL) was particularly poor for those with BED and individuals with BED also had poor physical HRQoL.

Generally speaking, patients with BED have been found to have poorer health with comorbid depressive and other psychiatric disorders, dysfunctional relationships and interpersonal functioning, chronic pain, obesity and diabetes.^{48,49} Hudson et al., (2010);⁵⁰ reported that binge eating and BED predisposed an individual to metabolic syndrome and that this occurred independently of weight gain, Type 2 diabetes and earlier onset diabetes. There was also evidence to suggest that the complications of diabetes are more severe and the outcomes poorer as a result of the nonadherence to recommended dietary advice. It is therefore not surprising that binge eating has been found to be a treatment limiting factor in those patients undergoing bariatric surgery as a loss of control experience in eating adversely impacts on both weight loss and quality of life where patients are unable to adhere to the post-surgical nutritional recommendations.⁵¹

Question 3

What are the current therapies and associated challenges/ease of access. Comment on the current treatment guidelines with respect to their implementation and any limitations in the Australian clinical practice setting?

⁴⁸Kessler RC et al The prevalence and correlates of binge eating disorder in the World Health Organization World Mental Health Surveys. *Biol. Psychiatry* 73, 904–914

⁴⁹ Javaras KN, et al 2008. Co-occurrence of binge eating disorder with psychiatric and medical disorders. *Journal of Clinical Psychiatry* 2008; 69: 226-273.

⁵⁰ Hudson JL, et al 2010. Longitudinal study of the diagnosis of components of the metabolic syndrome in individuals with binge eating disorder. *American Journal of Clinical Nutrition*, 2010; 91: 1568-1573

⁵¹ De Zwaan, M, et al 2010. Comprehensive interview assessment of eating behaviour 18-35 months after gastric bypass surgery for morbid obesity. *Surgical Obesity and Relationship Disorders* 2010; 6: 79-85.

Expert's response

It is a paradox that whilst patients are highly motivated to seek help for obesity, this is not the case for eating disorders where the outcomes are generally very good. Reviews suggest that fewer than 25% of patients with an eating disorder ever seek treatment for their eating disorder.⁵² This equates to around 700,000 Australians who remain untreated with an eating disorder. This is very evident with those with comorbidity, particularly people with non-purging forms of bulimia nervosa and BED who are much more likely to present to a clinic requesting help to lose weight than an eating disorder clinic. This is also in spite of the finding that the stigma of help seeking for an eating disorder is less than for obesity.⁵³

The current RANZCP clinical practice guidelines predate publication of the randomised controlled trials for efficacy of lisdexamfetamine. However, the recent NICE (2017) Guidelines do include this and summarise that: 'Appetite suppressants (lisdexamfetamine) showed favourable results compared with placebo on remission, changes in BMI and binge eating. There was also a trend of improvement in general physical functioning (though there was some uncertainty) in the appetite suppressant group, but no difference on general mental functioning. However, more people withdrew due to adverse events, and there was a trend towards higher depression scores in the appetite suppression arm compared with placebo. No evidence was found on the important outcomes of quality of life, all-cause mortality, relapse, or cost.'

NICE further commented on the lack of follow up data. However, since the publication of the NICE Guidelines, a one year open label follow-up study has been published.⁵⁴ This 12 month open label safety and tolerability trial reported the safety outcomes to be similar to those reported when it is used for ADHD. Reductions in binge eating were sustained over the 12 months.

In the Australian context, although psychiatrists are well trained in diagnosing psychiatric illness, few are trained in BED focussed Cognitive Behaviour Therapy (CBT) which is often the basis for guided self- help programs as well. Clinical psychologists do have this training but they are limited by Better Access to Mental Health Care which only permits 10 rebated sessions per year, and the most widely used individual based CBT therapy for BED in Australia is manualised CBT-E, trials of which have found that the majority of patients received 20 sessions over 20 weeks.⁵⁵

Furthermore, access to highly specialised psychological services is highly variable and is also limited by geography being notably poorer in regional and rural areas. Few clinical psychologists bulk bill so that there is already a high built in cost for individualised CBT. The cost would become even more burdensome when the Government rebate ceases to apply after 10 sessions with no safety net provisions. At times like this, many clinical psychologists/psychologists refer to psychiatrists (as suggested by Medicare). Furthermore, although clinical psychologists are all trained in evidence based therapies such as CBT, these are often for the management of anxiety and depression and there is a burden of access to highly skilled trained therapists in evidence-based treatments for eating disorders. Few clinical psychologists run group treatments for BED and we know of no psychiatrists who do so.

⁵² Hart LM, et al 2011. Unmet need for treatment in the eating disorders: a systematic review of eating disorder specific treatment seeking among community cases. *Clinical psychology review*. 2011; 31: 727-735.

⁵³ Star A et al., 2015 Perceived discrimination and favourable regard toward underweight, normal weight and obese eating disorder sufferers: implications for obesity and eating disorder population health campaigns. *BMC obesity*. 2015; 2: 4.

⁵⁴ Gasior M, et al 2017 A phase 3 ,multicentre, open label 12 month extension safety and tolerability trial of Lisdexamfetamine dimesylate in adults with Binge Eating Disorder. *Journal of Clinical Psychopharmacology* 2017,37 3 ,315-322

⁵⁵ Fairburn ,CG .2008 Cognitive Behaviour Therapy and Eating Disorders. New York. The Guilford Press 2008

Question 4

What is the role for pharmacological treatments in the medical management of BED?

Sponsor's response

To date, there is no approved pharmacological agent for BED in Australia and thus any use is off label. Medications such as fluoxetine and topiramate are potentially currently being used off label but the estimated prevalence of such practice within the Australian clinical setting is unknown. To our knowledge, there have been no studies to estimate such off label use. The RANZCP Clinical Practice Guidelines do refer to both topiramate and orlistat, with these recommended for those patients with BED co-morbid with obesity and consequential medical complications.²⁷

Brownley et al., (2016);⁵⁶ in a recent systematic review of BED in adults concluded that '*given the low strength of evidence derived from our qualitative findings, recommending self-help as a first line treatment would be premature*'. They went on to say that on the basis of their systematic review, there was as yet insufficient evidence for them to advise when and how to integrate psychological and pharmacological treatments for BED. In a thought provoking editorial entitled 'Binge-Eating Disorder Comes of Age',⁵⁷ Devlin, one of America's foremost psychiatrists in the field of eating disorders from Columbia University concluded that, '*given the array of psychological, behavioural, and pharmacologic treatment approaches currently available, how should we proceed after identifying the problem?*' Although Brownley and colleagues recommended cognitive and other forms of behavioural therapy, second generation antidepressants, topiramate, and lisdexamfetamine were the most supported treatments for binge eating in BED. They also pointed out that the comparative effectiveness and long term studies are lacking. Thus the practitioner is faced with a decision based on '*treatment availability, costs, adverse effects, patient preference, individual goals and patient specific factors, such as co-morbid depression or eating related obsessions and compulsions*'⁵⁸. The psychiatrist, trained in both pharmacological and psychological therapies, after an extensive clinical examination of the patient who thus determines the nature of the patient's treatment taking all the symptoms into consideration.

At the recent international conference on eating disorders in Prague (Czech Republic) convened by the Academy of Eating Disorders (AED) (June 2017), Professor James Mitchell from the National Research Institute (NRI) in Fargo, North Dakota (USA) presented a clinical workshop on the treatment of BED. Professor Mitchell is internationally regarded as one of the foremost authorities on the pharmacological management of BED. As BED has only recently been included as a diagnostic entity in DSM-5 (APA, 2013), he readily acknowledged that more research is needed to provide a stronger evidence base for the treatment of patients with BED. Professor James Mitchell has attempted to incorporate some of the above in his recommendations taking the current available state of scientific evidence and clinical intuition into account. His recommendations (www.nrifargo.com) as presented to the International Conference in Prague included the following points:

1. Trained practitioners in Psychological therapies are uncommon but trained practitioners in pharmacological therapies are common.
2. Medication with guided self-help is an accessible first step in treatment of BED
 - a. Lisdexamfetamine is an alternative to an antidepressant in uncomplicated BED.

⁵⁶ Brownley KA, et al 2016. Binge-Eating Disorder in Adults :A Systematic Review and Meta-analysis Binge-Eating Disorder: Treatment Effectiveness. *Annals of internal medicine*. 2016; 165: 409-420

⁵⁷ Devlin MJ 2016 Binge-Eating Disorder Comes of Age *Annals of internal medicine*. 2016; 165: 445-446.

⁵⁸ Brownley KA, et al 2016. Binge-Eating Disorder in Adults :A Systematic Review and Meta-analysis Binge-Eating Disorder: Treatment Effectiveness. *Annals of internal medicine*. 2016; 165: 445-446

- b. Lisdexamfetamine (or topiramate) is indicated in BED complicated by obesity.
3. Specialised psychological therapies such as CBT-E are second step treatments.

From the above, it would seem that international authorities agree that pharmacological treatments, alongside guided self-help and specialised psychological therapies, do have a role to play in the medical management of BED.

Question 5

What role Vyvanse can have in the management of BED?

Expert's response

Lisdexamfetamine would be the first pharmacological agent approved for the management of BED in Australia. It has been approved for use in the US and Canada. It would have a role as either initial treatment for those patients with uncomplicated BED, particularly if people are on waiting lists for psychological care, and it has a role as an adjunct to psychological care where psychotherapy alone cannot lead to a reduction in binge eating. This would particularly be the case if there was a medical co-morbidity present (such as diabetes) prompting the need for more active care.

Question 6

How would specialists manage risk of misuse if Vyvanse was approved?

Expert's response

The psychiatrist would be the gate keeper and as documented previously they are extremely well versed and trained in the assessment and diagnosis of eating disorders and to detect factitious disorder and substance seeking in those with addiction disorders. Binge eating is not just someone eating too much but to confirm the diagnosis the person has to meet specific diagnostic criteria. In order to do so, the psychiatrist will need to conduct an in depth interview.

BED patients often have at least one psychiatric co-morbidity, such as anxiety or depression, whilst others have more than one.⁵⁹ GCP involves developing a diagnostic formulation before instituting treatment so as to ensure that all aspects of the patient's personal, medical and psychiatric history are taken into consideration. Such good clinical practice is core to training for psychiatrists and should ensure that only those patients who meet diagnostic criteria receive the treatment they need taking all their co-morbidities into consideration. Psychiatrists are also medical practitioners and able to consider, monitor and manage in collaboration with family doctors and physicians, medical co-morbidities and complications.

Delegates comment regarding sponsors response

There are 18 references for evaluation in the supplementary data included in the response to ACM review. That information will require evaluation. An evaluation report will be prepared. After the evaluation further advice from the ACM (was) required.

VII. Clinical evaluation of supplementary information

A summary of the clinical evaluation of supplementary information is presented in this section. Further details of these clinical findings can be found in Attachment 3.

⁵⁹ Hudson JL, et al. 2007 The prevalence and correlates of eating disorders in the National Comorbidity Survey Replication. *Biological Psychiatry* 2007; 61: 348-358.

Introduction

In response to this submission, the first round clinical evaluation report (CER) was produced by the 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 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 (ACM meeting 3 on 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 below.

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 (see Attachment 2))
- The Delegate's request for ACM advice (dated 14 April 2017)
- Ratified minutes of ACM meeting 3: Item 2.02 lisdexamfetamine dimesilate (dated 2 June 2017)
- Information provided by the sponsor subsequent to the above, , 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
- RANZCP clinical practice guidelines for the treatment of eating disorders (2014).⁶⁰

⁶⁰ Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the treatment of eating disorders (2014), available at: <https://www.ranzcp.org/Files/Resources/Publications/CPG/Clinician/Eating-Disorders-CPG.aspx>

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

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.

Clinical efficacy

The BED studies were evaluated in the CER. The studies including the efficacy results are summarised in Attachment 3. The supplementary clinical evaluator's additional comments relating to study are provided below:

- Study 343:
 - No additional comment.
- Study 344:
 - No additional comment.
- Study 208:
 - No additional comment.
- Study 346:
 - 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.
- Study 345:
 - 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.

Safety

Presented below is an extract from the supplementary clinical evaluator's findings on safety. For the full report please see Attachment 3.

There were no new safety issues from the BED 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 Week 11 to 12) and a smaller increase was also noted in the placebo group (1 to 3 bpm) (Figure 1 Attachment 3). 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.

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.

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 clinical data. 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.

Consideration of issues raised by the delegate

In this section the issues of concern of the Delegate are considered and reviewed by the supplementary clinical evaluator. 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.

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;⁶⁰ 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.⁶¹

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 binational 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.

The supplementary clinical evaluator agrees that BED appears to be a valid and reliable diagnosis.

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,⁶² is the basis for the DSM-5 severity criteria, has been shown to be highly clinically relevant (correlated with psychopathology);⁶³ and has been used widely in formal assessments of the efficacy of both behavioural and pharmacologic treatments of BED.⁶⁴ 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'.

The supplementary evaluator notes the absence of EMA guidelines on BED, which would usually be consulted by a clinical evaluator when considering the appropriateness of an

⁶¹ Thomas JJ et al, 2014. Do DSM-5 Eating Disorder Criteria Overpathologize Normative Eating Patterns among Individuals with Obesity? *Journal of Obesity* 2014, Article ID 320803, 8 pages

⁶² Guerdjikova AI, et al 2017 Binge Eating Disorder. *Psychiatric Clinics* 2017; 40: 255-266

⁶³ Gianini L et al, 2017. Mild, moderate, meaningful? Examining the psychological and functioning correlates of DSM-5 eating disorder severity specifiers. *Int J Eat Disord*. 2017;1-11

⁶⁴ Peat CM et al, 2017. Comparative Effectiveness of Treatments for Binge-Eating Disorder: Systematic Review and Network Meta-Analysis. *Eur. Eat. Disorders Rev*. 2017

efficacy measure. The DSM-5 diagnosis and severity criteria depend upon binge eating episodes and not binge eating days (Table 2, Attachment 3); 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.

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 to 55 years of age at the time of consent, and the Phase III studies required subjects to have a BMI of ≥ 18 to ≤ 45 kg/m²; 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.

The supplementary 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.

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.

The supplementary 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.

While the supplementary evaluator believes it is possible to conduct clinical trials comparing lisdexamfetamine with psychotherapy such as CBT-Enhanced;⁶⁰ 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.⁶⁵ The

⁶⁵ Stines, L, Feeny, N. 2008 Unique Ethical Concerns in Clinical Trials Comparing Psychosocial and Psychopharmacological Interventions. *Ethics Behav.* 2008; 18: 234

sponsor indicated that the endpoint selection and design of the pivotal studies incorporated feedback from the US FDA.

The sponsor described how a dysfunction in dopamine and norepinephrine (noradrenaline) 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.⁶⁶

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. Shire 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.⁶⁷

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 guidelines⁶⁰ 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'.⁵⁸ 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 [information redacted], 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.

This supplementary 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.

⁶⁶ Kessler RM et al, 2016. The neurobiological basis of binge-eating disorder. *Neuroscience and Biobehavioral Reviews* 2016; 63: 223–238

⁶⁷ Agh T et al, 2016. The Cost Effectiveness of Lisdexamfetamine Dimesylate for the Treatment of Binge Eating Disorder in the USA. *Clin Drug Investig*. 2016 (doi:10.1007/s40261-016-0381-3)

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'.

It is noted by this supplementary 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 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.

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.

This supplementary 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'.

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.

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

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 Utilization Study in Australia, and the stricter controls due to lisdexamfetamine 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,⁴⁰ 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.^{41,42,43, 44}

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.

This supplementary 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.

Supplementary clinical 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 withdrawal⁷. 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 disorders⁶⁰ 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 in Attachment 3.

VIII. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations from the Delegate's overview for ACM 6 December 2017

The sponsor revised the proposed additional indication: Binge Eating Disorder (from June 2017 Pre-ACM response) to:

Binge Eating Disorder (BED)

Vyvanse is indicated for the treatment of moderate to severe BED in adults when nonpharmacological treatment is unsuccessful or unavailable. Treatment should be commenced and managed by a specialist.

Need for comprehensive treatment programme:

Vyvanse is indicated as an integral one 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.

Background

This submission to extend the indications of Vyvanse (lisdexamfetamine) to include treatment of BED was discussed at the June 2017 ACM 3 meeting and the committee

recommended that it not be approved. The sponsor has responded with additional information and further advice is now requested.

Lisdexamfetamine was first approved in 2013 for treatment of ADHD. Lisdexamfetamine is rapidly absorbed from the gastrointestinal tract and hydrolysed primarily to dexamphetamine, which is responsible for the drug's activity. It is thought to act by blocking the reuptake of noradrenaline and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space.

Binge eating disorder (BED) is defined according to DSM-5 as recurring episodes of eating significantly more food in a short period of time (for example 2 hours) than most people would eat under similar circumstances, with episodes marked by feelings of lack of control. The disorder is associated with marked distress and occurs on average at least once a week over three months. The condition also tends to have a long term remitting and relapsing course. Unlike those with bulimia nervosa or anorexia nervosa, people with BED will not regularly try to make up for the eating with compensatory behaviours such as vomiting or excessive exercise. This results in people with BED often being overweight or obese.

Psychotherapy is the current recommended first-line treatment. There are no medicines approved for treatment of BED in Australia. The sponsor reported that SSRIs, AEDs and ADHD medicines have been used in the treatment of BED.

Major issues of concern from the June 2017 ACM meeting

- 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.
- There was insufficient evidence to demonstrate that lisdexamfetamine is better than available treatments for BED; the sponsor has not compared lisdexamfetamine with a currently approved or recommended treatment for BED in an appropriately designed clinical trial. The ACM noted that at most, with further study data, lisdexamfetamine could be assessed as a possible third line therapy for BED.
- Longer term cardiovascular risk in patients with BED has not been adequately examined. The ACM considered this to be a concern given the history of amphetamine based weight loss products and noted that if the product had been developed for weight loss, there would have been a requirement for a cardiovascular outcome study. ACM noted that this requirement was sidestepped due to the proposed indication being for BED and not weight loss. While no cardiovascular risk was evident in the clinical program, the sample may have been too small, the trial duration too short and the population carefully selected.
- Other safety risks included:
 - that treatment related events were very frequent;
 - much of the patient population with BED would have contraindications to stimulant treatment with stimulant medication;
 - there were no firm long term efficacy data;
 - there were no long term safety data beyond 1 year;

- there is a risk of normalising amphetamine use for appetite suppression, a risk of off label use for weight loss, and a risk of abuse and of diversion out of the clinical setting.

Sponsor's response

The response to ACM concerns included a summary of current practice for the diagnosis and treatment of BED in Australia prepared by 2 leading experts in the treatment of BED [information redacted]. Both are authors of the 2014 edition of the RANZCP clinical practice guidelines for the treatment of eating disorders.

The above information as referred for supplementary clinical evaluation. The clinical evaluator, a psychiatrist, also re-considered the issues raised by the ACM.

Supplementary clinical evaluation

The following issues that were of concern were addressed in the supplementary clinical evaluation report.

The validity of BED as a distinct clinical condition

This issue has now been resolved. The ACM had previously agreed and it is further supported by evidence from the RANZCP and evidence supplied by the sponsor. BED is considered a valid diagnosis.

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

The clinical evaluator has noted that the DSM-5 diagnosis and severity criteria for BED depend upon binge eating episodes and not binge eating days; however, 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.

The appropriateness of subject selection for the pivotal studies

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 considered that 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 responded to this concern by noting 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.

The clinical 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.

The role of lisdexamfetamine in the management of BED

The ACM noted that whilst the results of the pivotal 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 clinical evaluator considers 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. This point was also referred to by the sponsor in the previously considered pre-ACM response.

Regarding the issue of the absence of an active comparator, the sponsor suggested that non-pharmacologic treatments have limited accessibility, no widely accepted standard, and that some literature suggests they have limited efficacy.¹⁸ 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. The clinical evaluator considered that while it is possible to conduct clinical trials comparing lisdexamfetamine with psychotherapy such as CBT-Enhanced, 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.

The sponsor indicated that the endpoint selection and design of the pivotal studies incorporated feedback from the US FDA.

The clinical evaluator further considered 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 conveys that management plans for BED ideally include psychotherapy.

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

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

The clinical evaluator has noted 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. The evaluator has proposed 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. Additionally the sponsor has 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.

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?

Restriction of use of lisdexamfetamine for initiation and ongoing treatment of BED should be restricted to psychiatrists. The evaluator and sponsor have agreed to this proposal.

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

The ACM considered that the risk of misdiagnosing BED and potential of abuse of lisdexamfetamine is high. The clinical evaluator considered that a restriction of the indication to psychiatrists, previously proposed by the ACM (and endorsed by the clinical evaluator) should minimise the potential for this medication to be used for weight loss in the absence of BED.

The evaluator further noted that 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.

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 clinical evaluator considers that the various measures described by the sponsor in the supplementary clinical evaluation report would ensure help that the risks involved in the use of lisdexamfetamine are minimised.

Additionally, the evaluator considers 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. The evaluator has included statements in the proposed PI entries under Indications and Dosage and Administration to reflect this.

The PI amendments recommended by the evaluator were listed in the supplementary clinical evaluation report but these are beyond the scope of the AusPAR.

Risk benefit analysis

Discussion

This submission to extend the indications of Vyvanse (lisdexamfetamine) to include a BED indication was proposed not to be approved after receipt of advice from the June 2017 ACM meeting. Following that meeting the sponsor submitted additional information, including support from two Australian psychiatrists with experience in the treatment of BED. Review of that information and reconsideration of previously submitted data has suggested it may be possible to allow limited access to lisdexamfetamine to a subgroup of patients with BED who do not have contraindications to treatment and who are able to receive regular specialist care for their condition.

The ACM is requested to consider the reports from Professors [information redacted] and the supplementary clinical evaluation report with its recommended amendments to the draft PI for Vyvanse. Specific advice has been requested (see below).

The Delegate noted that currently there is no Appendix D listing in the SUSMP for lisdexamfetamine. If an extension of indications to include BED is approved with a restricted prescribing authority as a condition of approval it would require referral to the Medicines Scheduling Committee for consideration. Appendix D provides for additional controls on possession or supply of poisons included in Schedule 4 or 8.

Summary of issues

1. Whether the proposed restrictions on patient population adequately address the risk of adverse cardiovascular outcomes in patients with BED.
2. Whether there should be an Appendix D listing in the SUSMP such that use is limited to authorised prescribers.
3. Whether authorised prescribers should be psychiatrists only or some additional medical practitioner group. If this is agreed then how should the authorisation for prescribing occur?
4. Optimal duration of use has not been fully explored. It is not clear whether use should be limited to a 12 week period initially or whether long term use is preferred.

Advice sought

The committee is requested to provide advice on the following specific issues:

1. Does the Committee consider that the proposals regarding amendments to the Indications, Precautions and Dosage and Administration as well as the proposed restriction of prescribing for BED would appropriately reduce the risk of adverse cardiovascular outcomes if Vyvanse were to be used in the treatment of BED?
2. There is currently no restriction in the SUSMP on medical practitioners prescribing lisdexamfetamine other than those applying to S8 medications. Does the committee consider there should be an Appendix D listing to restrict initiation and ongoing treatment of BED with lisdexamfetamine to psychiatrists or some other medical professional group?
3. Does the committee consider that short term use of Vyvanse in the management of BED would be appropriate?
4. If Vyvanse were to be approved for the treatment of BED which medical practitioners would be the most appropriate to prescribe treatment, given the limited access to psychiatrists for many patients?

The committee is (also) requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Proposed action

The Delegate was not in a position to say, at this time, that the application to extend the indications for Vyvanse (lisdexamfetamine) as proposed by the sponsor should be approved for registration.

Subject to amendment of the indication and other aspects of the PI the application to extend the indications for Vyvanse may be approved.

Response from sponsor

Introduction

The sponsor appreciates the opportunity to provide our response to matters on which the Delegate has asked for ACM advice.

The sponsor is seeking to extend the indication for Vyvanse for treatment of Binge Eating Disorder (BED) in Australia. Vyvanse has received marketing approval for BED in USA and Canada.

Sponsor's comments on the Pre-ACM delegate's overview

Question 1

Does the committee consider that the proposals regarding amendments to the Indications, Precautions and Dosage and Administration as well as the proposed restriction of prescribing for BED would appropriately reduce the risk of adverse cardiovascular outcomes if Vyvanse were to be used in the treatment of BED?

The sponsor accepts the TGA Delegate's proposed amendments to the PI.

Question 2

There is currently no restriction in the SUSMP on medical practitioners prescribing lisdexamfetamine other than those applying to S8 medicines. Does the committee consider there should be an Appendix D listing to restrict initiation and ongoing treatment of BED with lisdexamfetamine to psychiatrists or some other medical professional group?

The sponsor accepts the TGA Delegate's recommendation.

Question 3

Does the Committee consider that short term use of Vyvanse in the management of BED would be appropriate?

The sponsor accepts the TGA Delegate's recommending that the need for continued treatment with Vyvanse in BED patients beyond the initial 12 weeks be evaluated on an individual patient basis.

Question 4

If Vyvanse were to be approved for the treatment of BED which medical practitioners would be the most appropriate to prescribe treatment, given the limited access to psychiatrists for many patients?

The sponsor accepts the TGA Delegate's recommendation that initiation and management of Vyvanse treatment of BED be restricted to psychiatrists. For patients with limited access to psychiatrists, perhaps Vyvanse treatment can be initiated and managed by the local provider under supervision of a remote psychiatrist.

Company comments on delegate's request for PI and CMI changes

The supplementary evaluation report states 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 in the report. Minor change to the CMI has also been recommended.

The sponsor accepts the TGA Delegate's recommended changes to the PI and CMI. Updated copies of the proposed PI and CMI are included in the Pre-ACM response.

Advisory Committee Considerations from the ACM meeting 30 November to 1 December 2017

The Advisory Committee on Medicines (ACM), taking into account of the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Vyvanse Capsules containing 30 mg, 50 mg and 70 mg of lisdexamfetamine dimesilate to have an overall positive benefit-risk profile for the Delegate's amended indication:

Binge Eating Disorder (BED)

Vyvanse is indicated for the treatment of moderate to severe BED in adults when nonpharmacological treatment is unsuccessful or unavailable. Treatment should be commenced and managed by a specialist.

Need for comprehensive treatment programme:

Vyvanse is indicated as an integral one 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.

The initially proposed indication is as follows:

'The treatment of BED in adults'.

Subject to amendment of the indication and other aspects of the PI, the application to extend the indications for Vyvanse may be approved.

In making this recommendation the ACM noted that:

- BED is a distinct clinical condition with a valid diagnosis.
- 'Days of binge eating per week' as the primary efficacy measure in the pivotal efficacy studies of BED was considered to be acceptable.

In making this recommendation the ACM expressed concern that:

- the ongoing pharmacovigilance activity in the EU, including a pharmaco-epidemiology study of major cardiovascular events, was restricted to new users of Vyvanse for ADHD. The applicability of this post-market monitoring to BED was questioned given the different comorbidities and risk factors present in the BED patient population. The sponsor's provision of web based educational tools for prescribers were similarly restricted to the ADHD indication.
- although Vyvanse is not indicated or recommended for weight loss, use of other sympathomimetic drugs for weight loss have been associated with serious cardiovascular adverse events. The safety and effectiveness of Vyvanse for the treatment of obesity have not been established. The ACM expressed concern that there is a risk of diversion and misuse for the treatment of obesity since Vyvanse induced (modest) weight loss effects in the clinical trials.
- there was insufficient evidence that Vyvanse was more effective than currently available treatments. Evidence was presented that showed Vyvanse was not more effective than second generation SSRIs for the treatment of BED and it was suggested that Vyvanse constitute a third line option if psychotherapy and SSRI treatments had failed. However, the Delegate noted that this would not be feasible since second generation SSRIs are not indicated for BED in Australia.
- the pivotal clinical trials restricted study participation to patients with BED who did not have comorbid Axis I or Axis II disorders. These are very frequent comorbidities and thus the clinical trial population did not reflect the patient population presenting with BED in real world practice. There is concern that any safety assessment would not be reflective of the safety of Vyvanse were it to be used in the general BED patient population. Nevertheless, it was noted that 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.
- in the clinical trials, self-reporting was commonly employed to collect data, suggestive of subjectivity in the diagnosis. However, this is common in the field of psychiatry and is generally an accepted method of data acquisition.
- there was a general lack of discussion of non-pharmacological primary care options by the sponsor.

Proposed conditions of registration

The ACM agreed with the Delegate on the proposed conditions of registration and advised on the inclusion of the following:

- Treatment should be commenced and managed by a psychiatrist.
- Treatment duration should be a maximum of 12 weeks. Patients should then be reviewed. This latter recommendation was issued because of the paucity of long term efficacy data and the large response rate at Week 12 in the placebo group during the double blind period in the pivotal clinical trials.

Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments

The ACM agreed with the Delegate to the proposed amendments to the PI and CMI and specifically advised on the inclusion of the following:

Indications:

- 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 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.
- The long term use of Vyvanse should be limited since clinical data suggests that a significant proportion of patients may not require continued treatment with Vyvanse after an initial 12 weeks of treatment. Physicians should periodically re-evaluate the long term usefulness of the drug for the individual patient.

Precautions:

- Serious cardiovascular events have been reported with the use of sympathomimetic drugs, including Vyvanse, in the ADHD population. 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 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 & limited treatment duration.

Specific advice

The ACM advised the following in response to the Delegate's specific questions on the submission:

1. *Does the committee consider that the proposals regarding amendments to the Indications; Precautions; and Dosage and Administration as well as the proposed restriction of prescribing for BED would appropriately reduce the risk of adverse cardiovascular outcomes if Vyvanse were to be used in the treatment of BED?*

The ACM emphasised the importance of Vyvanse withdrawal after 12 weeks to limit associated cardiovascular risks. These include an arrhythmogenic effect (which is age independent and could potentially manifest in patients with subclinical channelopathies) and an adrenergic effect, which could potentially exacerbate existing ischaemic heart disease. The ACM agreed that a 12 week limit would mitigate the ischemic risk, but would not mitigate the risk in those with subclinical channelopathies. Given the clinical need for agents to treat BED and the relatively small risk associated with the latter, the ACM concluded that the overall risk benefit was positive.

2. *There is currently no restriction in the SUSMP on medical practitioners prescribing lisdexamfetamine other than those applying to S8 medicines. Does the committee consider there should be an Appendix D listing to restrict initiation and ongoing treatment of BED with lisdexamfetamine to psychiatrists or some other medical professional group?*

See answer to Question 4, below.

3. *Does the Committee consider that short term use of Vyvanse in the management of BED would be appropriate?*

The ACM agreed that short term use of Vyvanse in the management of BED (12 week limit) is appropriate, mitigating the risk of some adverse cardiovascular outcomes (existing ischaemic heart disease but not channelopathies) and may also mitigate the risk of misuse and abuse of Vyvanse.

Furthermore, potential unblinding in the clinical trials (specifically, Study 346) supports a treatment period limited to 12 weeks. It is likely that at least some patients in this trial who responded to lisdexamfetamine were aware that they were subsequently switched to placebo. The fact that 68% of these subjects did not relapse strengthens the argument that 12 weeks of active lisdexamfetamine treatment may be sufficient.

4. *If Vyvanse were to be approved for the treatment of BED which medical practitioners would be the most appropriate to prescribe treatment, given the limited access to psychiatrists for many patients?*

The ACM concluded that the prescribing of Vyvanse should be limited to psychiatrists. The suggestion that paediatricians, who would normally prescribe similar stimulants for ADHD, could also constitute another set of prescribers was considered inappropriate given the BED indication of Vyvanse is limited to adults. It was also noted that restricting prescribing to psychiatrists may prevent the continuation of treatment by GPs, and hence the possibility of long term use, after the initial prescription by psychiatrists.

The ACM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

Post-ACM negotiations

As a result of the findings of the ACM the sponsor submitted revised drafts of the PI and CMI. The revised indication included wording in the indication relating to long term use.

The Delegate had an issue with the proposed statement for long term use in the indications section because it does not clearly indicate that treatment should stop at 12 weeks and the patient be assessed. Given that around 68% of subjects in the clinical trial who ceased treatment didn't meet the criteria for relapse when given placebo during the long term study, the Delegate thought it really important that the indications not allow interpretations that permit constant use. The Delegate stated that it must be clear that treatment should stop to allow for the reassessment. This approach should also minimise the risk of adverse cardiovascular outcomes.

As a compromise it would be acceptable to (the Delegate) to replace the currently proposed long term use indication statement with the statement that appears in the 'Prescribing and Dispensing' section, as in the following example:

'Long term use: For BED the initial treatment period is 12 weeks. Patients should then be observed to assess whether further treatment with Vyvanse is required. Periodic re-evaluation of the usefulness of Vyvanse for the individual patient should be undertaken (see Clinical Trials).'

Wording related to cardiovascular risk was also included, as follows:

'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).'

The Delegate and the sponsor through additional correspondence reached agreement on the final wording of the new indication.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Vyvanse lisdexamfetamine dimesilate 20 mg, 30 mg, 40 mg, 50 mg, 60 mg and 70 mg capsules for oral use, indicated for:

Binge Eating Disorder (BED):

Vyvanse is indicated for the treatment of moderate to severe BED in adults when nonpharmacological treatment is unsuccessful or unavailable. Treatment should be commenced and managed by a psychiatrist.

Need for comprehensive treatment programme:

Vyvanse is indicated as part of a total treatment program for BED that optimally includes other measures (nutritional, psychological, and medical) for patients with this 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 Sections 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Cardiovascular Disease and 4.2 DOSE AND METHOD OF ADMINISTRATION.

Long term use:

For BED the initial treatment period is 12 weeks. Patients should then be observed to assess whether further treatment with Vyvanse is required. Periodic re-evaluation of the usefulness of Vyvanse for the individual patient should be undertaken. See Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical Trials.

Specific conditions of registration applying to these goods

The lisdexamfetamine dimesilate AU-RMP (version 3.1, dated 7 February 2017, data lock point 8 October 2015), included with submission PM-2016-01092-1-1, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

Attachment 1. Product Information

The PI for Vyvanse approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <<https://www.tga.gov.au/product-information-pi>> .

Attachment 2. Extract from the Clinical Evaluation Report

Attachment 3. Extract from supplementary Clinical Evaluation Report

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