PROFESSIONAL INFORMATION FOR

VYFOCIS

AMFETAMINES HAVE A HIGH POTENTIAL FOR ABUSE.

ADMINISTRATION OF AMFETAMINES FOR PROLONGED PERIODS OF TIME MAY LEAD TO MEDICINE DEPENDENCE. MISUSE OF AMFETAMINE MAY CAUSE SUDDEN DEATH AND SERIOUS CARDIOVASCULAR ADVERSE EVENTS.

SCHEDULING STATUS

S6

1. NAME OF THE MEDICINE

VYFOCIS 30, 30 mg, capsules

VYFOCIS 50, 50 mg, capsules

VYFOCIS 70, 70 mg, capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

30 mg capsules: each capsule contains 30 mg lisdexamfetamine dimesilate.

50 mg capsules: each capsule contains 50 mg lisdexamfetamine dimesilate.

70 mg capsules: each capsule contains 70 mg lisdexamfetamine dimesilate.

Sugar free.

For the full list of excipients, see **section 6.1**.

3. PHARMACEUTICAL FORM

Capsules (hard).

VYFOCIS 30:

Orange cap and white body, “ALV” printed axially on the orange cap, “564” printed axially on the white body, all printing in grey ink and containing white to pale yellow powder.

VYFOCIS 50:

Dark blue cap and white body, “ALV” printed axially on the dark blue cap, “566” printed axially on the white body, all printing in grey ink and containing white to pale yellow powder.

VYFOCIS 70:

Orange cap and blue body, “ALV” printed axially on the orange cap, “568” printed axially on the blue body, all printing in grey ink and containing white to pale yellow powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Attention Deficit Hyperactivity Disorder (ADHD)

VYFOCIS is indicated for the treatment of Attention Deficit Hyperactivity Disorder. Diagnosed according to the most recent DSM diagnostic criteria for ADHD in patients ≥ 13 years of age up to 55 years of age when treatment with methylphenidate and atomoxetine has failed. Treatment with VYFOCIS should be part of a comprehensive treatment program for ADHD.

Long term use

The need for continuation of treatment with VYFOCIS should be re-assessed every 6 months.

4.2. Posology and method of administration

Treatment should be initiated and supervised by a medical practitioner experienced in the treatment of patients with ADHD. Patients should be reviewed at least every 6 months to assess if there is an on-going need for treatment with VYFOCIS. Blood pressure and cardiovascular status should also be regularly reviewed.

Dosage should be individualised according to the therapeutic needs and response of the patient. Careful dose titration is necessary at the start of treatment with VYFOCIS.

VYFOCIS should be administered orally at the lowest possible dosage and should then be slowly adjusted to the lowest effective dose for each individual.
VYFOCIS should be taken in the morning with or without food; avoid afternoon doses because of the potential for insomnia.
VYFOCIS capsules may be taken whole, or the capsule may be opened and the entire contents emptied and mixed with a soft food such as yogurt or in a glass of water or orange juice. If the contents of the capsule include any compacted powder, a spoon may be used to break apart the powder in the soft food or liquid. The contents should be mixed until completely dispersed. The patient should consume the entire mixture of soft

food or liquid immediately; it should not be stored. The active ingredient dissolves completely once dispersed; however, a film containing the inactive ingredients may remain in the glass or container once the mixture is consumed. The patient should not take anything less than one capsule per day and a single capsule should not be divided. The maximum recommended dose is 70 mg/day; doses greater than 70 mg/day of VYFOCIS have not been studied. The effectiveness of VYFOCIS has not been studied in adults over 55 years of age. Due to reduced clearance in patients with severe renal insufficiency (GFR 15 to < 30 mL/min/1,73 m^2) the maximum daily dose should not exceed 50 mg. Further dosage reduction should be considered in patients undergoing dialysis (see **section 5.2** and **section 4.4**).
Lisdexamfetamine and dexamfetamine are not dialysable.

VYFOCIS should not be used in children under the age of 13 years as the available formulations are not appropriate for up or down titration to find an optimal dose in children aged 6 to 12 years. Safety and efficacy in children under the age of 6 years have not been established.

Treatment of ADHD

In patients who are either starting treatment for the first time or switching from another medication, 30 mg once daily in the morning is the recommended starting dose.
If the decision is made to increase the dose beyond 30 mg/day, daily dosage may be adjusted in increments of 20 mg in intervals no more frequently than weekly.
VYFOCIS should be administered orally at the lowest possible dosage.

VYFOCIS has not been studied in children under 6 years of age and up or down titration in children 6 to 12 years of age to optimise the dose needed cannot be achieved with the current available formulations.

4.3. Contraindications

VYFOCIS is contraindicated in patients with:

- known hypersensitivity to sympathomimetic amines or any of the excipients listed,
- advanced arteriosclerosis,
- symptomatic cardiovascular disease,
- moderate to severe hypertension,
- hyperthyroidism,
- glaucoma,
- agitated states,
- concomitant use of monoamine oxidase inhibitors (MAOI) or within 14 days after MAOI treatment (hypertensive crisis may result),
- phaeochromocytoma,
- tics, Tourette's syndrome,
- severe depression, anorexia nervosa, psychotic symptoms or suicidal tendency,
- known drug dependence or alcohol abuse,
- pregnancy and lactation (see **section 4.6**).

4.4. Special warnings and precautions for use

VYFOCIS has a potential for abuse, misuse, dependence, or diversion for non-therapeutic uses. Medical practitioners should assess the risk of abuse prior to prescribing and monitor for signs of abuse and dependence while on therapy. VYFOCIS should be prescribed cautiously to patients with a history of substance abuse or dependence. Careful supervision is required during withdrawal from abusive use since severe depression may occur. Withdrawal following chronic therapeutic use may unmask symptoms of the underlying disorder that may require follow-up.

Stimulants including VYFOCIS have a potential for abuse, misuse, or diversion that medical practitioners should consider when prescribing VYFOCIS. The risk of misuse may be greater in adults (especially young adults) than in paediatric use. Stimulants should be prescribed cautiously to patients with a history of substance abuse or dependence.

Patients should be cautioned against increasing the recommended dosage. Should psychological dependence occur, gradual withdrawal of the medication is recommended. Abrupt cessation following prolonged high dosage results in extreme fatigue and mental depression; changes have also been noted on the sleep EEG.

Manifestations of chronic intoxication with amfetamines include severe dermatoses, marked insomnia, irritability, hyperactivity and personality changes.

The most severe manifestation of chronic intoxication is psychosis, often clinically indistinguishable from schizophrenia.

Pre-treatment assessment

Before starting treatment with VYFOCIS, it is important to consider the patient's personal and family cardiac and psychiatric history. In patients with identified or potential cardiovascular or psychiatric risk factors, further investigation or specialist review may be considered.

Children, adolescents, or adults who are being considered for treatment with stimulant medications should have a careful history (including assessment for a family history of sudden death or ventricular dysrhythmia) and physical exam to assess for the presence of cardiac disease and should receive further cardiac evaluation if findings suggest such disease (e.g. electrocardiogram and echocardiogram). Patients who develop symptoms such as exertional chest pain, unexplained syncope, or other symptoms suggestive of cardiac disease during stimulant treatment should undergo a prompt cardiac evaluation.

Cardiovascular disease

Serious cardiovascular events have been reported with the use of sympathomimetic medicines, including VYFOCIS, in the ADHD population.

Sudden death and pre-existing structural cardiac abnormalities or other serious heart problems

Children and adolescents

Sudden death has been reported in children and adolescents taking CNS stimulants at usual doses, including those with structural cardiac abnormalities or other serious heart problems. Although some serious heart problems alone carry an increased risk of sudden death, stimulant products generally should not be used in children or adolescents with known serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac problems that may place them at increased vulnerability to the sympathomimetic effects of a stimulant medicine.

Adults

Sudden deaths, stroke, and myocardial infarction have been reported in adults taking stimulant medicines at usual doses for ADHD. Although the role of stimulants in these adult cases is also unknown, adults have a greater likelihood than children of having serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious cardiac problems. Adults with such abnormalities should also generally not be treated with stimulant medicines.

Hypertension and other cardiovascular conditions

Stimulant medications cause a modest increase in average blood pressure (about 2 to 4 mm Hg) and average heart rate (about 3 to 6 bpm), and individuals may have larger increases. While the mean changes alone would not be expected to have short-term consequences, all patients should be monitored for larger changes in heart rate and blood pressure. Caution is indicated in treating patients whose underlying medical

conditions might be compromised by increases in blood pressure or heart rate, e.g. those with pre-existing hypertension, heart failure, recent myocardial infarction, or ventricular dysrhythmia.

Psychiatric disorders

Pre-existing psychosis

Administration of stimulants may exacerbate symptoms of behaviour disturbance and thought disorder in patients with pre-existing psychotic disorder.

Bipolar illness

Particular care should be taken in using stimulants to treat ADHD patients with co-morbid bipolar disorder because of concern for possible induction of mixed/manic episodes in such patients. Prior to initiating treatment with a stimulant, patients with comorbid depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression.

Emergence of new psychotic or manic symptoms

Treatment emergent psychotic or manic symptoms, e.g. hallucinations, delusional thinking, or mania in children and adolescents without prior history of psychotic illness or mania can be caused by stimulants at usual doses. If such symptoms occur, consideration should be given to a possible causal role of the stimulant, and discontinuation of treatment may be appropriate.

Aggression

Aggressive behaviour or hostility is often observed in children and adolescents with ADHD and has been reported in clinical trials and the post-marketing experience of some medications indicated for the treatment of ADHD, including VYFOCIS. Stimulants may cause aggressive behaviour or hostility. Patients beginning treatment for ADHD should be monitored for the appearance of or worsening of aggressive behaviour or hostility.

Seizures

Stimulants may lower the convulsive threshold in patients with prior history of seizure, in patients with prior EEG abnormalities without previous seizures, and in patients without a history of seizures and no prior EEG evidence of seizures. In the presence of seizures, VYFOCIS should be discontinued.

Visual disturbance

Difficulties with accommodation and blurring of vision have been reported with stimulant treatment such as with VYFOCIS.

Tics

Stimulants have been reported to exacerbate motor and phonic tics and Tourette's syndrome. Therefore, clinical evaluation for tics and Tourette's syndrome in children and their families should precede use of stimulant medications (see **section 4.3**).

Long-term suppression of growth (height and weight)

VYFOCIS has been associated with dose-related reductions in weight in children, adolescents and adults in short-term studies. Although a causal relationship has not been established, suppression of growth (i.e. weight and/or height) has been reported with the long-term use of stimulants in children. Therefore, patients requiring long-term therapy should be carefully monitored. Patients who are not growing or gaining weight as expected should have their treatment interrupted.

Peripheral vasculopathy, including Raynaud's Phenomenon

Stimulants, including VYFOCIS, used to treat ADHD are associated with peripheral vasculopathy, including Raynaud's phenomenon. Signs and symptoms are usually intermittent and mild; however, very rare sequelae include digital ulceration and/or soft tissue breakdown. Effects of peripheral vasculopathy, including Raynaud's phenomenon, have been observed in post-marketing reports at different times and at therapeutic doses in all age groups throughout the course of treatment. Signs and symptoms generally improve after reduction in dose or discontinuation of the medicine. Careful observation for digital changes is necessary during treatment with ADHD stimulants. Further clinical evaluation (e.g. rheumatology referral) may be appropriate for certain patients.

Prescribing and dispensing

The least amount of VYFOCIS feasible should be prescribed or dispensed at one time in order to minimise the possibility of overdosage. Consideration should be given when using VYFOCIS in patients who use other sympathomimetic medicines.

Paediatric use

ADHD

VYFOCIS should not be used in children under the age of 13 years.

Current available formulations do not allow optimisation of the dose requirements (best benefit-risk balance) for children 6 to 12 years.

Safety and efficacy of VYFOCIS in children under the age of 6 years have not been established.

Adult patients aged over 55 years

Safety and efficacy have not been established in adult patients over the age of 55 years.

Use in hepatic impairment

No studies have been conducted in patients with hepatic impairment.

Use in renal impairment

Due to reduced clearance in patients with severe renal insufficiency (GFR 15 to < 30 mL/min/1,73 m^2) the maximum VYFOCIS daily dose should not exceed 50 mg. Further dosage reduction should be considered in patients undergoing dialysis (see **section 5**).

Lisdexamfetamine and dexamfetamine are not dialysable.

Effects on laboratory tests

Amfetamines, such as VYFOCIS can cause significant elevation in plasma corticosteroid levels. This increase is greatest in the evening. Amfetamines may interfere with urinary steroid determinations.

4.5. Interaction with other medicines and other forms of interaction

Medicines whose blood levels may be impacted by VYFOCIS

Extended release guanfacine: Administration of an extended release guanfacine in combination with VYFOCIS may induce a 19 % increase in guanfacine maximum plasma concentrations, whereas exposure (area under the curve; AUC) could be increased by 7 %. These small changes are not expected to be clinically meaningful. No effect on dexamfetamine exposure was observed following co-administration of extended release guanfacine and VYFOCIS.

Extended release venlafaxine: Administration of 225 mg extended-release venlafaxine, a CYP2D6 substrate, in combination with 70 mg VYFOCIS may induce a 9 % decrease in the Cmax and 17 % decrease in the AUC for the primary active metabolite o-desmetylvenlafaxine and a 10 % increase in Cmax and 13 % increase in AUC for venlafaxine. VYFOCIS may be a weak inhibitor of CYP2D6. Lisdexamfetamine has no effect on the AUC and Cmax of the composite of venlafaxine and o-desmetylvenlafaxine. These small changes are not expected to be clinically meaningful.

No effect on dexamfetamine exposure was observed following co-administration of extended-release venlafaxine and lisdexamfetamine.

Medicines and conditions that alter urinary pH and impact the urinary excretion and half-life of amfetamine

Ascorbic acid and other medicines or conditions that acidify urine increase urinary excretion and decrease half-life of amfetamine. Sodium bicarbonate and other medicines or conditions that alkalinise urine decrease urinary excretion and extend the half-life of amfetamine.

Monoamine oxidase inhibitors

Do not administer VYFOCIS concomitantly with monoamine oxidase inhibitors or within 14 days after discontinuing MAOI treatment. Concomitant use of MAOIs and CNS stimulants can cause hypertensive crisis. Severe outcomes including death may occur (see **section 4.3**).

Serotonergic medicines

Serotonin syndrome can occur in association with the use of amfetamines such as VYFOCIS, when given in conjunction with serotonergic medicines, including selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine (noradrenaline) reuptake inhibitors (SNRIs). It has also been reported in association with overdose of amfetamines, including VYFOCIS (see **section 4.9**).

Medicines whose effects may be reduced by amfetamines

Anti-hypertensives: Amfetamines may decrease the effectiveness of antihypertensive medications.

Medicines whose effects may be potentiated by amfetamines

Amfetamines potentiate the analgesic effect of narcotic analgesics.

Medicines that may reduce the effects of amfetamines

Chlorpromazine: Chlorpromazine blocks dopamine and norepinephrine (noradrenaline) receptors, thus inhibiting the central stimulant effects of amfetamines.

Haloperidol: Haloperidol blocks dopamine receptors, thus inhibiting the central stimulant effects of amfetamines.

Lithium Carbonate: The anorectic and stimulatory effects of amfetamines may be inhibited by lithium carbonate.

4.6. Fertility, pregnancy and lactation

Pregnancy

VYFOCIS should not be used in pregnancy as harm to the foetus cannot be excluded. Dexamfetamine, the active metabolite of lisdexamfetamine, crosses the placenta. Amfetamines such as VYFOCIS cause vasoconstriction and may decrease placental perfusion which may affect the developing foetus. It also stimulates uterine contractions

increasing the risk of premature delivery and low birth weight babies. There is some evidence, although inconclusive, that amfetamine use in early pregnancy, may be associated with an increased risk of pre-eclampsia.
Women of childbearing age being treated with VYFOCIS should be advised not to become pregnant.

Effects on infants

Infants born to mothers taking amfetamines should be monitored for symptoms of withdrawal such as feeding difficulties, irritability, agitation and excessive drowsiness.

Effects on embryo-foetal development

Lisdexamfetamine dimesilate had no apparent effects on embryo-foetal development or survival when administered orally to pregnant rats and rabbits throughout the period of organogenesis at doses of up to 40 and 120 mg/kg/day respectively. These doses resulted in respective plasma dexamfetamine AUC values which were 5 and 2-fold the AUC expected in adults at the maximum recommended dose of 70 mg and respective plasma lisdexamfetamine AUC values which were 12 and 40-fold the AUC expected in adults at the maximum recommended dose.
A study of lisdexamfetamine dimesilate has not been conducted in rats treated throughout gestation and lactation. Amfetamine sulphate (d- to l-enantiomer ratio of 3:1), when given orally to rats from early gestation through to weaning at doses 2, 6 and 10 mg total amfetamine base/kg/day, reduced the number of live born pups and pup viability during lactation. Body weight gain of offspring was reduced during lactation and

after weaning, development was delayed, and increases in locomotor activity were observed. The reproductive performance of the offspring was also reduced. Some effects were observed at the 2 mg/kg/day dose, which was associated with a plasma amfetamine AUC about half that expected in adults at the maximum recommended dose of 70 mg.

Breastfeeding

Women on treatment with VYFOCIS should not breastfeed their infants.

Amfetamines are excreted in human milk. There is a risk of severe adverse reactions in the infant including cardiovascular reactions, blood pressure and heart rate increases, suppression of growth and peripheral vasculopathy. Long term neurodevelopmental effects on infants from amfetamine exposure are unknown.

Fertility

The effect of VYFOCIS on human fertility has not been investigated.

4.7. Effects on ability to drive and use machines

VYFOCIS may affect the ability of patients to drive or use machinery. Patients should not drive or use machinery until they know how treatment with VYFOCIS affects them. VYFOCIS can cause dizziness, drowsiness and visual disturbances including difficulties with accommodation, diplopia and blurred vision.

4.8. Undesirable effects

Tabulated list of adverse reactions

MedDRA system organ class	**Side effects**	**Adolescents (13 to 17 years)**	**Adults**
Immune system Disorders	Anaphylactic reaction	Frequency unknown	Frequency unknown
	Hypersensitivity	Less frequent	Less frequent
Metabolism and Nutrition disorders	Decreased appetite	Frequent	Frequent
Psychiatric Disorders	Insomnia	Frequent	Frequent
	Agitation	Less frequent	Frequent
	Anxiety	Frequent	Frequent
	Logorrhea	Less frequent	Less frequent
	Libido decreased	Not reported	Frequent
	Depression	Frequent	Less frequent
	Tic	Less frequent	Less frequent
	Affect lability	Less frequent	Frequent
	Dysphoria	Less frequent	Less frequent
	Euphoria	Less frequent	Less frequent
	Psychomotor hyperactivity	Less frequent	Frequent
	Bruxism	Less frequent	Frequent
	Dermatillomania	Less frequent	Less frequent
	Psychotic episodes	Frequency unknown	Frequency unknown
	Mania	Less frequent	Less frequent
	Hallucination	Less frequent	Frequency unknown
	Aggression	Less frequent	Frequency unknown
Nervous system disorders	Headache	Frequent	Frequent
	Dizziness	Frequent	Frequent
	Restlessness	Frequent	Frequent
	Tremor	Frequent	Frequent
	Somnolence	Frequent	Less frequent
	Seizure	Frequency unknown	Frequency unknown

	Dyskinesia	Less frequent	Less frequent
	Dysgeusia	Less frequent	Less frequent
	Syncope	Less frequent	Less frequent
Eye disorders	Vision blurred	Frequency unknown	Less frequent
	Mydriasis	Less frequent	Frequency unknown
Cardiac disorders	Tachycardia	Frequent	Frequent
	Palpitation	Frequent	Frequent
	QTc prolongation	Frequency unknown	Frequency unknown
	Cardiomyopathy	Less frequent	Frequency unknown
Vascular disorders	Raynaud's phenomenon	Frequency unknown	Frequency unknown
Respiratory, Thoracic and Mediastinal Disorders	Dyspnoea	Frequent	Frequent
Gastrointestinal Disorders	Dry mouth	Frequent	Frequent
	Diarrhoea	Frequent	Frequent
	Constipation	Less frequent	Frequent
	Upper abdominal pain	Frequent	Frequent
	Nausea	Frequent	Frequent
	Vomiting	Frequent	Less frequent
Hepatobiliary disorders	Eosinophilic Hepatitis	Frequency unknown	Frequency unknown
Skin and Subcutaneous Tissue Disorders	Hyperhidrosis	Less frequent	Frequent
	Urticaria	Less frequent	Less frequent
	Rash	Less frequent	Less frequent
	Angioedema	Frequency unknown	Frequency unknown
	Stevens-Johnson Syndrome	Frequency unknown	Frequency unknown
Reproductive System and Breast Disorders	Erectile dysfunction	Less frequent	Frequent
General Disorders and Administration Site Conditions	Chest pain	Less frequent	Frequent
	Irritability	Frequent	Frequent
	Fatigue	Frequent	Frequent
	Feeling jittery	Frequent	Frequent
	Pyrexia	Frequent	Less frequent

Investigations	Blood pressure increased	Less frequent	Frequent
	Weight decreased	Frequent	Frequent

Description of selected adverse reactions

Suppression of growth in paediatric patients with ADHD

Weight

Weight change has been evaluated for children (age 6 to 12) and adolescents (age 13 to 17). Higher doses have been associated with greater weight loss.

Long term growth

Follow up of weight and height in children ages 7 to 10 years suggests that consistently medicated children (i.e. treatment for 7 days per week throughout the year) have a slowing in growth rate (on average, a total of about 2 cm less growth in height and 2,7 kg less growth in weight over 3 years), without evidence of growth rebound during this period of development.

Reporting of suspected adverse reactions

Suspected adverse reaction(s) are important to report as it allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on the SAHPRA website or to Cipla Medpro (Pty) Ltd. by e-mail to drugsafetysa@cipla.com or telephone to 080 222 6662 (toll free).

4.9. Overdose

Manifestations of acute overdosage with amfetamines include restlessness, tremor, hyperreflexia, rapid respiration, confusion, aggression, hallucinations, panic states, hyperpyrexia, rhabdomyolysis and other features of serotonin syndrome. Fatigue and depression usually follow the central nervous system stimulation. Cardiovascular effects include dysrhythmias, hypertension or hypotension, and circulatory collapse. Gastrointestinal symptoms include nausea, vomiting, diarrhoea, and abdominal cramps. Fatal poisoning is usually preceded by convulsions and coma.

Management of acute amfetamine intoxication is largely symptomatic and includes administration of activated charcoal and sedation. If acute severe hypertension complicates amfetamine overdosage, administration of intravenous phentolamine has been suggested. However, a gradual drop in blood pressure will usually result when sufficient sedation has been achieved.

Lisdexamfetamine and dexamfetamine are not dialysable. Acidification of the urine increases amfetamine excretion but is believed to increase risk of acute renal failure if myoglobinuria is present.

The prolonged release of VYFOCIS in the body should be considered when treating patients with overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological Class: A 1.6 Other central nervous system stimulants

Pharmacotherapeutic Group: Centrally Acting Sympathomimetics

ATC code: N06BA12

General

Lisdexamfetamine is a pharmacologically inactive pro-drug of dexamfetamine, which is a central nervous system stimulant.

Mechanism of Action

After oral administration, lisdexamfetamine is rapidly absorbed from the gastrointestinal tract and hydrolysed primarily in whole blood to dexamfetamine, which is responsible for the medicine's activity. Amfetamines are non-catecholamine sympathomimetic amines with CNS stimulant activity. The mode of therapeutic action of amfetamine in Attention Deficit Hyperactivity Disorder (ADHD) is not fully established, however it is thought to be due to its ability to block the reuptake of norepinephrine (noradrenaline) and dopamine into the presynaptic neuron and increase the release of these monoamines into the extra neuronal space. The parent active ingredient, lisdexamfetamine, does not bind to the sites responsible for the reuptake of noradrenaline and dopamine *in vitro*.

5.2. Pharmacokinetic properties

Absorption

After oral administration, lisdexamfetamine is rapidly absorbed from the gastrointestinal tract of healthy adults and children (6 to 12 years) with ADHD, thought to be mediated by the high capacity PEPT1 transporter.

In 18 paediatric patients (6 to 12 years) with ADHD, the Tmax of dexamfetamine was approximately 3,5 h following single-dose oral administration of lisdexamfetamine dimesilate either 30 mg, 50 mg, or 70 mg after an 8-hour overnight fast. The Tmax of lisdexamfetamine dimesilate was approximately 1 h.

Linear pharmacokinetics of dexamfetamine after single-dose oral administration of lisdexamfetamine dimesilate was established over the dose range of 30 mg to 70 mg in children aged 6 to 12 years and over the dose range of 50 mg to 250 mg in adults.

Dexamfetamine pharmacokinetic parameters following administration of lisdexamfetamine in adults exhibited low inter-subject (< 25 %) and intra-subject (< 8 %) variability. Safety and efficacy have not been studied above the maximum recommended dose of 70 mg.

Food (a high fat meal or soft food such as yogurt) or orange juice does not affect the observed AUC and Cmax of dexamfetamine in healthy adults after single-dose oral administration of 70 mg of VYFOCIS capsules. Food prolongs Tmax by approximately 1 hour (from 3,8 h at fasted state to 4,7 h after a high fat meal or to 4,2 h after soft food such as yogurt).

After an 8-hour fast, the AUC for dexamfetamine, following oral administration of lisdexamfetamine dimesilate in solution, and as intact capsules were equivalent.

Weight/Dose normalised AUC and Cmax for dexamfetamine were 22 % and 12 % lower, respectively, in adult females than in males on day 7 following a 70 mg/day dose

of lisdexamfetamine for 7 days. Weight/Dose normalised AUC and Cmax values were the same in girls and boys following single doses of 30 to 70 mg.

Distribution

There is no accumulation of dexamfetamine AUC at steady state in healthy adults and no accumulation of lisdexamfetamine dimesilate after once-daily dosing for 7 consecutive days.

Biotransformation

Lisdexamfetamine is converted to dexamfetamine and L-lysine, not by cytochrome P450 enzymes metabolism, but by metabolism in blood primarily due to the hydrolytic activity of red blood cells. Red blood cells have a high capacity for metabolism of lisdexamfetamine as *in vitro* data demonstrated substantial hydrolysis occurs even at low haematocrit levels.

Amfetamine is reported to be oxidised at the 4 position of the benzene ring to form 4-hydroxyamfetamine, or on the side chain α or ß carbons to form alpha-hydroxy-amfetamine or norepinephrine (noradrenaline), respectively. Norepinephrine (noradrenaline)and 4-hydroxy-amfetamine are both active and each is subsequently oxidised to form 4-hydroxy-norepinephrine (noradrenaline). Alpha-hydroxy-amfetamine undergoes deamination to form phenylacetone, which ultimately forms benzoic acid and its glucuronide and the glycine conjugate hippuric acid. Although the enzymes involved in amfetamine metabolism have not been clearly defined, CYP2D6 is known to be involved with formation of 4-hydroxy-amfetamine.

Elimination

Following the oral administration of a 70 mg dose of radiolabelled lisdexamfetamine dimesilate to 6 healthy subjects, approximately 96 % of the oral dose radioactivity was recovered in the urine and only 0,3 % recovered in the faeces over a period of 120 hours. Of the radioactivity recovered in the urine, 42 % of the dose was related to amfetamine, 25 % to hippuric acid, and 2 % to intact lisdexamfetamine. Plasma concentrations of unconverted lisdexamfetamine are low and transient, generally becoming non-quantifiable by 8 hours after administration. The plasma elimination half-life of lisdexamfetamine typically averaged less than 1 hour in studies of lisdexamfetamine dimesilate in volunteers.

Special populations

Age

The pharmacokinetics of dexamfetamine, as evaluated by clearance, is similar in paediatric (aged 6 to 12) and adolescent (aged 13 to 17) ADHD patients, and healthy adult volunteers after correcting for body weight. Following administration of lisdexamfetamine dimesilate in a study of 47 subjects aged 55 years of age or older, amfetamine clearance was approximately 0,7 L/h/kg for subjects 55 to 74 years of age and 0,55 L/hr/kg for subjects ≥ 75 years of age. This is slightly reduced compared to younger adults (approximately 1 L/hr/kg for subjects 18 to 45 years of age).

Sex

Following administration of lisdexamfetamine dimesilate, systemic exposure to dexamfetamine is similar for men and women given the same mg/kg dose.

Race

Formal pharmacokinetic studies for race have not been conducted.

Renal disease

In a pharmacokinetic study of lisdexamfetamine in subjects with normal and impaired renal function dexamfetamine clearance was reduced from 0,7 L/hr/kg in normal subjects to 0,4 L/hr/kg in subjects with severe renal impairment (GFR 15 to < 30 mL/min/1,73m^2) (see **section 4.4**). In subjects with ESRD requiring dialysis mean dexamfetamine clearance was reduced to 0,3 L/hr/kg both pre- and post-dialysis. Dialysis did not significantly affect the clearance of dexamfetamine.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Microcrystalline cellulose

Magnesium stearate

Croscarmellose sodium

Capsule shell

Gelatin (all strengths)

30 mg

Titanium dioxide (E171)

FD&C Red No. 3 (E127)

D&C Yellow No. 10 (E104)

50 mg

Titanium Dioxide (E171)

FD & C Blue No.1 (E133)

70 mg

Titanium Dioxide (E171)

FD&C Red No. 3 (E127)

D&C Yellow No.10 (E104)

FD&C Blue No.1 (E133)

Printing ink (all strengths)

Shellac

Propylene glycol

Titanium Dioxide (E171)

Black Iron Oxide (E172)

6.2. Incompatibilities

Not applicable.

6.3. Shelf Life

24 months.

6.4. Special precautions for storage

Store at or below 25 º C.

6.5. Nature and contents of container

Container type:

VYFOCIS capsules are packed in white high-density polyethylene (HDPE) white mouth round bottles with a white 38 mm polypropylene (PP) cap and 1 g silica gel desiccant cannister, inside a cardboard carton.

Pack size: 30 capsules

6.6. Special precautions for disposal and other handling

Any unused medicine or waste material should be disposed of by taking to your local pharmacy.

7. HOLDER OF CERTIFICATE OF REGISTRATION

CIPLA MEDPRO (PTY) LTD.

Building 9

Parc du Cap

Mispel Street

Bellville

7530

Customer Care: 080 222 6662

8. REGISTRATION NUMBER(S)

VYFOCIS 30: 56/1.6/1238

VYFOCIS 50: 56/1.6/1240

VYFOCIS 70: 56/1.6/1242

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

First authorisation: 20 January 2026

Latest renewal: Not applicable.

10. DATE OF REVISION OF THE TEXT