Vyvanse®
lisdexamfetamine dimesilate

THE FIRST PRODRUG STIMULANT*[1,2]

*DATE OF FIRST APPROVAL IN AUSTRALIA JULY 2013

A prodrug is a pharmacological agent that is administered in an inactive form and metabolised to its active form in the body.[3,4] The basic aim of any prodrug design is to enhance the attributes of the active drug, such as improved solubility, absorption, distribution, taste/odour, and prolonged systemic availability.[5-7]

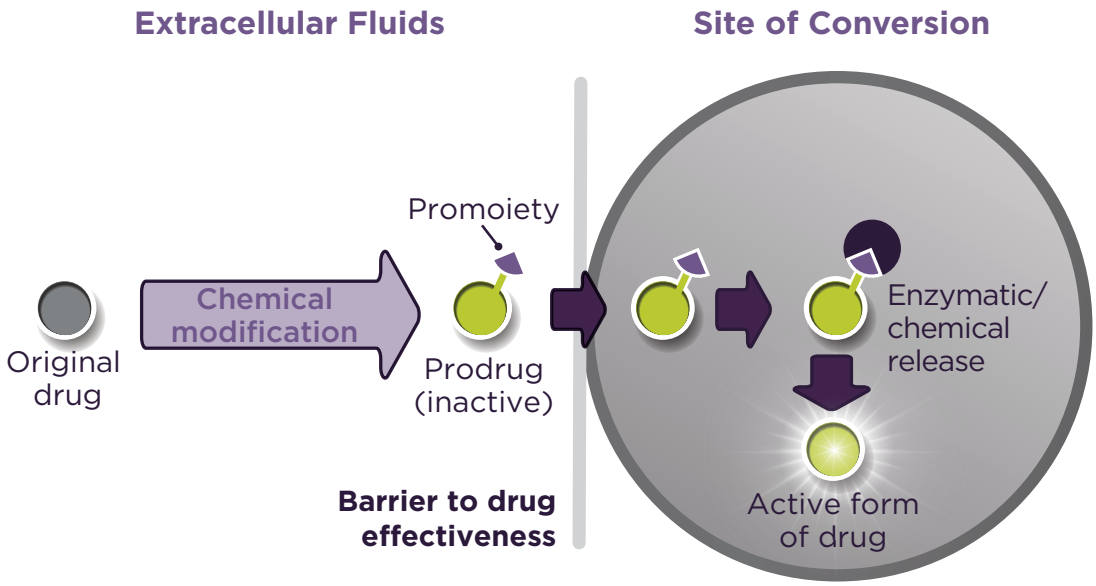
General information

Prodrug design and structure

Prodrugs are inactive or less active bioreversible derivatives of active drug molecules, which undergo enzymatic or chemical biotransformation before eliciting their pharmacological effects.[7] In most cases, prodrugs contain a carrier or promoiety.[8]

A promoiety is chemically bonded to the drug to form a prodrug in order to overcome physicochemical and biological barriers to drug delivery. This bond is bioreversible (enzymatically or non-enzymatically) and when triggered, the compound is converted *in vivo* to the active form of the drug (see diagram below).[5,7,9]

Prodrug: How it works[7]



Adapted from Huttunen KM, Rautio J. 2011.[7]

History and the present

The term prodrug was introduced by Adrien Albert in 1958, who described the alteration of the physicochemical properties of drugs to make them pharmacologically inactive until metabolised in the body to an active drug molecule.[10] It was not until the late 1970s that systematic prodrug research began.[7] In 2008, a third of all approved small-molecular-weight drugs* were prodrugs. Examples of these included various proton pump inhibitors and lisdexamfetamine dimesilate.[8]

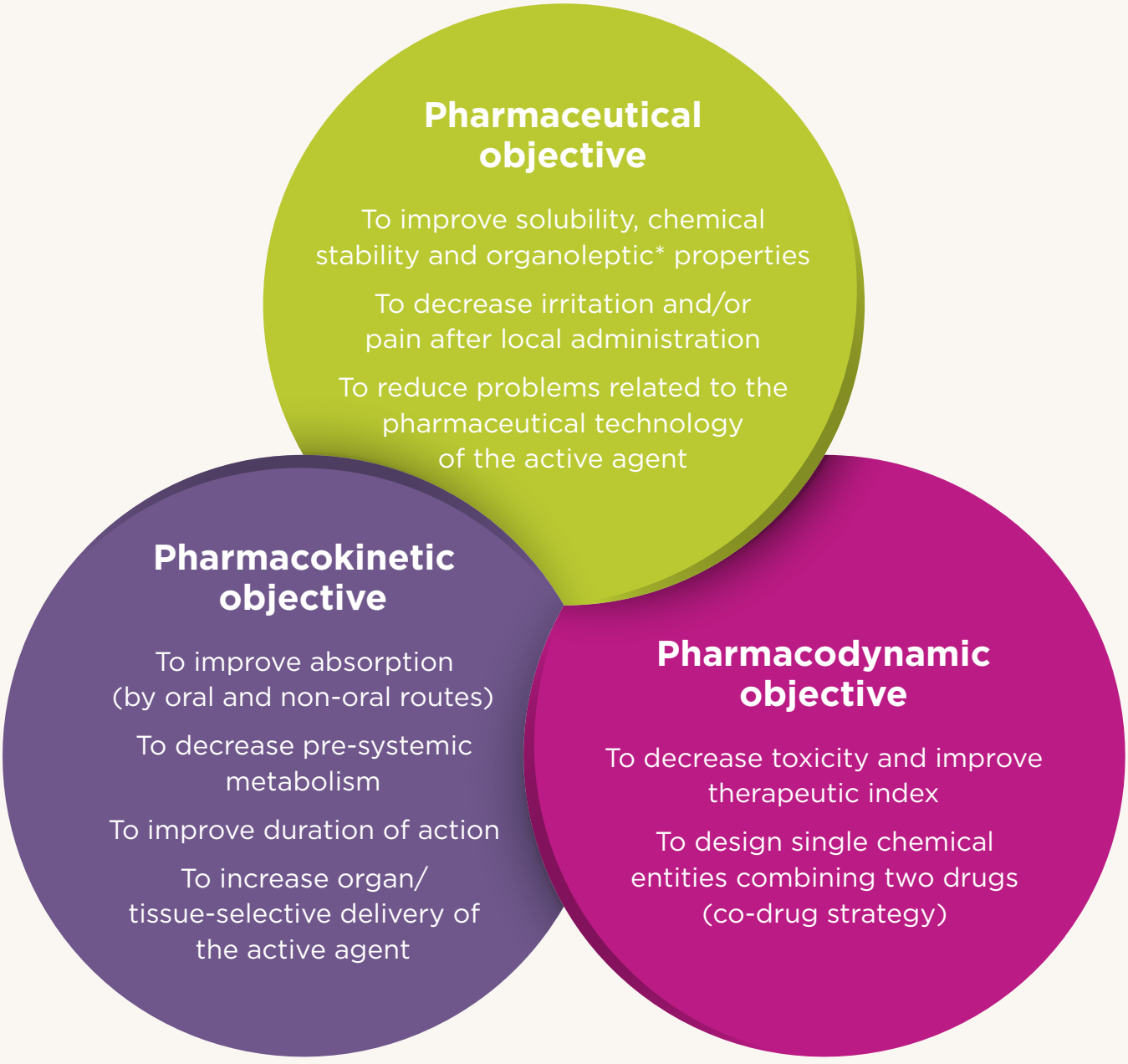
*Small-molecular-weight drug: Small (single molecule) drug of low molecular weight. It has little ability to initiate an immune response and remains relatively stable over time. Simple structure, well defined, independent of manufacturing process. An identical copy can be made.[11]

"An ideal prodrug has favorable administration, distribution, metabolism, excretion, and toxicity (ADMET) properties, is chemically stable in its dosage form, releases the active drug molecule at an appropriate rate at the desired site in the body, and releases a promoiety that is non-toxic." – Huttunen KM, Rautio J. 2011.[7]

A prodrug aims to increase the utility of active agents[7]

Prodrugs are designed to improve the pharmaceutical, pharmacokinetic and/or pharmacodynamic properties of medications. They may help overcome several barriers, for example, by improving low chemical stability, aqueous solubility, oral absorption/bioavailability or by preventing rapid pre-systemic metabolism and potential toxicity, inadequate site specificity or poor patient acceptance/compliance (such as unwanted adverse effects, unacceptable taste or odour, irritation or injection site pain).[7,12]

Prodrugs: Designed to help overcome barriers to drug effectiveness[6]



*Relating to perception by a sensory organ such as taste/odour.

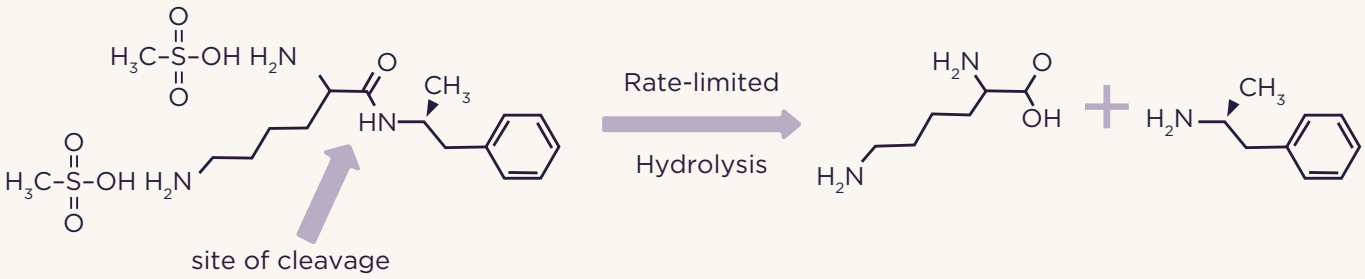
Adapted from Testa B. 2009.[6]

VYVANSE as a prodrug[1]

Pharmacology

- VYVANSE (lisdexamfetamine dimesilate, LDX) is a central nervous system stimulant prodrug of the phenythylamine and amphetamine chemical classes. Its chemical structure consists of *d*-amphetamine coupled with the naturally occurring essential amino acid *l*-lysine.[1,2]
- VYVANSE is rapidly absorbed in the intestine after oral administration. LDX is broken down by enzymes (enzymatic hydrolysis) to form *l*-lysine and the active metabolite *d*-amphetamine.[1,13,14]

***In vivo* conversion of LDX to *d*-amphetamine**



Lisdexamfetamine **l-lysine** ***d*-amphetamine**

Adapted from Krishnan S, Zhang Y. 2008.[2]

"Because of its versatility, the prodrug approach has enhanced the clinical usefulness of many pharmacological agents in the past, and as many as 10% of all approved small molecular drugs on the market today can be classified as prodrugs." – Huttunen KM et al. 2011.[8]

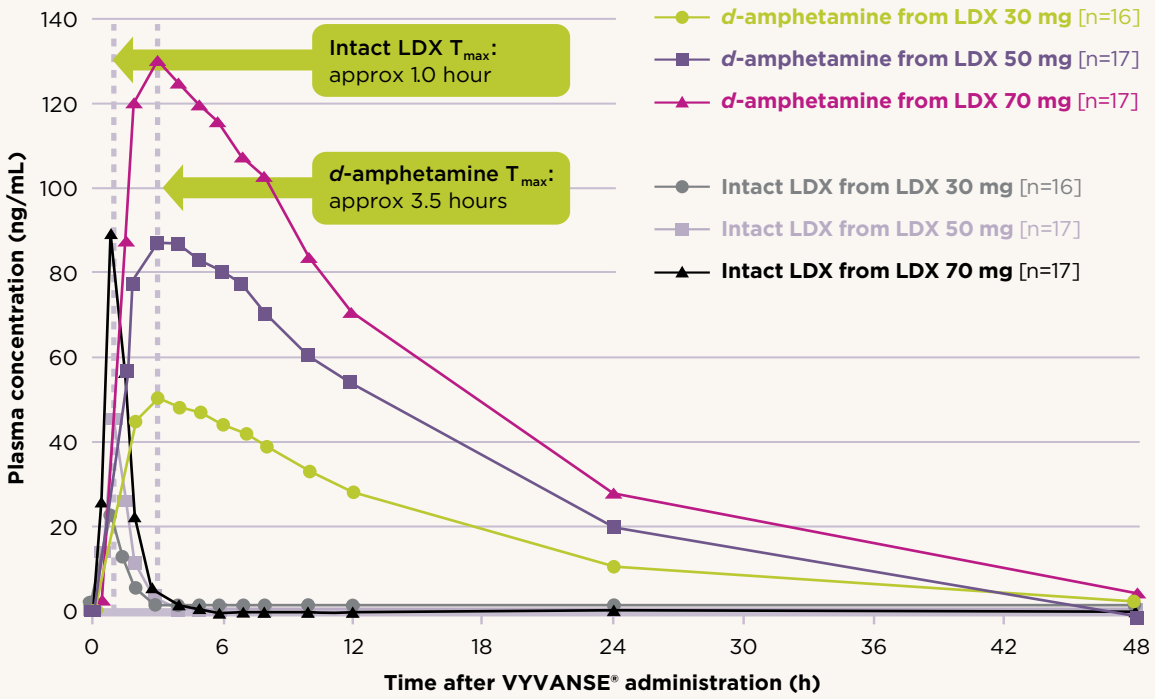
LDX, lisdexamfetamine dimesilate.

LDX hydrolysis and pharmacokinetics

Following oral administration, VYVANSE is hydrolysed in red blood cells, releasing therapeutically active *d*-amphetamine in a rate-limited manner.[13,14]

- Release of active *d*-amphetamine from the VYVANSE prodrug occurs predominantly as a result of aminopeptidase-like activity in red blood cell cytosol.[13,14]
- This rate-limiting process generates a *d*-amphetamine pharmacokinetic profile which appears to be consistent with the maintenance of efficacy of VYVANSE throughout the day following a single early morning dose.[13-16]

Linear dose-proportional increase in C_{max} and AUC for *d*-amphetamine (p<0.001) after treatment with LDX in children with ADHD[15]



Adapted from Boellner SW et al. 2010.[15]

Study design: Open-label, randomised, single dose, 3 period crossover study, with 6-day washout between periods, of 18 children with ADHD aged 6-12 years who required a medication change. All children had prior stimulant experience. Patients were given a single oral dose (after an 8-hour overnight fast) of VYVANSE 30, 50 or 70mg in a randomised sequence. Pharmacokinetic properties were calculated over the 48 hours after dosing. **Objectives:** The endpoints were objective measurements of pharmacokinetic parameters and relative bioavailability. **Results and conclusions:** These data suggest linear dose-proportional increase in C_{max} and AUC for *d*-amphetamine (p<0.001). Coefficient of Variation (CV) for C_{max} values of *d*-amphetamine post-dose were 18.1%, 19.5% and 19.4% with VYVANSE 30, 50 and 70mg, respectively. These findings suggest low interpatient variability in exposure to d-amphetamine. When AUC and C_{max} were normalised by dose and by weight, any differences seen by sex and age group were diminished. **Tolerability:** All AEs were mild or moderate. The most commonly reported AEs of 17 total patients with 30, 50 and 70mg VYVANSE respectively were: anorexia (n=4, 7 and 8), elevated blood pressure (n=2, 1 and 3), and abdominal pain (n=2, 2 and 2). No serious AEs were reported. One child was withdrawn because of pharyngitis considered unrelated to VYVANSE.[15]

ADHD, attention deficit hyperactivity disorder; **AE**, adverse event; **AUC**, area under the curve; **C_{max}**, maximum (peak) plasma drug concentration; **LDX**, lisdexamfetamine dimesilate; **T_{max}**, time to reach maximum (peak) plasma concentration.

VYVANSE as a prodrug[1]

VYVANSE as a prodrug uses a biological mechanism of drug delivery. VYVANSE absorption and conversion are not affected by variations in gastric pH, and therefore VYVANSE maximum concentration (Cmax) or its total exposure in a person (AUC) is not prone to pH-mediated food or drug interactions. Changes in gastrointestinal transit time are also unlikely to affect bioavailability of the active drug *d*-amphetamine. Food, particularly high fat meals can delay the time to maximum concentration by approximately 1 hour.*[1,2,13,17-19]

*Based on *in vitro* or healthy adult volunteers data which may not predict clinical effects.

In clinical studies conducted in children and adults, the effects of VYVANSE were ongoing at 13 hours after dosing in children and at 14 hours in adults when the product was taken once daily in the morning.[1]

Formulation and administration[1]

VYVANSE is administered as a single daily dose, taken in the morning, with or without food. Capsules may be taken whole, or opened and the contents emptied and mixed with a soft food such as yoghurt or in a glass of water or orange juice.[1]

OPTION 1

- Swallow the VYVANSE capsule whole, with or without food.

OPTION 2

1. Open the VYVANSE capsule and pour the powder into a glass of water or orange juice.
   Use all the powder, so you get all the medicine.
2. Using a spoon, break apart any powder that is stuck together. Stir the powder and water or orange juice until completely mixed together.
3. Drink the entire glass after mixing. Do not store it. Don't worry if there is a film or residue left in the glass afterwards – this is not the active ingredient.

OPTION 3

- VYVANSE can also be mixed with yogurt. Consume all the yogurt right away.

(Please follow **Option 2** or **3** if you prefer not to swallow a capsule)

Safety Information

Most common adverse events in Adult clinical trials ≥5%:

Dry mouth, nausea, constipation, decreased appetite, feeling jittery, increased heart rate, insomnia, anxiety, irritability, fatigue, headache, bruxism, upper abdominal pain, weight decreased, dizziness and diarrhoea.[1]

Please review Product Information before prescribing.
Product Information is available from Takeda Pharmaceuticals Australia Pty Ltd.
Phone: 1800 012 612. Email: medinfoAPAC@takeda.com

For further information about the appropriate selection of patients and prescribing of VYVANSE, please visit http://www.ldxguide.com/au (password: onetakeda)

PBS Information: Authority required. Attention deficit hyperactivity disorder (ADHD).
Refer to PBS Schedule for full authority information.
This product is not listed on the PBS for the treatment of Binge Eating Disorder (BED).

VYVANSE has a potential for abuse, misuse, dependence, or diversion for non-therapeutic uses. Physicians should assess the risk of abuse prior to prescribing and monitor for signs of abuse and dependence while on therapy. VYVANSE 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.

Minimum Product Information. VYVANSE® (lisdexamfetamine dimesilate). Indication: Attention Deficit Hyperactivity Disorder (ADHD): Indicated for treatment of ADHD. Treatment should be commenced by a specialist as part of a comprehensive treatment program and re-evaluated periodically during long-term use. Binge Eating Disorder (BED): Indicated for treatment of moderate to severe BED in adults when non-pharmacological treatment is unsuccessful or unavailable. Treatment should be commenced and managed by a psychiatrist. **Dosage and Administration:** VYVANSE should be initiated at 30 mg once daily in the morning (avoid afternoon doses due to potential for insomnia) and slowly adjusted to the lowest effective dose (no more frequently than weekly). Capsules may be taken whole, or opened and the contents emptied and mixed with a soft food such as yogurt or in a glass of water or orange juice. **Contraindications:** Advanced arteriosclerosis; symptomatic cardiovascular disease (eg cardiac arrhythmia, ischaemic heart disease); moderate to severe hypertension; hyperthyroidism; hypersensitivity or idiosyncratic reaction to sympathomimetic amines or any of the excipients; glaucoma; agitated states (eg severe anxiety, tension and agitation); administration during or within 14 days of cessation of MAOIs; phaeochromocytoma; tics, Tourette's syndrome; patients who exhibit severe depression, anorexia nervosa, psychotic symptoms or suicidal tendency; drug dependence or alcohol abuse. **Precautions:** Cardiovascular disease; psychiatric disorders (psychosis, bipolar disease, aggression); seizures; visual disturbance; long-term suppression of growth, peripheral vasculopathy including Raynaud's phenomenon. Renal impairment (severe renal insufficiency max dose 50mg/day; dose reduction for dialysis patients). No data in hepatic impairment. Pregnancy: Category B3. Women taking VYVANSE should refrain from breast feeding. Not studied in children <6 years or adults >55 years of age. **Interactions:** MAOIs (see Contraindications), antihypertensives, narcotic analgesics, antipsychotics, agents that alter urinary pH, serotonergic drugs. **Adverse Effects:** Very Common reactions: decreased appetite, insomnia, headache, dry mouth, upper abdominal pain, weight decreased. Common reactions: anorexia, agitation, anxiety, libido decreased, tic, affect lability, psychomotor hyperactivity, bruxism, aggression, dizziness, restlessness, tremor, somnolence, mydriasis, tachycardia, palpitation, dyspnoea, diarrhoea, nausea, vomiting, hyperhidrosis, rash, irritability, fatigue, feeling jittery, pyrexia, blood pressure increased, erectile dysfunction. Note: where frequency of adverse reactions varies across age groups (children, adolescents, adults), the adverse reaction is listed according to the highest frequency. (pi-01047. V1.0)

References: 1. VYVANSE® (lisdexamfetamine dimesilate) Approved Product Information. **2.** Krishnan S, Zhang Y. *J Clin Pharmacol* 2008;48:293-302. **3.** Sta´nczak A, Ferra A. *Pharmacol Rep* 2006;58:599-613. **4.** Ettmayer P *et al. J Med Chem* 2004;47:2393-2404. **5.** Rautio J *et al. Nat Rev Drug Discov* 2008;7:255-270. **6.** Testa B. *Curr Opin Chem Biol* 2009;13:338-344. **7.** Huttunen KM, Rautio J. *Curr Top Med Chem* 2011;11:2265-2287. **8.** Huttunen KM *et al. Pharmacol Rev* 2011;63:750-771. **9.** Patil SJ, Shirote PJ. *Int J Med Pharm Sci* 2011;1(7):1-13. **10.** Albert A. *Nature* 1958;182:421-422. **11.** Declerck PJ. *GaBi Journal* 2012;1:13-16. **12.** Karaman R. *Frontiers in Computational Chemistry* 2015;2:187-249. **13.** Pennick M. *Neuropsychiatri Dis Treat* 2010;6:317-327. **14.** Sharman J, Pennick M. *Neuropsychiatr Dis Treat* 2014;10:2275-2280. **15.** Boellner SW *et al. Clin Ther* 2010;32:252-264. **16.** Coghill D *et al. CNS Drugs* 2014;28:497-511. **17.** Ermer J *et al. J Clin Pharmacol* 2010;50:1001-1010. **18.** Krishnan SM *et al. Clin Drug Invest* 2008;28:745-755. **19.** Ermer J *et al. CNS Drugs* 2010; 24 (12):1020-1021.

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Date of Preparation January 2021. C-APROM/AU/Vyv/0019 Z20_391