

ACMD

Advisory Council on the Misuse of Drugs

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Minister for Crime Prevention, Jeremy Browne MP
Home Office
2 Marsham Street
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Dear Minister,

Re: Lisdexamfetamine advice

Earlier this year the Medicines and Healthcare products Regulatory Agency (MHRA) granted a licence for the use of Elvanse in the UK for the treatment of attention deficit/hyperactivity disorder (ADHD). As requested by the Home Office, I am writing to provide you with the Advisory Council on the Misuse of Drugs' (ACMD) consideration of the appropriate control measures under the Misuse of Drugs Act and Regulations for this new lisdexamfetamine dimesylate (L-lysine-D-amphetamine) based medicine.

Pharmacology

Lisdexamfetamine is an inactive pro-drug. After oral administration it is rapidly absorbed by the gastrointestinal tract and hydrolysed, primarily by the red blood cells, to dexamphetamine, which is responsible for the drug's activity. Dexamphetamine is one of the two stereoisomers of amphetamine and is controlled in the UK as a Class B, Schedule II substance under the Misuse of Drugs Act and Regulations.

Lisdexamfetamine is considered to be a New Active Substance under EU legislation because of the significant differences in efficacy that have been demonstrated between it and dexamphetamine. The conversion of lisdexamfetmaine to dexamphetamine occurs gradually, resulting in a significantly prolonged pharmacokinetic profile compared to orally administered dexamphetamine. The pharmacokinetic (PK) profile is very similar to the prolonged release amphetamine product Adderal XR. The rate-limited enzymatic conversion of lisdexamfetamine to d-amphetamine may result in different pharmacological effects on release and inhibition of re-uptake of brain monoamines and on its clinical efficacy in ADHD (see Heal et al 2013).

The conventional wisdom is that users of stimulant drugs desire delivery of maximum quantities of the drug to the brain in the shortest possible time – hence the use of snorting, smoking or intravenous administration. The pharmacokinetics of lisdexamfetamine given by these routes are similar to when it is given by the oral route. By all routes the time to reach peak plasma concentrations was long and the duration of effect prolonged. This forms part of the argument that recreational use of the drug is unlikely to be widespread and that diversion is not a great concern despite the fact that it would be easy to prepare solutions of the drug for administration by other routes (see Heal et al 2013).

Use and prevalence

Prior to licensing in the UK, lisdexamfetamine has been used for the treatment of ADHD in Brazil, Canada and the US. In the four years since it was first licensed (Feb 2007), there have been 1.5million person-years of treatment, of which 36% were age 6-12, 25% aged 13-17 and 38% adults¹. It was licensed in the UK in February 2013 and launched for the treatment of ADHD in March 2013. In their Evidence Summary NICE concluded (NICE 2013) that lisdexamfetamine produces clinically meaningful benefits in ADHD compared with placebo and the adverse effect profile appears similar to other stimulant drugs. They commented that the theoretical advantages in improved adherence and reduced abuse potential required further investigation in clinical practice. It is noteworthy that in the US where experience with this drug is more extensive it is subject to the same legal control (Schedule II) as other ADHD medications.

Diversion

Although an inactive pro-drug, the ACMD considers the risk of diversion and misuse for lisdexamfetamine to be high due to the ease of conversion to amphetamine which may, in turn, be readily converted to methamphetamine. Indeed, concerns have been raised around transportation, holding stocks and safe custody (DoH communication to NICE, April 2013, quoted in NICE 2013)

Harms

Lisdexamfetamine is itself an inactive pro-drug but it is rapidly metabolised to dexamphetamine which then has the potential to exert the physical and social harms associated with amphetamines as a class although there may be some differences attributable to its prolonged pharmacokinetic profile.

Harms associated with the use of amphetamines result, in the main, from their stimulatory effects brought about by inhibition of the re-uptake of monoamine neurotransmitters. Physical effects can include anorexia, insomnia, dizziness, headaches, tachycardia and hypertension. After chronic and/or high, doses convulsions, heart attacks, stroke and death have been reported. Psychologically amphetamines can improve alertness and concentration but can also give rise to anxiety or agitation. These periods of stimulation are frequently followed by rebound periods of depression and fatigue due, in part, to sleep deprivation. Performance in, for example, driving can then be negatively affected (see Heal et al, 2013).

¹ Information presented to the ACMD's Technical Committee at its meeting on the 07/02/2013 by the Medicines and Healthcare products Regulatory Agency.

Amphetamines have abuse potential and administration for prolonged periods may lead to drug tolerance and dependence although users of lisdexamfetamine would probably need to take proportionally larger amounts of the drug before dependence developed. In a paper specifically addressing this point, Jasinski (2009) concluded that, in a population of subjects with a history of stimulant abuse, abuse related liking scores equated the effects of 150mg of lisdexamfetamine with those of 40 mg of dexamphetamine. Lisdexamfetamine is pharmacologically inert but it is converted *in vivo* into d-amphetamine and, although the pharmacokinetics differs from those of other amphetamine preparations, they are not sufficiently different to justify treating lisdexamfetamine under misuse of drugs legislation in any way differently to other amphetamines.

Elvanse, which contains lisdexamfetamine, has only recently been granted a marketing authorisation in the UK. The ACMD considers that the potential social harms of lisdexamfetamine are commensurate with Class B dexamphetamine, as lisdexamfetamine gradually converts to dexamphetamine.

Recommendation

The ACMD concludes that the potential for harm and the risk of lisdexamfetamine diversion in the UK are likely to be similar to dexamphetamine. The ACMD therefore recommends that lisdexamfetamine should be controlled under Class B of the Misuse of Drugs Act 1971 and in Schedule II of the Misuse of Drugs Regulations 2001. It is noteworthy that the Royal Pharmaceutical Society has already advised that it should be treated as though it was a Schedule II drug (Royal Pharmaceutical Society, 2013)

Yours sincerely,



Professor Les Iversen FRS CBE

Cc Parliamentary Under Secretary of State for Health, Anna Soubry MP

References

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Jasinski DR (2009) Abuse liability and safety of oral lisdexamfetamine dimesylate in individuals with a history of stimulant abuse. *J Psychopharmacol* 23: 419-427.

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