Gwent Shared Care Protocol

Bwrdd Iechyd Prifysgol Aneurin Bevan University Health Board

LISDEXAMFETAMINE & DEXAMFETAMINE

for the treatment of Attention Deficit/Hyperactivity Disorder (ADHD) in Children and Adults

Protocol No. 29	**✶PLEASE CHECK http://www.wales.nhs.uk/sites3/page.cfm?orgid=814&pid=38180 FOR THE LATEST VERSION OF THIS PROTOCOL✶**
General guidance	The ABUHB Medicines and Therapeutics Committee endorsed this Protocol which outlines shared care arrangements for children (≥ 6 years of age), adolescents **and adults** taking the sympathomimetic amine dexamfetamine and its pro-drug lisdexamfetamine for the treatment of ADHD. This Protocol does NOT cover the shared care use of dexamfetamine or lisdexamfetamine in 1. children under the age of 6 years. This Protocol should be read in conjunction with: 1. The *Shared Care Agreement Form* (*see Page 7*). 2. The Summary of Product Characteristics (SmPC) for ▼Elvanse® see: http://www.medicines.org.uk/emc/medicine/27442 for ▼Elvanse Adult®: https://www.medicines.org.uk/emc/medicine/30377 or the SmPC for dexamfetamine: http://www.mhra.gov.uk/Safetyinformation/Medicinesinformation/SPCandPILs/index.htm 3. NICE CG72 (September 2008 last modified March 2013 http://guidance.nice.org.uk/CG72) – *Attention deficit hyperactivity disorder: Diagnosis and management of ADHD in children, young people and adults.* ***Note*** CG72 incorporates recommendations from NICE TA98 *and* TA102. It includes advice on use of dexamfetamine in ADHD but its publication pre-dates the UK availability of lisdexamfetamine.
1. Licensed indication	**Dexamfetamine** is indicated in narcolepsy. It is also indicated for children with refractory hyperkinetic states under the supervision of a physician specialising in child psychiatry. **Lisdexamfetamine** is indicated as part of a comprehensive treatment programme for ADHD in children **aged 6 years of age and over** when response to previous methylphenidate treatment is considered clinically inadequate. Treatment must be under the supervision of a specialist in childhood and/or adolescent behavioural disorders. Diagnosis should be made according to DSM-IV criteria or the guidelines in ICD-10 and should be based on a complete history and evaluation of the patient. Diagnosis cannot be made solely on the presence of one or more symptom. In adults, the presence of symptoms of ADHD that were pre-existing in childhood is required and should be confirmed retrospectively (according to the patient's medical record or, if not available, through appropriate and structured instruments or interviews). Based on clinical judgment, patients should have ADHD of at least moderate severity as indicated by at least moderate functional impairment in two or more settings (for example, social, academic, and/or occupational functioning), affecting several aspects of an individual's life. The specific aetiology of ADHD is unknown, and there is no single diagnostic test. Adequate diagnosis requires the use of medical and specialised psychological, educational, and social resources. A comprehensive treatment programme typically includes psychological, educational and social measures as well as pharmacotherapy and is aimed at stabilising children with a behavioural syndrome characterised by symptoms which may include chronic history of short attention span, distractibility, emotional lability, impulsivity, moderate to severe hyperactivity, minor neurological signs and abnormal EEG. Learning may or may not be impaired. Lisdexamfetamine is not indicated in all children with ADHD and the decision to use the drug must be based on a very thorough assessment of the severity and chronicity of the child's symptoms in relation to the child's age and potential for abuse, misuse or diversion.

	Appropriate educational placement is essential, and psychosocial intervention is generally necessary. The use of lisdexamfetamine should always be used in this way according to the licensed indication. **NOTE LISDEXAMFETAMINE AND DEXAMFETAMINE ARE NOT DIRECTLY INTERCHANGEABLE**
2. Background information	Amphetamines are non-catecholamine sympathomimetic amines with CNS stimulant activity. The mechanism of action of amphetamines for the treatment of ADHD is not fully understood; however, it is thought to be due to the ability to block the reuptake of norepinephrine and dopamine into the presynaptic neuron, and increase the release of these monoamines into the extraneuronal space. Lisdexamfetamine is a pharmacologically inactive prodrug, requiring metabolic activation by red blood cells to the active dexamfetamine. AWMSG advice (No. 2813 of December 2013) recommends lisdexamfetamine as an option for use within NHS Wales as part of a comprehensive treatment programme for ADHD in children aged six years of age and over **when response to previous methylphenidate treatment is considered clinically inadequate**. Treatment must be under the supervision of a specialist in childhood and/or adolescent behavioural disorders. ***Note*** AWMSG's advice places it alongside atomoxetine in the treatment pathway (i.e. after methylphenidate) rather than after atomoxetine (and methylphenidate) as recommended for dexamfetamine in NICE CG72: **NICE CG72** (*Note* publication pre-dates the UK availability of lisdexamfetamine) **states:** *1.5.6.3* ***Dexamfetamine*** *should be considered in* ***children and young people*** *whose ADHD is unresponsive to a maximum tolerated dose of methylphenidate or atomoxetine.* *1.7.1.6 Atomoxetine or* ***dexamfetamine*** *should be considered in* ***adults*** *unresponsive or intolerant to an adequate trial of methylphenidate (this should usually be about 6 weeks). Caution should be exercised when prescribing dexamfetamine to those likely to be at risk of stimulant misuse or diversion.* *1.5.5.6 If there is a choice of more than one appropriate drug, the product with the* ***lowest cost***** (taking into account the cost per dose and number of daily doses) should be prescribed.* * Daily net price of 60mg dexamfetamine = £10.20 (October 2014 Drug Tariff) and daily net price of lisdexamfetamine 70mg = £2.97. AWMSG advice (No. 2615 of October 2015) recommends lisdexamfetamine (Elvanse Adult®) as an option for use within NHS Wales as part of a comprehensive treatment programme for ADHD in adults.
3. Contraindications & cautions	**Contraindications:** i. Hypersensitivity to sympathomimetic amines or any of the excipients listed in the SmPC. ii. Concomitant use of MAOIs or within 14 days after MAOI treatment (hypertensive crisis may result). iii. Hyperthyroidism or thyrotoxicosis. iv. Agitated states. v. Symptomatic cardiovascular disease structural cardiac abnormalities and/or moderate or severe hypertension. vi. Advanced arteriosclerosis. vii. Substance misuse or dependence – this is a caution for lisdexamfetamine. viii. Tics and Tourette syndrome (discontinue if tics occur) – this is a caution for lisdexamfetamine. ix. Glaucoma. x. Lactation (amphetamines are excreted in human milk). **Caution** in individuals with a history of: i. Psychosis or bipolar disorder (possible induction of mixed / manic episodes) – dexamfetamine/lisdexamfetamine may exacerbate symptoms of behaviour disturbance and thought disorder. ii. Seizures – dexamfetamine/lisdexamfetamine may lower the seizure threshold.

iii. Cardiovascular disease or abnormalities – such individuals may be at increased vulnerability to the sympathomimetic effect of a stimulant.
iv. Renal or hepatic impairment.
v. Pregnancy – this is a contraindication for dexamfetamine.

Avoid abrupt cessation of dexamfetamine/lisdexamfetamine following prolonged high dose administration as extreme fatigue and mental depression may occur.

4. Dosage regimen

Treatment must be initiated under the supervision of an appropriate specialist in childhood and/or adolescent behavioural disorders.

NOTE LISDEXAMFETAMINE AND DEXAMFETAMINE ARE NOT DIRECTLY INTERCHANGEABLE

LISDEXAMFETAMINE

CHILD 6–17 years & **ADULT*** over 18 years, initially 30mg **once daily** in the morning, increased if necessary at weekly intervals by 20mg; max. 70mg daily (discontinue if response insufficient after 1 month).

DEXAMFETAMINE

ADULT* over 18 years [unlicensed use], initially 5mg twice daily, increased at weekly intervals according to response; max. 60mg daily.

CHILD 6–18 years, initially 2.5mg 2–3 times daily, increased if necessary at weekly intervals by 5mg daily, usual max. 1mg/kg (up to 20mg) daily (40mg daily has been required in some children)

Note Maintenance dose given in 2–4 divided doses

*** In adolescents whose symptoms persist into adulthood and who have shown clear benefit from treatment, it may be appropriate to continue treatment into adulthood.**

Long-term use

Pharmacological treatment of ADHD may be needed for extended periods. The specialist electing to use dexamfetamine/lisdexamfetamine for extended periods (over 12 months) should re-evaluate its usefulness at least yearly, and consider trial periods off medication to assess the patient's functioning without pharmacotherapy, preferably during times of school holidays.

5. Drug Interactions

Check *BNF* Appendix 1 before co-prescribing any other drug.

Dexamfetamine/Lisdexamfetamine has the following interaction information:

Chlorpromazine	effects of dexamfetamine/lisdexamfetamine possibly reduced
Guanethidine	**dexamfetamine/lisdexamfetamine antagonises hypotensive effect**
MAOIs	**risk of hypertensive crisis when dexamfetamine/lisdexamfetamine given with MAOIs, avoid dexamfetamine/lisdexamfetamine for at least 2 weeks after stopping MAOIs** This risk extends to concurrent use of dexamfetamine/lisdexamfetamine with **moclobemide** (a reversible MAO-A inhibitor), **rasagiline** & **selegiline** (MAO-B inhibitors) and **linezolid** (a reversible, non-selective MAO inhibitor).
Ritonavir	effects of dexamfetamine possibly reduced

As dexamfetamine/lisdexamfetamine are sympathomimetic amines the following are potential interactions:

Antipsychotics	hypertensive effect of sympathomimetics antagonised
Apraclonidine	avoidance of sympathomimetics advised by manufacturer of apraclonidine
Doxapram	increased risk of hypertension when sympathomimetics given with doxapram
Ergotamine	increased risk of ergotism when sympathomimetics given with ergotamine
Isoflurane	**avoidance of sympathomimetics advised by manufacturer of isoflurane (risk of ventricular arrhythmias)**
Oxytocin	risk of hypertension when vasoconstrictor sympathomimetics given with oxytocin (due to enhanced vasopressor effect)

6. Adverse drug reactions

Dexamfetamine/lisdexamphetamine has the potential to replicate the physical and social harms associated with amphetamines. Physical effects can include anorexia, insomnia,

All serious adverse events should be reported to MHRA/CHM using the Yellow Card.	dizziness, headaches, rapid heartbeat and hypertension. After chronic and/or high doses, convulsions, heart attacks, stroke and death have been reported. Common adverse effects associated with dexamfetamine/lisdexamfetamine include, mydriasis, labile mood, malaise, growth restriction in children

Adverse event	*Approximate frequency*	*Management*
Decreased appetite, insomnia, headache, upper abdominal pain, weight loss	Very Common (frequency ≥ 1/10)	**If severe or persistent discuss with specialist**
Tics, agression	Common	**Discuss with specialist**
Anorexia, affect lability, psychomotor hyperactivity, dizziness, drowsiness, mydriasis, dry mouth, diarrhoea, nausea, vomiting, rash, irritability, fatigue, pyrexia	(≥1/100 to <1/10):	**If severe or persistent discuss with specialist**
Hypersensitivity, agitation, anxiety, logorrhea, depression, dysphoria, dermatillomania, mania, hallucination, restlessness, tremor, vision blurred, tachycardia, palpitation, dyspnoea, hyperhidrosis, urticaria, feeling jittery, blood pressure increased	Uncommon (≥1/1,000 to <1/100)	**Stop drug and discuss with specialist**

7. Baseline investigations Children and adolescents	**To be undertaken by specialist:** A complete history should be taken, documenting: concomitant medicines; past and present medical and psychiatric disorders or symptoms; family history of sudden cardiac death, unexplained death, or malignant arrhythmia; and accurate pre-treatment height and weight on a growth chart. Physical examination for the presence of heart disease (**including BP and pulse**). The use of dexamfetamine/lisdexamfetamine is contraindicated in symptomatic cardiovascular disease (*see Section 3*).
8. Ongoing monitoring Children, adolescents and adults	**To be undertaken by specialist:** Monitor for aggressive behaviour or hostility during initial treatment. Growth (in children and adolescents), psychiatric, and cardiovascular status should be continually monitored. • Blood pressure and pulse should be recorded on a centile chart at each adjustment of dose and at least every **6 months**. • Height, weight, and appetite should be recorded at least **six-monthly** (with maintenance of a growth chart for children and adolescents). • Development of *de novo* or worsening of pre-existing psychiatric disorders should be monitored at every adjustment of dose and then at least **every six months** and at every visit. Patients should be monitored for the risk of diversion, misuse, and abuse of dexamfetamine/lisdexamfetamine.
9. Pharmaceutical aspects	**No special considerations.**
10. Specialist contact details	Advice can be obtained from the local Child Psychiatry, Adult Psychiatry and Community Paediatric Services from 9 to 5pm Monday to Friday

Child psychiatry: 01633 436830 01633 436831 01633 436832 01633 436944	**Learning Disabilities:** 01633 623553	**Community Paediatrics:** via responsible Consultant Secretary
Adult psychiatry: contact local General Adult Community Mental Health Team *see:* http://howis.wales.nhs.uk/sitesplus/866/page/52574		

11. Criteria for shared care	All Wales criteria for Shared Care can be found at: http://www.awmsg.org/docs/awmsg/medman/Criteria%20for%20Shared%20Care.pdf GMC guidance on Shared Care (2013) states: *Decisions about who should take responsibility for continuing care or treatment after initial diagnosis or assessment should be based on the patient's best interests, rather than on convenience or the cost of the medicine and associated monitoring or follow-up.* *Shared care requires the agreement of all parties, including the patient. Effective communication and continuing liaison between all parties to a shared care agreement are essential.*
12. Responsibilities of Specialists (Secondary Care)	i. To assess and diagnose ADHD in accordance with the recommendations in NICE CG72. ii. To undertake the baseline clinical valuations (as detailed in *Section 7*). iii. To provide a patient information leaflet indicating the risks and benefits associated with dexamfetamine/lisdexamfetamine, and to discuss these with the child or young person and their family or carers. iv. To advise the patient/parent or carer on potential side effects and the action to be taken should they occur; particularly the development of any symptoms suggestive of cardiac disease. v. To confirm patient/parent or carer's understanding and consent to treatment. vi. To initiate dexamfetamine/lisdexamfetamine and to increase the dose (according to response) up to the usual maintenance dose and to prescribe a trial of **4 weeks on a maintenance dose** to evaluate the full effectiveness of dexamfetamine/lisdexamfetamine. The development of any aggressive behaviour or hostility should be monitored during the initial treatment period. vii. Once dexamfetamine/lisdexamfetamine has been evaluated as effective and well tolerated, to send the GP a *Shared Care Agreement Form* (*Page 7*) inviting them to participate in shared care management of the patient. viii. To monitor the patient in accordance with the ongoing monitoring schedule (*Section 8*). ix. **To inform the GP of dosage schedule, monitoring measurements and progress of treatment after each appointment**. x. To inform the GP if the patient fails to attend and clearly indicating that the patient is taking dexamfetamine/lisdexamfetamine. xi. **To re-evaluate the long term usefulness of dexamfetamine/lisdexamfetamine for the individual patient with trial periods off medication to assess the patient's functioning without pharmacotherapy this should be performed at least once yearly (preferably during times of school holidays in the case of children).** xii. To ensure that monitoring responsibility is transferred from child to adult services once the patient reaches 18 years of age.
13. Responsibilities of patients/parents or carers	➢ **To attend hospital and GP clinic appointments. Failure to attend will result in the medication being stopped.** ➢ To report any adverse events immediately to their specialist or GP (particularly development of any exertional chest pain, unexplained syncope, or other symptoms suggestive of cardiac disease).
14. Responsibilities of Primary Care	i. To return the *Shared Care Agreement Form* (*Page 7*) to the requesting specialist within one week of receipt. ii. To issue ongoing prescriptions for dexamfetamine/lisdexamfetamine as per dose recommended by specialist. Both dexamfetamine and lisdexamfeatine are Class B drugs in paragraph 1(a) under Part II of Schedule 2 to the 1971 Act and is inserted into Schedule 2 to the 2001 Regulations. It is subject to the following regulations:

Safe Custody Regulations apply	Controlled Drug Prescription requirements	Prescription valid for	Address of the prescriber required to be in the UK	EEA and Swiss prescribers can legally prescribe	Prescription is repeatable	Controlled drug Requisition necessary	Denature before disposal
Yes	Yes	28 days	Yes	No	No	Yes	Yes

	iii. To monitor for the risk of diversion, misuse, and abuse of dexamfetamine/lisdexamfetamine. iv. To contact the patient/parent or carer if they fail to attend appointments with specialist and if necessary refuse to issue further prescriptions until specialist supervision has occurred. v. Whenever practical, to ask the patient/parent or carer about any adverse reactions, particularly in relation to any symptoms suggestive of cardiac disease (*see Section 6 above*).
15. Responsibilities of all prescribers	**Dexamfetamine – report any suspected serious adverse reaction** **Lisdexamfetamine – report any suspected adverse reaction to MHRA via the "yellow card scheme." http://yellowcard.mhra.gov.uk/**
16. Supporting documentation / information	*BNF and BNFc* Section 4.4 CNS stimulants & drugs used for ADHD Patient information leaflet for Elvanse®: https://www.medicines.org.uk/emc/PIL.27443.latest.pdf and Elvanse Adult®: https://www.medicines.org.uk/emc/PIL.30368.latest.pdf AWMSG appraisal information on lisdexamfetamine: 1. http://www.awmsg.org/awmsgonline/app/appraisalinfo/188 2. Adults http://www.awmsg.org/awmsgonline/app/appraisalinfo/2534 NICE CG72: http://guidance.nice.org.uk/CG72 Scottish Medicines Consortium advice on lisdexamfetamine (May 2013): http://www.scottishmedicines.org.uk/SMC_Advice/Advice/863_13_lisdexamfetamine_dimesylate_Elvanse/lisdexamfetamine_dimesylate_Elvanse NICE Evidence summary: new medicine (ESNM) 19. Attention deficit hyperactivity disorder in children and young people: lisdexamfetamine dimesylate (2013): http://publications.nice.org.uk/esnm19-attention-deficit-hyperactivity-disorder-in-children-and-young-people-lisdexamfetamine-esnm19/

Shared Care Agreement Form

CONSULTANT REQUEST

To: Dr.

Your patient:	**NHS No. (10digit):**
was seen on:	
with a diagnosis of:	
I recommend that the following drug is initiated:	

This drug has been accepted as suitable for shared care by the *ABUHB MTC*. I agree to the responsibilities set out in the protocol SCP No. 29 (*copy attached and also at: http://www.wales.nhs.uk/sites3/page.cfm?orgid=814&pid=38180*).

I am requesting your agreement to sharing the care of this patient. The preliminary tests set out in the protocol have been carried out. I am currently prescribing the stabilising treatment.

I would like you to undertake treatment from:
The initial treatment will be:
The baseline tests are:

If you undertake treatment I will reassess the patient in ____ weeks. You will be sent a written summary within 14 days. I will accept referral for reassessment at your request.

The medical staff of the department is available at all times to give you advice.

Consultant Name:	**Signature:**
Department:	
Hospital:	**Date:**
Contact Telephone No's:	

GP RESPONSE (*Please circle the appropriate number below detailing your response*)

1. I am willing to undertake shared care as set out in SCP No. 29 for this patient.
2. I would like further information. Please contact me on: _____
3. I am unable to undertake shared care for this patient because: (*Please state*)

_____

G.P. Signature _____ Date _____

Practice Address/Stamp _____

PLEASE RETURN WHOLE COMPLETED FORM OR A COPY TO THE REQUESTING CONSULTANT WITHIN 1 WEEK