Cardiff & Vale (C&V) UHB Corporate Medicines Management Group (c MMG)

SHARED CARE

DRUG: METHYLPHENIDATE, LISDEXAMFETAMINE & ATOMOXETINE

PROTOCOL NUMBER: CV01

INDICATION: Attention deficit hyperactivity disorder (ADHD) as part of a comprehensive treatment programme in children aged 6 years of age and over, young people and adults.

General Guidance

This protocol sets out details for the shared care of patients taking **methylphenidate, lisdexamfetamine and atomoxetine** and should be read in conjunction with the General Guidelines for Shared Care and the current NICE Guideline (NG 87 March 2018).
Sharing of care requires communication between the specialist, GP and patient. The intention to share care should be explained to the patient by the doctor initiating treatment. **The doctor who prescribed the medication legally assumes responsibility for the drug and the consequences of its use.** The prescriber has a duty to keep themselves informed about the medicines they prescribe, their appropriateness, effectiveness and cost. They should also keep up to date with the relevant guidance on the use of the medicines and on the management of the patient's condition.

Background

Methylphenidate, lisdexamfetmine & atomoxetine are recommended options for use as outlined in NICE Guideline (NG87) where drug treatment is deemed appropriate as part of a "comprehensive treatment programme" for children, young people and adults with a diagnosis of Attention Deficit/ Hyperactivity Disorder (ADHD)
A diagnosis of ADHD should only be made by a specialist psychiatrist, paediatrician or appropriately qualified healthcare professional with training and expertise in the diagnosis of ADHD.
The assessment should include, a clinical and psychosocial assessment, a developmental and psychiatric history, observer reports and assessment of the person's mental state.

Symptoms of hyperactivity/impulsivity and or inattention should:

- meet the diagnostic criteria in ICD for hyperkinetic disorder or in DSM for ADHD
- be associated with at least moderate psychological, social and/or educational or occupational impairment based on interview and /or direct observation in multiple settings,
- be pervasive, occurring in two or more important settings including social, familial, educational and /or occupational settings.

ADHD should be considered in all age groups, with symptom criteria adjusted for age- appropriate changes in behavior. The possibility of any co-existing disorders or conditions/disorders, which better explain the symptoms, should be explored. Rating scales may be used to aid the assessment but the diagnosis of ADHD cannot be based solely on these or on observations.
The decision regarding which drug to prescribe should be based on the following:

- Presence of co-morbidities (e.g. tic disorders, Tourette's syndrome, epilepsy)
- Different adverse effects profiles of the drugs
- Specific compliance issues e.g. need to administer a mid-day dose at school or work
- Potential for drug diversion/misuse

Prior to prescribing, it is necessary to conduct a baseline evaluation of a patient's cardiovascular status including blood pressure and heart rate. A comprehensive history should document concomitant medications, past and present co-morbid medical and psychiatric disorders or symptoms, family history of sudden cardiac/unexplained death and include an accurate recording of pre-treatment height and weight on a growth chart.

Responsibilities

A. Consultant responsibilities

1. When treatment is **initiated** send Shared Care request form with Shared Care Protocol to GP.
2. Initiate therapy following full discussion with the patient/carer of different treatment options, benefits and risks.
3. Comprehensive baseline assessment, initial prescribing and baseline and continued monitoring.
4. Titrate medication adjusting dose as appropriate and undertake monitoring of clinical response and side effects.
5. Liaise with GP, school and any other agency involved with the patient, and provide a comprehensive treatment programme for the patient
6. When a GP positive response to SC has been received and patient has been stabilised send a letter to GP "handing over" the Shared Care of the patient to the GP.
7. Respond to any request from GP to review the patient due to adverse effects of therapy.
8. Advise the GP on continuing, changing or stopping drug following medical review of the patient and associated drug therapy
9. Notify GP if patient is failing to attend for appropriate monitoring and advise GP on appropriate action.
10. Review patient at 18 years of age and refer to appropriate adult services if patient is to continue on medication. Advise GP of decision.
11. Advise GP if new medication prescribed and prescribe until stable. Once stable inform GP who will recommence prescribing.

B. GP responsibilities.

1. Within one week of receipt return the completed Shared Care request form to indicate whether or not willing to undertake shared care.
2. Prescribe ADHD medication as part of the shared care agreement.
3. Monitor the general health of the patient
4. Report adverse effects of therapy to the consultant and the Medicines and Health products Regulatory Agency (MHRA)
5. Act on advice provided by the Consultant if patient does not attend for appropriate monitoring.
6. On receipt of advice that a new medication for ADHD has been prescribed remove previous ADHD medication from the patient's repeat medciation.
7. Prescribe new ADHD medication ONLY when a handover letter from secondary care confirms the dose and that the patient is now stable on the new medication.
8. *monitoring will be undertaken by the Secondary Care Health Professional until the patient is stable on treatment and at least every 6 months thereafter. If the GP becomes aware in the interim that the patient is experiencing an adverse effect or unexplained symptom such as weight loss and does not have an imminent appointment with the Consultant, they should request that the appointment be expedited.

C. Patient / carer responsibilities

1. Report any adverse effects
2. Complete any monitoring forms requested by the specialist
3. Order repeat prescriptions and store safely
4. Attend all medical / other appointments as necessary

Monitoring in secondary care

Pre- treatment assessment

- Full mental health and social assessment
- Full history and physical examination
- BP & HR
- Assessment of history of exercise syncope, undue breathlessness and cardiovascular symptoms
- ECG if there is past medical or family history of serious cardiac disease, a history of sudden death in young family members or abnormal findings on cardiac examination.
- Height & weight
- Enquiry about history of seizures or tics
- Risk assessment for substance misuse or drug diversion
- Concomitant medications

During treatment

- BP & HR before and after each dose change and every 6 months. Sustained resting tachycardia, arrhythmia or systolic BP >98th centile (or significant increase) measured on 2 occasions should prompt dose reduction Height every 6 months in children & young people
- Weight
    - children 10 years or younger - at 3 months and every 3 months if concerns about weight otherwise every 6 months
    - children over 10 years & young people – at 3 months and 6 months after starting treatment then every 6 months
    - adults - every 6 months
- Children and young people - plot height & weight on growth chart & review
- Monitor for side effects

Dosage Regimen

General Principles

Prescribers should be familiar with the pharmacokinetic profiles of all medications and preparations available for ADHD to ensure the treatment is tailored effectively to the individual needs of the child, young person or adult.

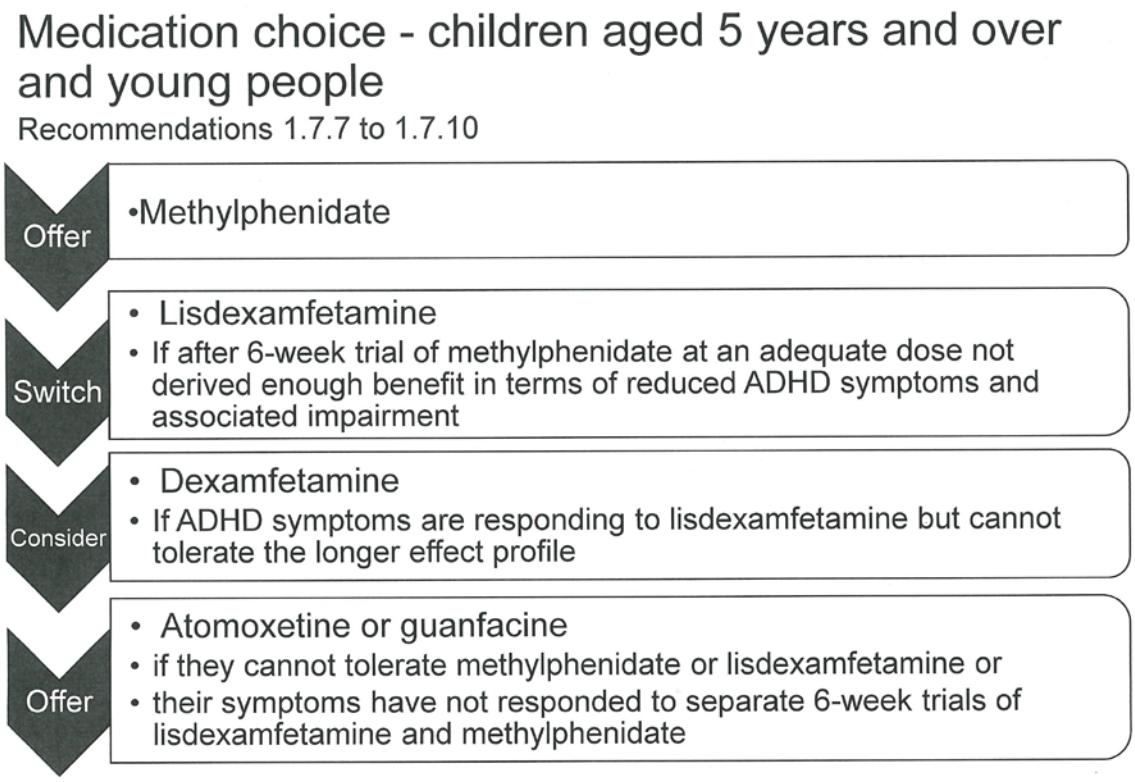
Prescribers should be familiar with the requirements for controlled drug legislation governing prescription and supply of stimulants.

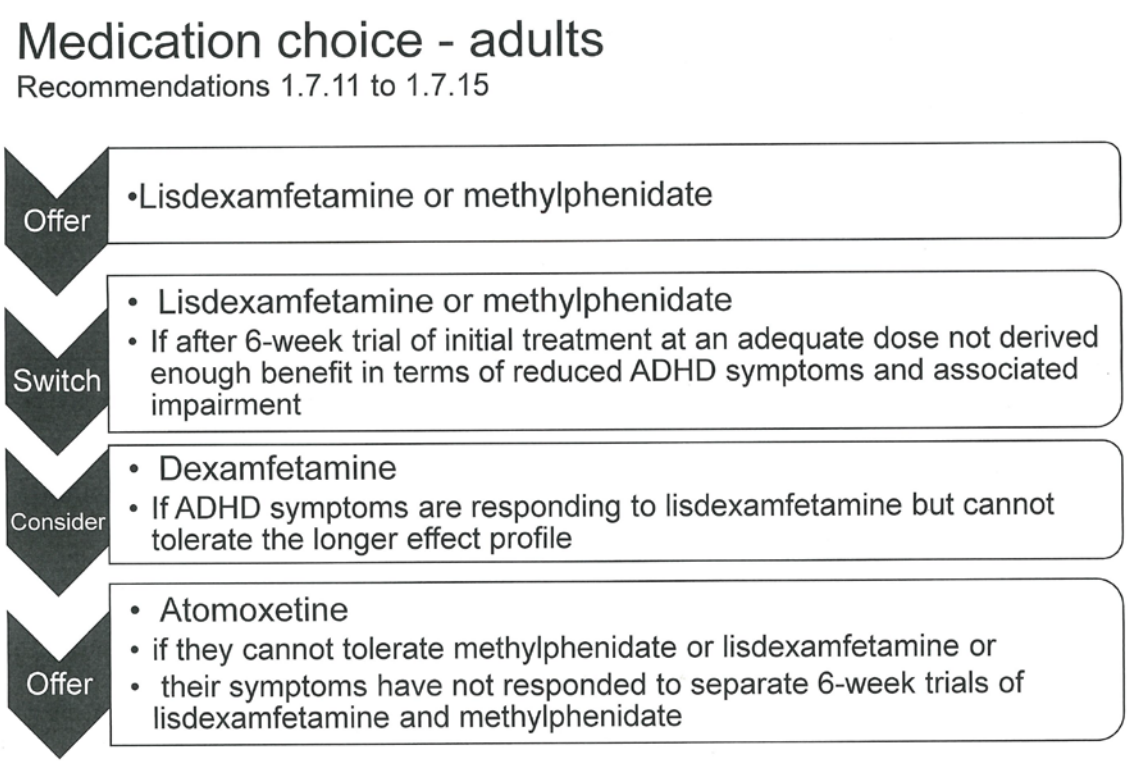
During the titration phase, doses should be gradually increased until there is no further clinical improvement in ADHD symptoms and side effects are tolerable.

Following titration and dose stabilisation, prescribing and monitoring should be carried out under shared care arrangements with primary care.

Side effects resulting from drug treatment for ADHD should be routinely monitored and documented in patients notes. If side effects become troublesome a reduction in dose should be considered.

Summary of NICE NG87 recommended on medication choice





	Methylphenidate Immediate Release	Methylphenidate modified release		
Brand name	Prescribe generically (brands include Ritalin, Medikinet)	**Xaggitin XL** (Previously Xenidate XL and Concerta XL were the preferred brands)	**Equasym XL**	**Medikinet XL**
Strength	5mg,10mg,20mg tablets	18mg, 27mg, 36mg, 54mg tablets	10mg, 20mg, 30mg capsules	5mg, 10mg, 20mg, 30mg, 40mg, 50mg, 60mg capsules
Indication	As part of a comprehensive treatment programme for ADHD in children aged 6 and over. Treatment of ADHD in children under 6 years of age is **unlicensed**. Treatment of ADHD in adults is **unlicensed**. NICE: Offer medication for ADHD only if symptoms are still causing a persistent significant impairment in at least one domain after environmental modifications have been implemented and reviewed.			
Place in Therapy	**First line**	**First line,** if once daily dosing and 12-hour action is required, or there are concerns about diversion (22% immediate release and 78% extended)	**First line,** if once daily dosing and 8-hour action is required or there are concerns about diversion. (Equasym XL 30% immediate release and 70% extended; Medikinet XL 50% immediate release and 50% extended)	
Controlled Drug	**Yes**	**Yes**	**Yes**	**Yes**
Dose in children 6 years and over	5mg once or twice a day. Titrate by weekly increments of 5-10mg/day against symptoms and side effects. **Max:** 60mg/day in 2 – 3 divided doses.	As per IR tablets, using an equivalent dose. Not usually for initiation of treatment- use 18mg in the morning if required. **Max:** 54mg once a day.	As per IR tablets, using an equivalent dose. Initiate treatment using 10mg capsules daily Equasym XL- before breakfast. Medikinet XL- with breakfast. **Max:** 60mg once a day	
Unlicensed dose in children	Can be increased to 2.1mg/kg daily in divided doses up to a maximum of 90mg under specialist supervision. Discontinue after 1 month if no response **4-5 years(unlicensed):** 2.5mg twice a day, increased by 2.5mg at weekly intervals. **Max** 1.4mg/kg in 2-3 doses	6 years and over - Can be increased to 2.1mg/kg daily in divided doses up to a maximum of 108mg under specialist supervision. Discontinue after 1 month if no response	6 years and over - Can be increased to 2.1mg/kg daily in divided doses up to a maximum of 90mg under specialist supervision. Discontinue after 1 month if no response	
Dose in adults (unlicensed)	5mg 2 or 3 times a day. Titrate against symptoms and side effects at weekly intervals. **Max**: 100mg/day in up to 4 divided doses.	As per plain tablets, using an equivalent dose. If initiating treatment use 18mg daily, adjusted at weekly intervals. Usually given once daily, but not more than twice daily **Max:** 108mg daily	As per plain tablets, using an equivalent dose. Initiate treatment using 10mg capsules daily. (Equasym XL- before breakfast. Medikinet XL- with breakfast) Usually given once daily, but not more than twice daily. **Max:** 100mg once a day	
Pregnancy **Breast Feeding**	Limited experience in Pregnancy – Avoid unless potential benefit outweighs risk Limited information available – Avoid, Consider discontinuing methylphenidate			
Monitoring in adults by specialist	Pulse & BP before and after dose changes and then every 6 months; Weight every 6 months.			
Monitoring in children by specialist	Monitor BP/ HR Monitor Weight: every 3 months if there is concern about weight otherwise every 6 months for children aged 10 years and under; at 3 months & 6 months in young people and children over 10 years and every 6 months thereafter Monitor Height every 6 months for children and adolescents and recorded on growth chart			
Drug Interactions	Warfarin; Phenytoin; Valproate; Carbamazepine;; Tricyclic antidepressants; SSRIs; Clonidine; Risperidone MAOIs During treatment or within a minimum of 14 days of discontinuing those drugs, due to risk of hypertensive crisis.			

	Methylphenidate IR (continued)	Methylphenidate modified release (continued)
Contraindications & warnings	Known sensitivity to methylphenidate • Glaucoma • Phaechromocytoma • Hyertensive crisis during treatment with non-selective, irreversible monoamine oxidase (MAO) inhibitors, or within a minimum of 14 days of discontinuing those drugs • Hyperthyroidism or thyrotoxicosis • Diagnosis or history of severe depression, anorexia nervosa/anorexic disorders, suicidal tendencies, psychotic symptoms, severe mood disorders, mania, schizophrenia, psychopathic/borderline personality disorder. • Diagnosis or history of severe and episodic (Type 1) Bipolar (affective) disorder (that is not well controlled) • Pre-existing cardiovascular disorders including severe hypertension, heart failure, arterial occlusive disease, angina, haemodynamically significant congenital heart disease, cardiomyopathies, myocardial infarction, potentially life-threatening arrhythmias and channelopathies (disorders caused by the dysfunction of ion channels) • Pre-existing cerebrovascular disorders cerebral aneurysm, vascular abnormalities including vasculitis or stroke or known risk factors for cerebrovascular disorders	
Side effects (common or significant)	At the beginning of treatment: Nervousness, insomnia (may be difficulty falling asleep- this may be due to the effect of methylphenidate itself or its effect having worn off-the timing of the last dose may need adjustment?) , decreased appetite (common on initiation but often transient) **CNS** – headache, drowsiness, dizziness, dyskinesia, psychomotor hyperactivity Seizures – if exacerbated in patient with epilepsy or new seizures medication should be discontinued immediately **Skin** – rash, pruritus, urticaria, arthralgia, hair loss. **GI** – abdominal pain, nausea/vomiting, dry mouth, weight loss, diarrhoea GI upsets are usually mild and transient. Can be alleviated by concomitant food intake. If it doesn't resolve discontinue medication and consult specialist. **Blood** – very rarely leucopenia, anaemia, thrombocytopenia Discontinue medication if WBC <4.0 $x10^9$ /L. This is reversed on discontinuation. **CVS** – tachycardia, palpitations, arrhythmias, changes in heart rate and BP (usually increase). BP >95th centile on 2 occasions or significant increase should prompt dose reduction and referral to specialist. **Heart disease- Symptoms require prompt specialist cardiac evaluation.** **Psychiatric disorders-** associated with causing or worsening e.g. depression, suicidal thoughts, hostility, anxiety, agitation, psychosis and mania. Refer to specialist for advice. **Motor and verbal tics** - associated with exacerbation or onset. If these persist beyond a few days specialist advise should be sort re dose reduction or discontinuation **Other** – fever, cough. **In children- Weight Loss –Growth Retardation-** strategies include – taking medication with or after food rather than before meals, eating additional snacks early morning or late evening when stimulant effects have worn off. Eating high calorie food of good nutritional value. This is reversible on discontinuation of medication. Consider a planned break at weekends or school holiday.	

	Lisdexamfetamine	Atomoxetine
Brand name	Elvanse	Strattera
Strength	20mg,30mg,40mg,50mg ,60mg 70mg caps. Adult: 30mg, 50mg, 70mg caps	10mg,18mg,25mg,40mg,60mg caps and 4mg/ml oral solution
Indication	As part of a comprehensive treatment programme for ADHD in children aged 6 and over, when response to previous methylphenidate is considered clinically inadequate. Treatment of ADHD in adults.	As part of a comprehensive treatment programme for ADHD in children aged 6 and older, in adolescents and in adults.
Place in Therapy	**Children & Young people - Second line** For those who have not derived enough benefit from an adequate (NICE suggest 6 weeks) trial of methylphenidate **Adults – First line**	**Third line** If methylphenidate and lisdexamfetamine have not been tolerated or if symptoms have not responded to adequate trials of each
Controlled Drug	**Yes**	**No**
Dose in children 6 years and over	30mg once daily in the morning or 20mg if appropriate. Titrate according to response/ tolerability. May be increased at weekly intervals by 10-20mg increments. **Max:** 70mg once a day	**<70kg:** initially 0.5mg/kg/day minimum of 7 days, then titrated according to response and tolerability. Recommended maintenance dose is approx. 1.2mg/kg/day. **Unlicensed:** 1.8mg/kg/day (up to 120mg.) **>70kg**: initially 40mg/day minimum of 7 days titrated according to response and tolerability. Recommended maintenance dose is 80mg. Max dose 100mg **Unlicensed max**: 120mg. Once a day in the morning or 2 evenly divided doses (morning & late afternoon/ early evening) if not tolerated/inadequate response
Dose in adults	30mg once daily in the morning. Titrate according to response/ tolerability. May be increased at weekly intervals by 20mg increments. **Max**: 70mg daily	40mg/day minimum of 7 days, then titrate as required. BNF- start at 0.5mg/Kg if <70kg Usual maintenance dose 80-100mg/day. **Unlicensed max** dose 120mg. Once a day in the morning or 2 evenly divided doses (morning & late afternoon/ early evening). if not tolerated/inadequate response
Pregnancy **Breast Feeding**	Manufacturer advises use only if potential benefit outweighs risk Manufacturer advises avoid – present in human breast milk	Manufacturer advises use only if potential benefit outweighs risk Avoid – present in milk in animal studies
Monitoring in adults by specialist	Pulse & BP before and after dose changes and then every 6 months; Weight every 6 months.	
Monitoring in children by specialist	Monitor BP/ HR Monitor Weight: every 3 months in children aged 10 years and under; at 3 months and 6 months in young people and children over 10 years and every 6 months thereafter Monitor Height every 6 months for children and adolescents and recorded on growth chart	
Other monitoring		Monitor for sexual dysfunction with and refer back to specialist if a problem.
Drug Interactions	MAOIs & Moclobemide, Tricyclic antidepressants, SSRIs, SNRIs, Lithium, Haloperidol, lHIV protease inhibitors, Opioids	CYP2D6 inhibitors eg Fluoxetine & Paroxetine Drugs that increase the QT interval.e.g. neuroleptics, class 1A & III antiarrythmics, moxifloxacin, erythromycin, methadone, mefloquine, tricyclic antidepressants, lithium Drugs that lower the seisure threshold.e.g. antidepressants, neurolepics, mefloquine bupropion or tramadol. Drugs that cause electrolyte imbalance MAOIs During treatment or within a minimum of 14 days of discontinuing those drugs, due to risk of hypertensive crisis.

	Lisdexamfetamine (continued)	Atomoxetine (continued)
Contraindications & warnings	Hypersensitivity to lisdexamfetamine or excipients • During treatment with non-selective, irreversible monoamine oxidase (MAO) inhibitors, or within a minimum of 14 days of discontinuing those drugs, due to risk of hypertensive crisis • Symptomatic cardiovascular disease including moderate to severe hypertension and advanced arteriosclerosis structural abnormalities • Hyperexcitability or agitated states • Hyeprthyroidism, thyrotoxicosis • Glaucoma As with other stimulants also be aware of: • Misuse, dependence or diversion and risk of drug tolerance • Cardiovascular events, cardiomyopathy • Psychosis • Exacerbation of polar disorder • Increased aggression and tics • Increased risk of seizures • Potential visual disturbance	Hypersensitivity to the active substance or to any of the excipients • Not in combination with monoamine oxidase inhibitors (MAOI). Atomoxetine should not be used within a minimum of 2 weeks after discontinuing therapy with MAOI. Treatment with MAOI should not be initiated within 2 weeks after discontinuing atomoxetine. • Narrow-angle glaucoma • Severe cardiovascular or cerebrovascular disorders **(**may include severe hypertension, heart failure, arterial occlusive disease, angina, haemodynamically significant congenital heart disease, cardiomyopathies, myocardial infarction, potentially life-threatening arrhythmias and channelopathies. Severe cerebrovascular disorders may include cerebral aneurysm or stroke. • Pheochromocytoma or a history of pheochromocytoma Also be aware of: Congenital or acquired long QT interval or family history Discontinue in patient with liver disease. Suicide related behaviour has been reported. Aggression, oppositional behaviour, anger and emotional lability are more common. Increased risk of seizures
Side effects (common or significant)	**CNS**- restlessness, irritability, tremor, dizziness, insomnia, headache. Seizures – if exacerbated in patient with epilepsy or new seizures medication should be discontinued immediately **GI** - dry mouth, anorexia, abdominal pain, nausea, vomiting, diarrhoea, weight loss. GI upsets are usually mild and transient. Can be alleviated by concomitant food intake. If it doesn't resolve discontinue medication and consult specialist. **CVS** - tachycardia, palpitations, and increased blood pressure BP >95th centile on 2 occasions or significant increase should prompt dose reduction and referral to specialist. **Psychiatric disorders**: Aggression, anxiety emotional lability, psychosis, euphoria. Refer to Specialist for advice. **Motor and verbal tics**: associated with exacerbation or onset. If these persist beyond a few days specialist advise should be sort re dose reduction or discontinuation **Others**: dyspnoea, rash, fever.	**CNS** – headache, somnolence, dizziness, insomnia. Usually transient. **GI** - abdominal pain, nausea, vomiting, constipation, dyspepsia, dry mouth, weight loss- usually transient. Minor side effects may be reduced by dividing the daily dose into two 12 hour intervals. **CVS**- increased BP and pulse rates, QT prolongation, orthostatic hypotension BP >95th centile on 2 occasions or significant increase should prompt dose reduction and referral to specialist. **Skin** – rash, dermatitis **Psychiatric disorders:** Refer to Specialist for advice Rare - psychotic or manic symptoms, Suicide-related behaviour (suicide attempts and suicidal ideation) has been reported in patients treated with atomoxetine, monitor patients for appearance or worsening of suicide related behaviours. Common- Hostility, mood swings, irritability - particularly during initial months or after a dose change **Motor and verbal tics**: associated with exacerbation or onset. If these persist beyond a few days specialist advise should be sort re dose reduction or discontinuation **Liver toxicity**: very rare. **Other**- decreased appetite, fatigue, lethargy, dysmenorrhoea, urinary retention, sexual dysfunction.

Directions for Administration

	Methylphenidate	Methylphenidate modified release		
Brand name	Prescribe generically (brands include Ritalin, Medikinet)	**Xaggitin XL** (Previously Xenidate XLXL and Concerta XL were the preferred brands)	**Equasym XL**	**Medikinet XL**
	Swallow whole or disperse in water and give immediately	Swallow whole	Swallow whole or the contents of the capsule can be sprinkled on a tablespoon of apple sauce and swallowed immediately without chewing.	Swallow whole or the contents of the capsule can be sprinkled on a tablespoon of apple sauce or yogurt and swallowed immediately without chewing

	Lisdexamfetamine	Atomoxetine
Brand name	Elvanse	Strattera
	Swallow whole or mix the contents of the capsule with soft food such a as yogurt or in a glass of water or orange juice. The contents should be dispersed completely and given immediately.	Swallow capsules whole. Liquid preparation is available

Stimulant dose equivalents (mg)

IR-MPH	Xaggitin XL	Equasym XL	Medikinet XL
10	-	10	10
15	18	-	15
20	27	20	20
30	36	30	30
-	-	-	
45	54	-	45
60	72*	60	60

IR-MPH: immediate-release methylphenidate; Xaggitin XL, Equasym XL and Medikinet XL brands of modified-release methylphenidate
(Xaggitin XL & Xenidate XL) are bioequivalent to Concerta XL) * Licensed up to 54 mg (in children

The drug information in this document should be used in conjunction with the appropriate SPC.

Further Information

NICE Clinical Guideline NG 87 Attention Deficit Hyperactivity Disorder – Diagnosis and Management for ADHD in Children, Young People and Adults. March 2018 https://www.nice.org.uk/guidance/ng87
SPC for each drug www.emc.medicnes.org.uk
BNF for children

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