Powys Shared Care Agreement: December 2014

ATOMOXETINE

for the treatment of Attention Deficit/Hyperactivity Disorder (ADHD) in children, adolescents and adults

	✶PLEASE CHECK (POWYS FORMULARY WEBSITE ADDRESS) FOR THE LATEST VERSION OF THIS PROTOCOL✶
General guidance	This agreement outlines shared care arrangements for patients taking atomoxetine for the treatment of Attention Deficit / Hyperactivity Disorder (ADHD). This Protocol should be read in conjunction with: ➢ The *Shared Care Agreement Form* (*see below*). ➢ The Summary of Product Characteristics (Data Sheet) for Strattera®: http://www.medicines.org.uk/ ➢ NICE CG72 (September 2008, last modified March 2013 http://www.nice.org.uk/Guidance/CG72). *Attention deficit hyperactivity disorder: Diagnosis and management of ADHD in children, young people and adults.* **Note**: NICE CG72 incorporates recommendations from NICE TA98 and TA102.
1. Licensed indication	Atomoxetine is indicated for the treatment of ADHD in **children of 6 years and older**, in **adolescents** and in **adults** as part of a comprehensive treatment programme. Treatment must be initiated by a specialist in the treatment of ADHD such as a paediatrician, child/ adolescent psychiatrist or psychiatrist. Diagnosis should be made according to the current DSM criteria or the guidelines in ICD. **In adults**, the presence of **symptoms of ADHD that were pre-existing in childhood should be confirmed.** Third-party corroboration is desirable and atomoxetine should not be initiated when the verification of childhood ADHD symptoms is uncertain. Diagnosis cannot be made solely on the presence of one or more symptoms of ADHD. Based on clinical judgement, patients should have ADHD of at least moderate severity, as indicated by at least moderate functional impairment in 2 or more settings (e.g. social, academic and / or occupational functioning), affecting several aspects of an individual's life. **Additional information for the safe use of this product:** A comprehensive treatment programme typically includes psychological, educational and social measures and is aimed at stabilising patients 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. Pharmacological treatment is not indicated in all patients with this syndrome and the decision to use the drug must be based on a very thorough assessment of the severity of the patient's symptoms and impairment in relation to the patient's age and the persistence of symptoms.
2. Background information	Atomoxetine's precise mechanism of action in the treatment of ADHD is not clear but it is thought that it works by selectively inhibiting the pre-synaptic noradrenaline transporter, thus inhibiting noradrenaline reuptake. While both atomoxetine and stimulants increase intrasynaptic concentrations of dopamine and noradrenaline in the cortex, it is thought that atomoxetine differs from a stimulant in having less effect on subcortical brain regions associated with motivation and reward. As atomoxetine is neither a stimulant medication nor a controlled drug it has less potential for misuse and therefore does not require the same strict prescribing and storage conditions as methylphenidate, dexamfetamine and lisdexamfetamine. It is also not thought to carry the potential for inducing dependence or causing euphoria. **NICE CG72** states that: • *When a decision has been made to treat **children** or **young people** with ADHD with drugs, healthcare professionals should consider:*

	○ *Methylphenidate for ADHD without significant comorbidity* ○ *Methylphenidate for ADHD with comorbid conduct disorder* ○ *Methylphenidate or **atomoxetine** when tics, Tourette's syndrome, anxiety disorder, stimulant misuse or risk if stimulant diversion are present* ○ ***Atomoxetine** if methylphenidate has been tried and has been ineffective at the maximum tolerated dose, or the child or young person is intolerant to low or moderate doses of methylphenidate* *Following a decision to start treatment in **adults** with ADHD, methylphenidate should normally be tried first* (UNLICENSED use). *Atomoxetine (dexamfetamine or lisdexamfetamine) should be considered in adults unresponsive or intolerant to an adequate trial of methylphenidate (this should usually be about 6 weeks).*
3. Contraindication & Cautions	Atomoxetine is contraindicated in: • Known sensitivity to atomoxetine or to any of the excipients. • Narrow angle glaucoma (an increase in mydriasis was seem in clinical trials). • In combination with MAOI. Atomoxetine should not be initiated within 2 weeks of discontinuing an MAOI. An MAOI should not be initiated within 2 weeks of discontinuing atomoxetine. • Diagnosis or history of phaeochromocytoma. • Diagnosis or history of: ○ Severe cardiovascular disorders (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) *OR* ○ Severe cerebrovascular disorders (cerebral aneurysm or stroke) <u>Cautions:</u> Suicide-related behaviour: more frequently observed amongst children and adolescents treated, with careful monitoring required for appearance or worsening of suicide related behaviour (*see section 8*). Sudden death and pre-existing cardiac abnormalities: atomoxetine should only be used with caution in patients with known serious structural cardiac abnormalities and in consultation with a cardiac specialist. Cardiovascular effects: most patients taking atomoxetine experience a modest increase in heart rate (mean <10 beats per minute) and / or increase in blood pressure (mean <5mmHg) (*see section 6)*. Atomoxetine should be used with caution in patients with congenital or acquired long QT or a family history of QT prolongation *(see section 5).* Hepatic effects*:* cases of spontaneous liver injury (including acute liver failure) have rarely been reported with atomoxetine *(see section 6).* Seizures: use atomoxetine with caution in patients with a history of seizure. Discontinuation of atomoxetine should be considered in any patient developing a seizure or experiencing an unexplained increase in seizure frequency. Growth and development: should be monitored in children and adolescents during treatment with atomoxetine *(see section 8).* **Depression, anxiety, tics and psychotic or manic symptoms**: have been rarely reported with atomoxetine *(see section 8).*
4. Dosage regimen	**ADULT** over 18 years and body-weight >70kg. Initially 40mg daily for 7 days, increased according to response. The usual maintenance dose is 80mg to 100mg daily. This may be increased to a maximum and unlicensed dose of 120mg daily, under the direction of the specialist. **CHILD** aged 6 to 18 years and body-weight >70kg. Initially 40mg daily for 7 days, increased according to response. The usual maintenance dose is 80mg daily. This may be increased to a

maximum and unlicensed dose of 120mg daily, under the direction of the specialist.

ADULT AND CHILD over 6 years and body-weight ≤70kg. Initially 500microg/kg daily for 7 days, increased according to response. The usual maintenance dose is 1.2mg/kg daily. This may be increased to a maximum and unlicensed dose of 1.8mg/kg daily (maximum 120mg daily), under the direction of the specialist.

In **moderate hepatic insufficiency** (Child-Pugh class B), reduce both initial and target doses to 50% of the usual dose.

In **severe hepatic deficiency** (Child-Pugh class C), reduce both initial and target doses to 25% of the usual dose.

Note the total daily dose may be given *either* as a single morning dose or in 2 divided doses with the last dose no later than early evening.

In adults with ADHD a trial of 6 weeks on a maintenance dose should be allowed to evaluate the full effectiveness of atomoxetine.

5. Drug Interactions

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

Drug / Class	Interaction
Amiodarone	Increased risk of ventricular arrhythmias. ***Note:*** amiodarone has a long half life. There is a potential for drug interactions to occur for several weeks (or even months) after treatment has been stopped.
Antidepressants	Possible increased risk of convulsions.
Antidepressants, tricyclic	Increased risk of ventricular arrhythmias.
Anti-psychotics	**Increased risk of ventricular arrhythmias when atomoxetine is given with antipsychotics which *prolong the QT interval.***
Bupropion (Zyban®)	Possible increased risk of convulsions.
Disopyramide	Increased risk of ventricular arrhythmias.
Diuretics	Risk of ventricular arrhythmias with atomoxetine increased by hypokalaemia caused by diuretics.
Erythromycin	Increased risk of ventricular arrhythmias when atomoxetine is given with *parenteral* erythromycin. ***Note***: interactions do not apply to small amounts of erythromycin used topically.
Fluoxetine	Metabolism of atomoxetine possibly inhibited by fluoxetine.
Monoamine Oxidase Inhibitors (MAOI)	In combination with MAOI. Atomoxetine should not be initiated within 2 weeks of discontinuing an MAOI. An MAOI should not be initiated within 2 weeks of discontinuing atomoxetine. ***Note***: moclobemide is a reversible MAO-An inhibitor and rasagiline and selegeline are MAO-B inhibitors; the antibacterial linezolid is a reversible, non-selective MAO inhibitor.
Mefloquine	Increased risk of ventricular arrhythmias.
Methadone	Increased risk of ventricular arrhythmias.
Moxifloxacin	Increased risk of ventricular arrhythmias.
Paroxetine	Metabolism of atomoxetine possibly inhibited by paroxetine.
Salbutamol	Increased risk of cardiovascular side effects with *parenteral* salbutamol.
Sotalol	Increased risk of ventricular arrhythmias.
Tramadol	Possible increased risk of convulsions.

Note: atomoxetine is metabolised by the CYP2D6 pathway, therefore strong/ moderate inhibitors of CYP2D6 such as SSRIs, bupropion, quinidine, cincalcet, duloxetine, ritonavir and terbinafine may lead to 3 or 4 times higher levels of atomoxetine ($C_{SS\ max}$) when co-prescribed.

6. Adverse drug reactions

All serious adverse

Common adverse effects associated with atomoxetine include abdominal pain, nausea and vomiting, decreased appetite with associated weight loss, dizziness and slight increases in heart rate and blood pressure. These effects are normally transient and may not require

<table>
<tr><td>events should be reported to MHRA/CHM using the Yellow Card.</td><td>discontinuation of treatment.
Very rarely liver toxicity (manifested by elevated hepatic enzymes and bilirubin with jaundice) have been reported.
Sexual dysfunction (erectile and ejaculatory dysfunction) and dysmenorrhoea should be monitored as potential side effects of atomoxetine (NICE CG72).
Seizures are a potential risk for atomoxetine.
Suicide-related behaviours (suicidal ideation and suicide attempts) have been reported in patients treated with atomoxetine.

<table>
<tr><th>Adverse event</th><th>Approximate frequency</th><th>Management</th></tr>
<tr><td>Palpitations, sustained resting tachycardia, arrhythmia or systolic blood pressure > 95th percentile (or a clinically significant increase) measured on 2 occasions</td><td>8-12% of children and adolescents
6-10% of adults
Experience more pronounced changes in heart rate (≥ 20 beats per minute) and blood pressure (≥15 to 20mmHg)</td><td>Stop drug and discuss</td></tr>
<tr><td>Abnormal liver function tests (LFT) or jaundice</td><td>Rare≥ 1/10,000 to < 1/ 1,000</td><td>Stop drug and discuss</td></tr>
<tr><td>Agitation, anxiety, suicidal thinking, self-harming behaviour or unusual changes in behaviour</td><td>Uncommon ≥ 1/ 1,000 to < 1/ 100
(Psychosis rare in adults)</td><td>Stop drug and discuss</td></tr>
</table>
</td></tr>
<tr><td>7. Baseline investigations</td><td>To be undertaken by a 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.
i) Physical examination for the presence of heart disease (including BP and pulse). The use of atomoxetine is contraindicated in certain pre-existing cardiovascular disorders (see section 3) unless specialist cardiac advice has been obtained.
ii) Assessment for co-existence of psychiatric and depressive disorders, as well as anxiety, agitation or tension, should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression.
iii) Assessment of hepatic function (liver function tests / LFT).</td></tr>
<tr><td>8. Ongoing monitoring
(see NICE CG72)</td><td>To be undertaken in Secondary care
i) Height should be measured (with maintenance of a growth chart) every 6 months in children and young people.
ii) Weight should be measured 3 and 6 months after drug treatment ahs started and every 6 months thereafter in children, young people and adults. Appetite should be questioned in cases of weight loss.
iii) Blood pressure and pulse (recorded on a centile chart in children) – at each dose adjustment and then at least every 6 months. Patients with additional risk factors for cerebrovascular disease (such as a history of cardiovascular disease or those on drugs that elevate blood pressure) should be assessed at every visit for neurological signs and symptoms.
iv) Emergence or worsening of agitation, anxiety, suicidal thinking, self-harming or other unusual behaviour – at least every 6 months.
Liver damage is a rare and idiosyncratic adverse effect of atomoxetine and routine liver function tests are not recommended.</td></tr>
<tr><td>9. Pharmaceutical particulars</td><td>The capsules are not intended to be opened.
Atomoxetine is an ocular irritant. In the unlikely event that the capsule contents come into contact with the eyes then the eyes should be flushed immediately with water.</td></tr>
<tr><td>10. Specialist contact details</td><td>Advice can be obtained from the local Child Psychiatry and Community Paediatric Services 9 to 5pm Monday to Friday</td></tr>
</table>

	Child psychiatry: 01874 715662 / 01686 617450 — **Community Paediatrics:** 01874 615684 / 01686 617455
11. Criteria for shared care	Prescribing responsibility will only be transferred when: ➢ Treatment is for a specified indication. ➢ Treatment has been initiated and established by the Specialist Centre. ➢ The patient's initial reaction to and progress on the drug is satisfactory. ➢ The patient's general physical, mental and social circumstances are such that he/she would benefit from shared care arrangements.
12. Responsibilities of Specialists (Secondary Care)	➢ **Complete full assessment**: diagnose and assess eligibility for drug therapy (NICECG72) as part of a treatment programme that includes psychological, behavioural and educational advice and interventions. ➢ **Confirm patient/carer understanding and consent** to treatment. ➢ **Undertake the baseline clinical valuations** (as detailed in *Section 7*). ➢ **Provide patient/carer with relevant information** on use, and the need for monitoring of medication. Obtain consent for any unlicensed use. Consider offering carers of children under 18 years of age the option of support from the 'Strattera® support service'. ➢ **Advise on side effects** and the action to be taken should they occur and discuss these with the child, adolescent or adult and where necessary their family or carers. Pay particular attention to the potential of atomoxetine to increase agitation, anxiety, suicidal thinking and self-harming behaviour in some people, especially during the first few weeks of treatment. They should also be warned about the potential for liver damage in rare cases with atomoxetine (usually presenting as abdominal pain, unexplained nausea, malaise, darkening of the urine or jaundice). ➢ **Whenever practical** ask the patient / parent or carer about any adverse reactions, particularly in relation to the development or worsening of agitation, anxiety, suicidal thinking, self-harming behaviour and unusual changes in behaviour, as well as any abdominal pain, unexplained nausea, malaise, darkening of the urine or jaundice (*see Section 6).* ➢ **Confirm** patient, parent or carers understanding or consent to treatment. ➢ **Initiate treatment** and increase the dose (according to response) up to the usual maintenance dose and to prescribe a trial of 12 weeks on a maintenance dose to fully evaluate the effectiveness of atomoxetine. ➢ **Communicate with the GP and request shared care** (once atomoxetine has been evaluated as effective and well tolerated), advising if the prescribing request is outside of license. ➢ **Monitor** the patient in accordance with the on-going monitoring schedule (*Section 8).* ➢ **After each appointment** inform the GP of dosage schedule, monitoring measurements and progress of treatment. ➢ **Clinically review** the treatment at least annually, sending a written summary and updated treatment plan to the GP. ➢ **Inform the GP if the patient fails to attend** clearly indicating that the patient is taking atomoxetine. ➢ **Provide any other advice** or information for the GP if required including rapid referral arrangements and contacts. ➢ **Consider a trial of withdrawal of medication when the condition is stable. This should be performed at least once a year, under careful supervision.** For children this should preferably be done during school summer holidays. ➢ **Ensure that monitoring responsibility is transferred** from child to adult services once the patient reaches 18 years of age.
13. Responsibilities of patients/carers	➢ **Attend hospital and GP clinic appointments. Failure to attend will result in the medication being stopped (on specialist advice).** ➢ Report any adverse events immediately to their specialist or GP (particularly development or worsening of agitation, anxiety suicidal thinking or self-harming behaviour or any abdominal

	pain, unexplained nausea, malaise, darkening of the urine or jaundice).
14. Responsibilities of Primary Care	➢ **Return the *Shared Care Agreement Form*** (*below*) to the requesting specialist within 14 days of receipt. ➢ **Issue ongoing prescriptions** for atomoxetine as per dose recommended by the specialist. ➢ **Check for drug interactions** in BNF Appendix 1 before co-prescribing any other drugs and to particularly avoid co-prescribing other drugs that produce QT prolongation, drugs that can cause electrolyte disturbances and those that inhibit CYP2D6 e.g. SSRI, bupropion, duloxetine and terbinafine. ➢ **Contact the patient / parent or carer** if they fail to attend appointments with the specialist and if necessary refuse to issue further prescriptions until specialist supervision has occurred. ➢ **Whenever practical** ask the patient / parent or carer about any adverse reactions, particularly in relation to the development or worsening of agitation, anxiety, suicidal thinking, self-harming behaviour and unusual changes in behaviour, as well as any abdominal pain, unexplained nausea, malaise, darkening of the urine or jaundice (*see Section 6).*
15. Responsibilities of all prescribers	➢ **Any suspected serious adverse reaction to an established drug should be reported to MHRA via the "yellow card scheme." http://yellowcard.mhra.gov.uk/**
16. Supporting documentation / information	***BNF*** Section 4.4 CNS stimulants and drugs used for ADHD. **Patient information leaflet** for Strattera® http://www.medicines.org.uk/emc/PIL.14549.latest.pdf **MHRA's Advice** May 2012 – effect on heart rate and blood pressure http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/CON152776 January 2012 – increases in blood pressure and heart rate – new contraindications, warnings and advice for monitoring http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON140666 March 2009 – risk of psychotic or manic symptoms http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON088115 February 2005 – risk of liver problems http://www.mhra.gov.uk/home/groups/pl-p/documents/websiteresources/con019460.pdf **FDA Drug Safety Communication**: Safety Review Update of Medications used to treat Attention-Deficit/Hyperactivity Disorder (ADHD) in **children** and **young adults** (November 2011): http://www.fda.gov/Drugs/DrugSafety/ucm277770.htm the medications studied included stimulants (amfetamine products and methylphenidate) and atomoxetine. *"A large retrospective cohort study in children and young adults (aged 2-24 years) did not show an association between use of ADHD drugs and cardiovascular events, which include MI, stroke or sudden cardiac death. These study results were not consistent with the increase in sudden death estimated in a previous study, however a small to modest increase in risk cannot be excluded."* Safety Review Update of Medications used to treat Attention-Deficit/Hyperactivity Disorder (ADHD) in **adults** (December 2011): http://www.fda.gov/Drugs/DrugSafety/ucm279858.htm

CONSULTANT REQUEST

To: Dr.

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

This drug has been accepted as suitable for shared care by the *xxxxx*. I agree to the responsibilities set out in the protocol SCP No. xx (*copy attached*). This should be read in conjunction with the definition of shared care at: http://www.wales.nhs.uk/sites3/Documents/371/Doc%202%20Defining%20shared%20care.pdf

I am requesting your agreement to sharing the care of this patient. The preliminary tests set out in the agreement 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 are available to give you advice between 9 – 5pm, Monday to Friday.

Consultant Name:	**Signature:**
Department:	
Hospital:	**Date:**
Contact Telephone Numbers:	

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

1. I am willing to undertake shared care as set out in latest Powys Atomoxetine SCA 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 reason*)

_____

G.P. Signature _____ Date _____

Practice Address/Stamp _____

PLEASE RETURN WHOLE COMPLETED FORM OR A COPY TO THE REQUESTING CONSULTANT WITHIN 14 days.

Thank you.