Aripiprazole oral *(Abilify®)* (Amber)

for the treatment of schizophrenia/treatment and recurrence prevention of mania

AREAS OF RESPONSIBILITY FOR THE SHARING OF CARE

This shared care agreement outlines how responsibility for prescribing aripiprazole for schizophrenia or treatment and recurrence prevention of mania might be shared between specialist and general practitioner (GP). GPs are invited to participate. If the GP is not confident to undertake these roles, then he or she is under no obligation to do so. In such an event, the total clinical responsibility for the patient for the diagnosed condition remains with the specialist. If a specialist asks the GP to prescribe this drug, the GP should reply to this request as soon as practicable.

Sharing of care assumes communication between the specialist, GP and patient. The intention to share care is usually explained to the patient by the doctor initiating treatment. It is important that patients are consulted about treatment and are in agreement with it. This shared care is intended to apply to those patients who have been initiated on treatment (and assessed as benefiting) by a specialist in the care of patients with schizophrenia/mania in accordance with NICE CG 178 / CG 185

The doctor who prescribes this medication legally assumes clinical responsibility for aripiprazole and the consequences of its use.

RESPONSIBILITIES and ROLES (insert as much additional text as appropriate)

	Specialist responsibilities
1	Initiate treatment and prescribe the first 3 months of treatment of aripiprazole.
2	Discuss the benefits and side effects of treatment with the patient.
3	Ask the GP whether he or she is willing to participate in shared care, and discuss the shared care arrangement with the patient & obtain their consent.
4	Supply GP with summary within 14 days of a hospital out-patient review or in-patient stay.
5	Review the patient's condition and monitor response to treatment regularly where indicated.
6	Give advice to the GP on when to stop / adjust treatment.
7	Report adverse events to the MHRA & GP http://yellowcard.mhra.gov.uk/
8	Ensure that clear backup arrangements exist for GPs to obtain advice and support.
9	Assess patient, establish diagnosis and develop care plan. Ensure care plan contains correct contact details for care co-ordinator/ key worker and specialist consultant psychiatrist. Forward a copy of the care plan to the GP.
10	To undertake physical health screen and assessment when patient is admitted to mental health services, including screening for possible risk factors for venous thromboembolism (VTE) before and during treatment with aripiprazole and preventive measures undertaken. Please see NICE CG92 for guidance on venous thromboembolism.
11	The choice and formulation of the antipsychotic should be a joint decision between the patient (discuss with carer where patients lack capacity) and the specialist taking into consideration the risks and benefits of the treatment (including the relative potential of individual antipsychotics to cause side-effects such as extrapyramidal side effects (EPSEs) and metabolic side-effects, including weight gain) including the action to be taken should side effects occur.
12	To provide the patient with verbal and written information on drug prescribed including a patient information leaflet (PIL). Information on mental health conditions, treatments and medication can be found at: http://www.choiceandmedication.org/awp/
13	Confirm the patients understanding and consent to treatment (discuss with carer where patient lacks capacity).
14	Ensure patient is fully informed about their treatment including any plans of pregnancy. Aripiprazole should only be given to pregnant women when, in the judgement of the attending physician the potential benefits outweigh the possible risk.
15	Provide counselling to patient and carer about implications of diagnosis; include written information about signs and symptoms, course, prognosis and treatments, local care and support groups, financial and legal advice.
16	Ensure that arrangements of appropriate blood tests has been made. Blood tests may be taken at the GP surgery providing appropriate communication with the GP and the GP is in agreement with this. Secondary care is responsible for the interpretation and monitoring of these blood test results for the first 3 months of treatment.
17	Review results of any baseline tests and relay any abnormal findings to the GP with appropriate advice.
18	Communicate promptly with the GP when treatment is changed.
19	Inform GP of concurrent therapy (as this may interact with other medication patient gets from GP; purchases OTC or on-line.
20	To review patient / provide advice as requested via the GP or Primary Care Liaison Service as necessary.
21	To review the patient and treatment at least once a year until the patient is discharged from the mental health service where this is possible
22	Any verbal communication between primary and secondary care should be confirmed in writing.

General Practitioner responsibilities	
1	Reply to the request for shared care as soon as practicable (preferably within 3 weeks of receipt of request) using the shared care agreement signature sheet for aripiprazole to participate in shared care.
2	Prescribe aripiprazole at the dose recommended after 3 months for those patients who have been assessed as benefiting from treatment.
3	Ensure compatibility with other concomitant medication.
4	Refer promptly to specialist when any loss of clinical efficacy is suspected (e.g. worsening of disease-related symptoms, new symptoms suggestive of disease recurrence or progression) or intolerance to therapy occurs.
5	Report to and seek advice from the specialist on any aspect of patient care that is of concern to the GP and may affect treatment.
6	Stop treatment on the advice of the specialist.
7	Report adverse events to the specialist and MHRA. http://yellowcard.mhra.gov.uk/
8	If the GP decides not to prescribe aripiprazole, it should still be added to the patients repeat medication as a "non issued' item for information and safety purposes. For EMIS systems: The quantity should be set to *0 or 1. On the dose line it should read: 'Hospital prescribing only. Do not prescribe'.This process should also be done during the stabilisation period before the GP takes over the prescribing.
9	Adjust the dose / stop drug as advised by the specialist.
10	Inform specialist team of any change in the patient's medication that may interact with medication patient receives from secondary care.
11	To request specialist review or seek specialist advice when necessary.
12	Once the patient has been discharged from specialist Mental Health services, advice may be sought from the Primary Care Liaison Service on any aspect of the patient's mental health that is of concern to the GP.
13	Monitor patients overall health and compliance with medication and ask about side effects.
14	Any verbal communication between primary care and the specialist team should be confirmed in writing.

Patient's / carers role	
1	Attend all appointments with GP and specialist.
2	Report to the specialist or GP if he or she does not have a clear understanding of the treatment.
3	Share any concerns in relation to treatment with medicine.
4	Inform specialist or GP of any other medication being taken, including over-the-counter products or those purchased on-line.
5	Report any adverse effects or warning symptoms (e.g. deterioration in mental state) to the specialist or GP whilst taking the medicine (and for up to 2 months after it has been stopped).

Primary Care Liaison Service responsibilities	
1.	Accept referrals by registered GPs in line with DoH guidance
2.	To advise GP on appropriate action regarding any issues they may have on patient's management regarding shared care.
3.	To try and resolve the issue(s) raised by the GP or to refer to the specialist team as appropriate.
4.	Rapid and prioritised specialised mental health assessment with recommendation/s for care and treatment within multiple care pathways.
5.	Determination of the nature and severity of mental health needs with consequent sign posting and pathway facilitation.
6.	Provide rapid and accessible on-going support & advice to the non-specialist workforce.

BACK-UP ADVICE AND SUPPORT

Contact details	Telephone No.	Fax:	Email address:
Specialist:			
AWP Team			
Primary Care Liaison Service, Sandalwood court, Swindon. 8am – 8pm then intensive service.	01793 835 787	01793 836 817	

SUPPORTING INFORMATION

Summary of condition

Psychosis and the specific diagnosis of schizophrenia represent a major psychiatric disorder (or cluster of disorders) in which a person's perception, thoughts, mood and behaviour are significantly altered. The symptoms of psychosis and schizophrenia are usually divided into 'positive symptoms', including hallucinations (perception in the absence of any stimulus) and delusions (fixed or falsely held beliefs), and 'negative symptoms' (such as emotional apathy, lack of drive, poverty of speech, social withdrawal and self-neglect). Each person will have a unique combination of symptoms and experiences. Over a lifetime, about 1% of the population will develop psychosis and schizophrenia. The first symptoms tend to start in young adulthood, at a time when a person would usually make the transition to independent living, but can occur at any age.

Licensed indications

Aripiprazole is indicated for:

1. the treatment of schizophrenia in adults and in adolescents aged 15 years and older.
2. the treatment of moderate to severe manic episodes in Bipolar I Disorder and for the prevention of a new manic episode in adults who experienced predominantly manic episodes and whose manic episodes responded to aripiprazole treatment.
3. the treatment up to 12 weeks of moderate to severe manic episodes in Bipolar I Disorder in adolescents aged 13 years and older.

Expected / established place in local treatment pathway

Where there are metabolic issues which are either current or caused by previous antipsychotic therapy (e.g. weigh gain, glucose/lipid disturbance, ECG abnormalities etc). Aripiprazole is expected to be available as generic in ~ May 2015 making it a more cost effective treatment option.

Dosage and administration

Usual range is 10mg to 30mg once daily depending on age and indication.

Adults

Schizophrenia: Starting dose 10 or 15 mg / day. Usual maintenance dose 15 mg / day.
Maximum daily dose should not exceed 30mg daily.

Manic episodes in Bipolar I Disorder: 15 mg / day as monotherapy or combination therapy. Some patients may benefit from a higher dose. Maximum daily dose should not exceed 30 mg daily.

Recurrence prevention of manic episodes in Bipolar I Disorder: for preventing recurrence of manic episodes in patients who have been receiving aripiprazole as monotherapy or combination therapy, continue therapy at the same dose. Adjustments of daily dosage, including dose reduction should be considered on the basis of clinical status.

Contraindications: Hypersensitivity to the active substance or to any of the excipients.

Precautions for use:

Suicidality

The occurrence of suicidal behaviour is inherent in psychotic illnesses and mood disorders and in some cases has been reported early after initiation or switch of antipsychotic therapy, including treatment with aripiprazole. Close supervision of high-risk patients should accompany antipsychotic therapy. Results of an epidemiological study suggested that there was no increased risk of suicidality with aripiprazole compared to other antipsychotics among adult patients with schizophrenia or bipolar disorder.

Cardiovascular disorders

Aripiprazole should be used with caution in patients with known cardiovascular disease (history of myocardial infarction or ischaemic heart disease, heart failure, or conduction abnormalities), cerebrovascular disease, conditions which would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medicinal products) or hypertension, including accelerated or malignant.

Venous thromboembolism

Cases of venous thromboembolism (VTE) have been reported with antipsychotic drugs. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with aripiprazole and preventive measures undertaken.

Conduction abnormalities
In clinical trials of aripiprazole, the incidence of QT prolongation was comparable to placebo. As with other antipsychotics, aripiprazole should be used with caution in patients with a family history of QT prolongation.

Tardive dyskinesia
In clinical trials of one year or less duration, there were uncommon reports of treatment emergent dyskinesia during treatment with aripiprazole. If signs and symptoms of tardive dyskinesia appear in a patient on aripiprazole, dose reduction or discontinuation should be considered. These symptoms can temporally deteriorate or can even arise after discontinuation of treatment.

Extrapyramidal symptoms
If signs and symptoms of EPSEs appear, dose reduction and close clinical monitoring should be considered.

Neuroleptic Malignant Syndrome (NMS)
NMS has been associated with antipsychotic treatment. In clinical trials, rare cases of NMS were reported during treatment with aripiprazole. Clinical manifestations include hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac dysrhythmia. Additionally, elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. If a patient develops signs and symptoms indicative of NMS, or has unexplained high fever, all antipsychotic medication including aripiprazole, must be discontinued.

Seizure
In clinical trials, uncommon cases of seizure were reported during treatment with aripiprazole. Therefore, aripiprazole should be used with caution in patients who have a history of seizure disorder or have conditions associated with seizures.

Hyperglycaemia
Hyperglycaemia and diabetes mellitus: Hyperglycaemia has been reported during treatment with aripiprazole. Patients with diabetes mellitus or with risk factors for diabetes mellitus (e.g. obesity or family history of diabetes) should be monitored regularly for signs and symptoms (e.g. polydipsia, polyuria, polyphagia and weakness) for hyperglycaemia or worsening of glucose control.

Weight gain
Weight gain has been reported post-marketing among patients prescribed aripiprazole; usually in those with significant risk factors such as history of diabetes, thyroid disorder or pituitary adenoma. In clinical trials aripiprazole has not been shown to induce clinically relevant weight gain in adults. In clinical trials of adolescent patients with bipolar mania, aripiprazole has been shown to be associated with weight gain after 4 weeks of treatment. Weight gain should be monitored in adolescent patients with bipolar mania. If weight gain is clinically significant, dose reduction should be considered

Effects on ability to drive and use machines

As with other antipsychotics, patients should be cautioned about operating hazardous machines, including motor vehicles, until they are reasonably certain that aripiprazole does not affect them adversely. (Some paediatric patients with Bipolar I Disorder have an increased incidence of somnolence and fatigue).

Side-effects

Common (1/100 to < 1/10):
Akathisia and nausea are the most commonly reported side effects for aripiprazole.

Psychiatric disorders:
Common: restlessness, insomnia, anxiety

Nervous system disorders
Common: extrapyramidal disorder, akathisia, tremor, dizziness, somnolence, sedation, headache

Eye disorders
Common: Blurred vision

Gastrointestinal disorders
Common: Dyspepsia, vomiting, nausea, constipation, salivary hypersecretion

General

Common: Fatigue

Please note that the following convention has been used for the classification of side-effects: very common (≥ 1/10), common (≥ 1/100 to <1/10), uncommon (≥ 1/1,000 to <1/100), rare (≥ 1/10,000 to <1/1000) and very rare (<1/10,000).

Refer patient back to the specialist if any of these side-effects cause concern. Refer to the SPC for a full list of adverse effects & further information http://www.medicines.org.uk.

This medicine does not have black triangle (▼) status. Serious suspected reactions (even if well recognised or causal link uncertain) should be reported to the MHRA.

Monitoring

Baseline monitoring by AWP Specialist team:

1. Weight & BMI/Waist circumference if possible.
2. Blood pressure & pulse
3. ECG,
4. Creatinine Phosphokinase,
5. Fasting blood lipids
6. Glycosylated haemoglobin (HbA1c)
7. Fasting blood glucose,
8. Prolactin,
9. LFTs, U&Es & FBC,
10. Ask service user about adverse drug reactions; smoking status; alcohol and illicit drug use.
11. *Venous thromboembolism (VTE) risk assessment including e.g. reduced mobility. Refer to NICE CG92 for guidance on venous thromboembolism.

*MHRA - VTE risk associated with antipsychotics: Antipsychotic use may be associated with an increased risk of VTE. At present there are insufficient data available to determine any difference in risk between atypical and conventional antipsychotics, or between individual drugs. All possible risk factors for VTE should be identified before and during antipsychotic treatment and preventative measures taken.

Subsequent tests

There are no mandatory monitoring requirements for aripiprazole but it is recommended monitoring is done nonetheless as prevalence of metabolic disorders is high in this group of patients.

At 3 months by AWP Specialist:

1. Weight & BMI/Waist circumference if possible
2. Blood lipids
3. Glycosylated haemoglobin (HbA1c)
4. Fasting blood glucose

Annual review by Primary Care:

1. Weight & BMI/Waist circumference if possible
2. Creatinine phosphokinase (monitor for NMS)
3. Blood lipids
4. Glycosylated haemoglobin (HbA1c)
5. Fasting blood glucose
6. LFTs
7. FBC

If possible, assess patient for VTE risk and consider preventative measures.

The following should be monitored and recorded throughout treatment as per NICE CG 178

1. Response to treatment, including any changes in symptoms and behaviour
2. Side effects of treatment, taking into account overlap between certain side-effects and clinical features of schizophrenia (for example, the overlap between akathisia and agitation or anxiety) and impact on functioning.
3. Emergence of movement disorders
4. Adherence
5. Assessment of nutritional status, diet and level of physical activity
6. Ask about smoking status at each consultation

7. Ask about alcohol and illicit drug use
8. Overall physical health.
9. After withdrawal from antipsychotic medication, continue monitoring for signs and symptoms of relapse for at least 2 years.

Management of side effects and when to refer to AWP Specialist team

Side effect	Action
Raised prolactin: If symptoms arise e.g. ***in women***: amenorrhoea, menstrual disorders, galactorrhoea and reduced libido. ***in men:*** reduced libido, impotence & gynaecomastia. *The longer the patient is exposed to hyperprolactinaemia, the greater the risk of reduced bone density and hypogonadism**.***	Reduce dose or alternative oral antipsychotic may be necessary. **Refer to AWP specialist team for advice**. Treatment with calcium and vitamin D should be considered and started by the GP. ***Please refer to the flow chart for monitoring prolactin in those prescribed antipsychotics.***
Significant weight gain > 5% over baseline Antipsychotics are associated with weight gain especially in first 6 to 9 months of treatment. (average 2 to 10lb or ~0.9Kg to 4.5Kg).	Offer lifestyle advice - encourage healthy balanced diet and regular exercise. Recommend annual follow-up by GP. **Refer to AWP specialist team for advice if necessary**.
QTc interval After any dose increases or any concerns with cardiac function e.g. previous abnormality or additional risk factor. Routine QTc monitoring is advised for long term management. Non-psychotropic drugs associated with QT prolongation include: Erythromycin, clarithromycin, ampicillin, co-trimoxazole, some quinolones quinidine, amiodarone, sotalol, chloroquine, mefloquine, Quinine, methadone, tamoxifen, diphenhydramine, domperidone.	
<440 msec (men) or <470 msec (women)	None unless abnormal T wave morphology.
>440 msec (men) >470 msec (women) but <500 msec	Consider reducing dose; repeat ECG. Refer to cardiologist if necessary.
>500 msec	Stop suspected causative drug(s) and refer to cardiologist immediately.
Abnormal T wave morphology	Review treatment and refer to cardiologist immediately.
Raised blood glucose or HbA_{1C} from upper threshold May indicate IFG. Signs / symptoms of hyperglycaemia include polydipsia, polyuria, polyphagia and weakness, or worsening of glucose control.	Offer lifestyle advice. Obtain fasting sample (preferred) & HbA_{1C} **Refer to AWP specialist team for advice.**
Raised blood lipids	**Refer to AWP specialist team for advice.**
Tardive Dyskinesia A wide variety of movements can occur such as: lip smacking or chewing, tongue protrusion (fly catching), choreiform hand movements, pelvic thrusting. Can lead to difficulty speaking, eating or breathing. Can be worse under stress.	A reduction in dose, discontinuation or change to an alternative. e.g. atypical LAI or atypical oral if appropriate. **Refer to AWP specialist team for advice.**
Extrapyramidal side effects – pseudo parkinsonism e.g. tremor, rigidity, hypersalivation, bradykinesia, akathisia, acute dystonia.	An anticholinergic may be prescribed e.g. procyclidine 5mg tds prn but must be reviewed at least every 3 months (can cause euphoria). **Refer to AWP specialist for advice**
Development / suspected Venous thromboembolism especially for those at risk e.g. reduced mobility, post-surgery. Antipsychotic use may be associated with an	**Refer to AWP specialist team for advice.**

increased risk of venous thromboembolic events All possible risk factors for VTE should be identified before and during antipsychotic treatment and preventative measures taken. NICE CG92 & MHRA	
Suspected Neuroleptic Malignant Syndrome (NMS))presentation varies considerably) Signs and symptoms include: fever, diaphoresis (sweating), rigidity, confusion, fluctuating consciousness, fluctuating blood pressure, tachycardia, raised CPK, leucocytosis, & altered LFTs.	Discontinue antipsychotic. **Contact specialist immediately.** Call for ambulance. Repeat CPK.
Reduced Full Blood Count (FBC)	Stop suspect drug if neutrophils fall below 1.5 x 10^9/L. **Refer to AWP specialist team for advice**.
Reduced GFR	Consider reducing dose if GFR is reduced.
Raised LFTs	Stop drug if hepatitis suspected (transaminases x 3 upper limit of normal) or functional damage (PT/albumin change)
Somnolence / drowsiness	Advise patient not to drive or operate machinery. **Refer to specialist team for advice if necessary.**
Insomnia	**Refer to specialist team for advice if necessary.**
Constipation	Recommend a high fibre diet. Consider adding a bulk-forming and / or stimulant laxative.
Dry mouth	Suggest sugar-free gum or occasional boiled sweets or artificial saliva.
Hypotension / dizziness	Advise patient to take time when getting up.

Drug Interactions

Due to its α1-adrenergic receptor antagonism, aripiprazole has the potential to enhance the effect of some antihypertensive agents. Enhanced sedation likely when taken with other centrally acting drugs e.g. alcohol.

Potent inhibitors of CYP2D6 e.g. fluoxetine, paroxetine (and quinidine) may increase levels of aripiprazole so dose reductions of aripiprazole are advised. Potent inhibitors of CYP3A4 e.g. itraconzaole & ketoconazole can also increase aripiprazole levels, requiring dose reduction of aripiprazole. Upon discontinuation of the CYP2D6 or 3A4 inhibitor, the dosage of aripiprazole should be increased to the level prior to the initiation of the concomitant therapy.

Potent inducers of CYP3A4 e.g. carbamazepine likely to reduce levels of aripiprazole; dose of Aripiprazole should be doubled when taken concomitantly with carbamazepine. Same applies with other potent inducers of CYP3A4 e.g. rifampicin, rifabutin, phenytoin, phenobarbital, primidone, efavirenz, nevirapine and St. John's Wort. Upon discontinuation of potent CYP3A4 inducers, the dosage of aripiprazole should be reduced to the level prior to the initiation of the concomitant therapy.

Please also refer to Appendix 1 of the current BNF - 'bulleted points' denote significant interactions

Advice to patient
Oro-dispersible tablets should be placed on the tongue and allowed to dissolve, or be dispersed in water and swallowed.

Cost (Drug Tariff November 2014 for 28 days supply).

Drug strength and formulation	Cost (£)
Aripiprazole 5mg tablets	96.04
Aripiprazole 10mg tablets / orodispersible	96.04
Aripiprazole 15mg tablets / orodispersible	96.04
Aripiprazole 30mg tablets	192.08
Aripiprazole oral solution 1mg/mL (150mL) with measuring cup	*102.90

(*BNF 86)

References:

1. Summary of product characteristics for aripiprazole www.medicines.org.uk
2. Shared Care Guidance Aripiprazole oral, BNSSG December 2013. See here for Shared Care page for BNSSG.
3. NICE CG 178 (Feb 2014) Psychosis and schizophrenia in adults: Treatment and management
4. NICE CG 185 (Sept 2014) Bipolar disorder: the assessment and management of bipolar disorder in adults, children and young people in primary and secondary care
5. D Taylor et al. Maudsley Prescribing Guidelines 11th Edition (latest edition)
6. MHRA Public assessment report The risk of venous thromboembolism associated with antipsychotics June 2009
7. MHRA Drug Safety update June 2009 Antipsychotics Risk of venous thromboembolic events

Author: Formulary Pharmacist, AWP Mental Health NHS Trust in collaboration from members of the AWP Medicines Optimisation Group (includes consultants, senior nursing staff, pharmacists, clinical risk manager, Head of Medicines Management and occasionally representatives from finance) and the 3Ts working formulary group.

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Date of review: 2 years from date of approval or earlier if guidance changes.