

**SECTION 2: TREATMENT OF PSYCHOSIS**



Formulary and  
Prescribing Guidelines



## 2.1 Principles of Antipsychotic Prescribing

Where possible, choice of antipsychotic should be made **jointly** by the patient and the clinician responsible for treatment based on an informed discussion of the relative benefits of the drugs and their side-effect profiles. Where more than one drug is appropriate, an antipsychotic of low acquisition cost should be selected.

'As Required' (PRN) antipsychotics should only be prescribed when absolutely necessary. On-call doctors should prescribe 'once only' doses of antipsychotics on the 'Once Only' section of the medication chart and not routinely add them to the 'PRN' side of the card. Ward doctors should only prescribe 'PRN' antipsychotics for a maximum of 6 doses or 7 days, whichever is the shorter. Once this period has expired, treatment should be reviewed by a senior doctor and the requisite changes made to the regular section of the medication chart. **PRN antipsychotics should not** be automatically re-written.

PRN intramuscular antipsychotics may be employed when oral (PO) dosing is not possible. The intramuscular dose (IM) is usually lower than the corresponding oral dose (due to the absence of first pass effect). For example, 6 mg haloperidol IM is considered equivalent to 10 mg haloperidol PO. Separate prescriptions should be written for PO and IM antipsychotics. **Do not write PO/IM for any antipsychotic medication** – always specify the route of administration and the corresponding dose separately. PRN doses of intramuscular antipsychotic medication should be reviewed every seven days.

Detailed information on the treatment of psychosis in children and adolescents can be found in section 12. Further guidance on prescribing for older adults and for antenatal/postnatal service users can be found in section 11 and section 20, respectively.

People with borderline or antisocial personality disorders are prescribed antipsychotic or sedative medication only for short-term crisis management or treatment of comorbid conditions.

### Toxicity and antipsychotics

Blood level monitoring of clozapine is advised<sup>12</sup> in certain situations, see clozapine section below. Blood level monitoring of other antipsychotics for toxicity may also be helpful in certain circumstances, where testing and reference values are available. For example in the event of symptoms suggestive of toxicity or when concomitant medicines may interact to increase antipsychotic drug levels.

Assays and suggested reference values for therapeutic blood concentrations are known to be available for amisulpride, aripiprazole, olanzapine, quetiapine, risperidone and sulpiride, although availability of testing may vary locally (as at October 2020).

Prescribers should refer to the full Summaries of Product Characteristics for other important warnings, interactions, and recommendations, for clozapine and other individual antipsychotics.

## 2.2 Approved Drugs in the treatment of Psychosis in Adults

Drug <sup>1</sup>	Formulation <sup>2</sup>	
<b>Typical Antipsychotics (First Generation Antipsychotics (FGA))</b>		<b>Comments</b>
Haloperidol	Caps 500 micrograms Tabs 1.5mg, 5mg, 10mg, Liquid 2mg/ml Injection 5mg/ml	
Chlorpromazine	Tabs 25mg, 50mg, 100mg Liquid 25mg/5ml, 100 mg/5ml	
Flupentixol	Tabs 3mg	
Sulpiride	Tabs 200mg, 400mg Liquid 200mg/5ml	
Trifluoperazine	Tabs 1mg, 5mg Liquid 1mg/5ml, 5mg/5ml	
Zuclopenthixol	Tabs 2mg, 10mg, 25mg Injection, Zuclopenthixol acetate 50 mg/mL (Acuphase)	

Drug <sup>1</sup>	Formulation <sup>2</sup>	
<b>Atypical Antipsychotics (Second Generations Antipsychotics (SGA))</b>		
Risperidone	<b>Tabs 0.5mg, 1mg, 2mg, 3mg, 4mg, 6mg</b> Liquid 1mg/ml Orodispersible tablets 0.5mg, 1mg, 2mg, 3mg, 4mg	
Amisulpride	Tabs 50mg, 100mg, 200mg, 400mg Liquid 100mg/ml	
Aripiprazole	Tabs 5mg, 10mg, 15mg, 30mg Orodispersible tabs 10 mg, 15 mg Oral solution 1mg/ml <u>Injection 7.5mg/ml (immediate release)</u>	
Clozapine	Tabs 25mg, 100mg	<b>(Consultant initiation only)</b>
Lurasidone	<b>Tabs 18.5mg, 37mg, 74mg</b>	For use within its licensed indication as a third line antipsychotic once other atypical options (including aripiprazole) have been considered and have either failed to manage the patient's condition or are not suitable due to a contraindication or intolerance. This includes treatment of patients with schizoaffective disorder who fulfil criteria for treatment of schizophrenia in line with NICE guidance.

Drug <sup>1</sup>	Formulation <sup>2</sup>	
<b>Olanzapine</b>	<b>Tabs 2.5mg, 5mg, 7.5mg, 10mg, 15mg, 20mg</b> Orodispersible tabs 5mg, 10mg, 15mg, 20mg Injection, 5 mg/mL (non-depot)	Patients should be transferred to standard formulation as soon as possible and always prior to discharge
<b>Quetiapine</b>	<b>Tabs 25mg, 100mg, 150mg, 200mg, 300mg</b> XL tabs 50mg, 200mg, 300mg, 400mg.	Patients should be discharged on standard release
<b>Depot Injections</b>		
Flupentixol decanoate	Injection 20mg/ml, 40mg/2ml, 50mg/0.5ml, 100mg/ml, 200mg/ml	
Fluphenazine decanoate	Injection 25mg/1ml, 100mg/ml	New patients not to be initiated on treatment
Haloperidol decanoate	Injection 50mg/ml, 100mg/ml	
Risperidone (Risperdal Consta®)	(Long-acting) Injection 25mg, 37.5mg, 50mg (Consultant initiation only)	Consultant initiation Initiation form to be completed and sent to pharmacy
Aripiprazole (Abilify Maintena®)	(Long acting ) Injection 400mg (Consultant initiation only)	Consultant initiation Initiation form to be completed and sent to pharmacy
Zuclopenthixol <u>decanoate</u>	Injection 200mg/ml, 500mg/ml	
Paliperidone	Xeplion® (monthly) 50mg, 100mg, 150mg PFS	Consultant initiation Initiation form to be completed and sent to pharmacy
	Trevicta® (3 monthly) 175mg, 263mg, 350mg, 525mg	Patients should be adequately treated with monthly paliperidone palmitate injectable for four months or more, and not require dose adjustment.

**SGAs highlighted in bold** are associated with lower acquisition costs. If more than one SGA is appropriate for a particular service user, one with a low acquisition cost should be prescribed to ensure cost effectiveness within the health economy.

Clinicians are reminded that **Quetiapine XL** still remains considerably more expensive than the standard release tablet. It has been agreed at MMG/CCGs that suitable service users should be transferred to standard release formulations as highlighted in Appendix 9.

**Cariprazine** is non-formulary (MMG minutes December 2019). The conditions of its use are:

- Consultant initiation only.
- Applications for use of cariprazine must be made on a non-formulary drug request form, and MMG approval obtained, before treatment commences.
- Prescribing is not to be passed to GP.
- Treatment is only for adult patients with schizophrenia who continue to have prominent and debilitating negative symptoms on their current antipsychotic

regimen, and have a Scale for the Assessment of Negative Symptoms (SANS) score of  $\geq 50$ .

- Patients are to be monitored for response to cariprazine, including the patient's overall clinical status and improvements in the SANS score, to be measured at baseline and again at 6 months, and only continued if there is a  $\geq 50\%$  improvement in the SANS score.
- Female patients of childbearing potential must be advised to avoid pregnancy while on cariprazine, and must use highly effective contraceptive methods during treatment and for at least 10 weeks following the last dose of cariprazine.

## 2.3 NICE Clinical Guidelines

### [NICE CG178, Feb 2014. Schizophrenia in ADULTS<sup>9</sup>](#)

NICE CG178 covers treatment and management of schizophrenia and related disorders (schizoaffective disorder, schizophreniform disorder, and delusional disorder) in adults (of 18 years and older). **This guideline does not relate to late-onset schizophrenia.**

For patients with newly diagnosed schizophrenia, oral antipsychotic medication should be offered when deemed necessary. The choice of antipsychotic medication should be made by the service user and healthcare professional together, taking into account the views of the carer if the service user agrees. Provide information and discuss the likely benefits and possible side effects of each drug, including:

- metabolic (including weight gain and diabetes)
- extrapyramidal (including akathisia, dyskinesia and dystonia)
- cardiovascular (including prolonging the QT interval)
- hormonal (including increasing plasma prolactin)
- other (including unpleasant subjective experiences).

**Do not use loading doses** of antipsychotics and **do not initiate regular combination** antipsychotic therapy. (Only use combinations of antipsychotics for short periods, e.g. during change-over of agents).

An ECG should be done if:

- The patient has a specific cardiovascular risk (including elevated BP), or an established personal history of cardiovascular disease;
- the service user is being admitted as an inpatient
- This is a baseline requirement specified in the SPC

**Upon initiation of an antipsychotic** (which should be considered as an individual therapeutic trial) - record indication(s), expected benefits and risks, and estimate a time interval for a change in symptoms (and emergence of side-effects). Start with a dose at the lower end of the licensed range and titrate upwards slowly within the dose range in the BNF or SPC. **Record (with justification)** the use of an unlicensed dosage(s) range outside that specified in the BNF/SPC.

**Monitor** and record throughout treatment (and especially during titration) efficacy (including changes in symptoms and behaviour), side-effects, adherence and physical health. **Record rationale** for continuing, changing or stopping medication (and the effects of such changes). Allow a trial of an antipsychotic at optimum dosage for at least 4-6 weeks.

Be aware of any non-prescribed therapies (complimentary therapies), and usage of tobacco, alcohol, illicit drugs and non-prescription medications by the patient. Discuss with the service user any possible interference that the aforementioned may have with the effects of prescribed medications. Discuss also the safety and efficacy of non-prescribed therapies.

Review every seven days or after six doses PRN antipsychotic medication with respect to indication, frequency of administration, benefits, and side-effects. Calculate whether the antipsychotic dose (regular and PRN) is above BNF/SPC maxima.

**During the early post-acute phase**, service users should be informed about the high risk of relapse if medication is stopped within 1-2 years. If it is decided to withdraw medication, this must be done gradually with regular monitoring of signs and symptoms of relapse for at least 2 years after withdrawal. For patients presenting with an **acute episode** (exacerbation or recurrence) – an oral antipsychotic should be offered (taking into account the clinical response and side effects of previous and current medication).

RT (Rapid Tranquillisation) should be offered to people who pose an immediate threat to themselves or others during an acute episode (please see [NICE NG10](#), EPUT procedural guideline [CLPG52](#) or section 8 of this formulary for further information.)

#### [NICE CG120 March 2011. Psychosis with co-existing substance misuse](#)<sup>8</sup>

This guideline covers the assessment and management of adults and young people (aged 14 years and older) who have a clinical diagnosis of psychosis with co-existing substance misuse. CG 120 makes the following recommendations in relation to the use of antipsychotics for this specific group.

- Antipsychotics should be used in accordance with [NICE CG178](#)<sup>9</sup> (schizophrenia) or NICE CG185 (bipolar disorder, *section 3*) because there is no evidence for any differential benefit for one antipsychotic over another for people with psychosis and co-existing substance misuse.
- Use depot/long acting injectable antipsychotics according to [NICE CG178](#)<sup>9</sup> in managing covert non-adherence with treatment of psychosis and not as a specific treatment for psychosis and coexisting substance misuse.
- When prescribing medication for adults and young people with psychosis and coexisting substance misuse:
  - Take into account the level and type of substance misuse, especially of alcohol, as this may alter the metabolism of prescribed medication, decrease its effectiveness and/or increase the risk of side effects
  - Warn the person about potential interactions between substances of misuse and prescribed medication
  - Discuss the problems and potential dangers of using non-prescribed substances and alcohol to counteract the effects or side effects of prescribed medication

NICE NG181 (August 2020). Rehabilitation for adults with complex psychosis <sup>11</sup>

For people with complex psychosis whose symptoms have not responded adequately to an optimised dose of clozapine alone, consider augmenting clozapine with the following, depending on target symptoms:

- an antipsychotic, for example aripiprazole for schizophrenia and related psychoses and/or
- a mood stabiliser for psychosis with significant affective symptoms and/or
- an antidepressant if there are significant depressive symptoms in addition to the psychotic condition.

Be aware of potential drug interactions and note that not all combinations of treatments may be in accordance with UK marketing authorisations. Any off-licence prescribing should be communicated in writing with the person's GP. Seek specialist advice if needed, for example from another psychiatrist specialising in treatment-resistant symptoms or a specialist mental health pharmacist.

Optimise the dosage (as tolerated) of medicines used to manage complex psychosis (see recommendations 1.9.1 and 1.9.9) according to the BNF and therapeutic plasma levels in the first instance.

Only use multiple medicines, or doses above BNF or summary of product characteristics limits, to treat complex psychosis:

- if this is agreed and documented by the multidisciplinary team and the person (and their family, carer or advocate, as appropriate)
- as a limited therapeutic trial, returning to conventional dosages or monotherapy after 3 months, unless the clinical benefits of higher doses or combined therapy clearly outweigh the risks
- if the medicines are being used to treat specific symptoms that are disabling or distressing
- after taking into account drug interactions and side effects, for example be cautious when adding an antidepressant to clozapine for someone who has experienced symptoms of mania
- if systems and processes are in place for monitoring the person's response to treatment and side effects (monitoring may include physical examination, ECG and appropriate haematological tests)

Regularly review medicines used to manage complex psychosis and monitor effectiveness, adverse effects and drug interactions, including monitoring for constipation for those taking clozapine. Follow recommendations in the NICE guidelines on medicines optimisation and multimorbidity.

If pharmacological treatment is not effective, consider stopping the medicine:

- following a thorough review of treatment
- after agreeing and documenting the decision at a meeting with a multidisciplinary team and the person (and their family, carer or advocate, as appropriate)
- with caution, particularly if the person has been on the medicine for many years
- by reducing the dose slowly and closely monitoring the person for symptoms of relapse.

Monitor drug levels to check adherence and guide dosing:

- At least annually and as needed for clozapine and mood stabilising anti-epileptic medicines.

Consider monitoring prolactin levels annually if the person is taking a medicine that raises prolactin, and more regularly if they have symptoms.

Consider annual ECGs for everyone with complex psychosis in rehabilitation services, and more regularly if they are taking medicines, combinations of medicines or medicines above BNF or summary of product characteristics limits that may alter cardiac rhythm (for example, causing prolonged QT interval).

Be aware that people may be using non-prescription substances (for example, alcohol, smoking or drugs) to cope with their symptoms, which may affect their prescribed medicines.

Consider referring for a second opinion from a relevant specialist when treating people whose symptoms have not responded well to standard treatment, and after following recommendations in the NICE guideline on medicines optimisation.

#### Adherence to medicines

Rehabilitation services should promote adherence to medicines in line with the NICE guideline on medicines adherence. Strategies to promote adherence could include avoiding complex medicine regimens and polypharmacy wherever possible.

#### Helping people to manage their own medicines

Offer people the opportunity to manage their own medicines through a graduated self-management of medicines programme if they have been assessed as able to take part. Follow recommendations on self-management plans in the NICE guideline on medicines optimisation.

Be flexible in tailoring the self-management of medicines programme and choice of equipment to the person's needs and preferences. This could include using monitored dosage systems together with a reminder system (for examples, charts or alarms).

### **2.3 Relative Side-Effects of Antipsychotics (Typical and Atypical)<sup>5</sup>**

### 2.3.1 Recommended Rating Scales

The Liverpool University Neuroleptic Side Effect Rating Scale (LUNSERS) can be used for clients on any antipsychotic, however it is lengthy and can be time consuming, and patients may also need help understanding some of the terminology. The Glasgow Antipsychotic Side-effect Scale (GASS) is easy to use and quick to complete, however it should only be used for patients on second generation antipsychotics. Additional tools such as the Abnormal Involuntary Movement Scale (AIMS), or the Simpson Angus Scale may be necessary if there is evidence of tardive dyskinesia.

### 2.3.2 Monitoring of Side-Effects for Long Acting Injections

As a benchmark and to establish the impact of side effects, all patients should be offered the opportunity to complete either a GASS if on an atypical Long Acting Injection (LAI) (e.g. paliperidone) or a LUNSERS if on an older typical LAI (e.g. flupentixol); to measure the side effects of their LAI. This should be offered routinely at least every 6 months, prior to the prescriptions six monthly review, and approximately six weeks after initiation of a LAI, or when there has been dosage alteration.

Completion of GASS or LUNSERS can be carried out either in the depot clinics, by the care coordinator, or on a ward.

If the dose needs to be reduced to alleviate side effects, it is important to recognise that the plasma-drug concentration may not fall for some time after reducing the dose. It may take a month or longer before side effects subside. Side effects should be reassessed by repeating GASS or LUNSERS approximately 6 weeks after the dose alteration.

### 2.3.3 Side-Effect Profile and Choice of Antipsychotic

Where possible, the choice of antipsychotic should be made jointly by the patient and the clinician responsible for treatment based on an informed discussion of the relative benefits of the drugs and their side-effect profiles (see table below/overleaf).

**Where more than one drug is appropriate, an antipsychotic of low acquisition cost should be chosen.**

Other side-effects not mentioned in the table do occur. Refer to prescribing information (SPC for individual drug) and discuss with patient and/or carer as necessary/relevant. For example, when prescribing chlorpromazine – warn of its potential to cause skin photosensitivity and the need to use sunscreen. The table below (adapted from Maudsley, 12<sup>th</sup> edition illustrates an approximation of relative side effects from available evidence.)

Drug	Anti-cholinergic	Diabetes	EPSE	Hypotension	Sedation	Weight Gain	Prolactin elevation
Amisulpride	--	+	+	--	--	+	+++
Aripiprazole	--	-	+/-	--	--	+/-	--
Chlorpromazine	++	++	++	+++	+++	++	+++
Clozapine	+++	+++	--	+++	+++	+++	--
Flupentixol	++	+	++	+	+	++	+++
Fluphenazine	++	+	+++	+	+	+	+++

Drug	Anti-cholinergic	Diabetes	EPSE	Hypotension	Sedation	Weight Gain	Prolactin elevation
Haloperidol	+	+/-	+++	+	+	+	+++
Olanzapine	+	+++	+/-	+	++	+++	+
Perphenazine	+	+/-	+++	+	+	+	+++
Quetiapine	+	++	--	++	++	++	-
Risperidone	+	+	+	++	+	++	+++
Sulpiride	-	+	+	--	-	+	+++
Trifluoperazine	+/-	+/-	+++	+	+	+	+++
Zuclopenthixol	++	+	++	+	++	++	+++

-- little            + low / transient            ++ moderate            +++ high incidence,

## 2.4 Physical Health Monitoring of Adults taking Antipsychotics<sup>4</sup>

People with psychosis or schizophrenia, especially those taking antipsychotics, should be offered a combined healthy eating and physical activity programme. If a person has rapid or excessive weight gain, abnormal lipid levels or problems with blood glucose management, offer interventions in line with relevant NICE guidance (see Obesity [NICE clinical guideline 43], Obesity: identification, assessment and management of overweight and obesity in children, young people and adults [Nice Clinical Guideline 189], Lipid modification [NICE clinical guideline 181], Preventing type 2 diabetes [NICE public health guidance 38]) and Maintaining a healthy weight and preventing excess weight gain amongst adults and children NG7. See [Appendix 1](#) for details of physical health monitoring required.

## 2.5 High Dose Antipsychotic Therapy (HDT)<sup>1</sup>

The prescribing of high dose antipsychotics occurs in two ways:

- A single antipsychotic (including PRN, and by all routes) prescribed at a dose in excess of the maximum BNF recommended dose
- The combined use of two or more antipsychotics (including PRN, and by all routes) where the total of the individual doses, expressed as a percentage of the BNF maximum recommended dose, exceeds 100%.

High dose antipsychotic therapy should be prescribed following the guidance in Appendix 7 of CPG13 using the monitoring tool in [Appendix 2](#) of this document.

If a patient is being treated in accordance with Section 58 of the Mental Health Act, their T2 or T3 must state the HDT percentage BNF prescribed.

POMH-UK has created an easy to use dose converter which can aid calculation:

Antipsychotic	Equivalent doses <sup>4</sup>	Range of values <sup>4</sup>	Maximum dose <sup>2</sup>
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Antipsychotic	Equivalent doses <sup>4</sup>	Range of values <sup>4</sup>	Maximum dose <sup>2</sup>
<b>FGAs – oral</b>			
Chlorpromazine	100mg/day	-	1000mg/day
Flupentixol	3mg/day	2-3mg/day	18mg/day
Fluphenazine	2mg/day	2-5mg/day	20mg/day
Haloperidol	3mg/day	1.5-5mg/day	20mg/day (see BNF)
Sulpiride	200mg/day	200-270mg/day	2400mg/day
Trifluoperazine	5mg/day	2.5-5mg/day	None (?30mg/day)
Zuclopenthixol	25mg/day	25-60mg/day	150mg/day
<b>SGAs – oral</b>			
Amisulpride	It is inappropriate to covert SGA doses into 'equivalents' since the dose-response relationship is usually well defined for these drugs.		1200mg/day
Aripiprazole			30mg/day
Clozapine			900mg/day
Olanzapine			20mg/day
Quetiapine			750-800mg/day
Risperidone			16mg/day (see BNF)
<b>Depot</b>			
Flupentixol decanoate	10mg/week	10-20mg/week	400mg/week
Fluphenazine decanoate	5mg/week	1-12.5mg/week	50mg/week
Haloperidol decanoate	15mg/week	5-25mg/week	300mg/ 4 weeks
Zuclopenthixol decanoate	100mg/week	40-100mg/week	600mg/week

There is **no evidence to support the routine use of HDT** – either as a single agent or as combinations of antipsychotics; although in a minority of cases it may prove effective<sup>1</sup>. Thus, the implementation of such therapy should only be after evidence-based strategies have failed and where diagnosis has been re-confirmed, adherence to medication has been verified, adjuvant medication has been optimised (for example, antidepressants and mood stabilisers), akathisia has been dismissed and substance misuse has been eliminated. POMH-UK has produced an “[antipsychotic dosage ready reckoner](#)” to aid the calculation of total daily prescribed antipsychotic dose as a percentage of the BNF maximum. This can be downloaded from the Pharmacy and Medicines Management pages of the Trust intranet or printed copies obtained from Pharmacy.

HDT should only be attempted as a carefully monitored, explicit, therapeutic trial with an individual risk-benefit assessment by a Consultant Psychiatrist, in consultation with the clinical team and the patient (and the patient’s advocate – if the patient so wishes).

As HDT is a limited therapeutic trial – **the dose should be reduced back to conventional levels** after a 3-month period unless the (documented) clinical benefits outweigh the risks. **Supplementary prescribers are not permitted to prescribe high dose antipsychotic therapy.**

The decision to commence a patient on an elective trial of antipsychotic medication at a dose higher than the maximum BNF recommended dose is the responsibility of the patient’s consultant. Non-medical prescribers should not make the decision to proceed to the use of high dose antipsychotics.

The reason for the treatment, should be documented using a high dose therapy (HDT) form (see Appendix 7, CLPG 13), and the patient be given an explanation why they are receiving a trial of high dose medication. Forms are available on wards and in the pharmacy departments. If an individual patient is not informed then an explanation as to why that was not done should be documented in the patient’s healthcare record.

**Risk factors to be considered** (with documentation) include:

- Gender (women are more predisposed to QTc prolongation than men)
- Increasing age
- Renal/hepatic function
- Drug interactions (either interacting drug inhibits the metabolism of the antipsychotic and/or prolongs the QTc itself: for example, erythromycin, tricyclic antidepressants, certain antihypertensives (e.g. sotalol))
- Established cardiac history (history of an MI and/or arrhythmia(s))
- Cardiovascular risk factors (history of smoking, heavy alcohol ingestion, obesity)
- Electrolyte disturbances (e.g. if patient is on a diuretic).

An **ECG must be carried out** before initiating high dose antipsychotic therapy (to establish a baseline and exclude cardiac contra-indications, including QTc prolongation). Thereafter an ECG should be carried out after a few days and, subsequently every 1-3

months<sup>1</sup> (and when clinically indicated; should HDT be perpetuated). It is appropriate to monitor and record urea and electrolytes concomitantly.

Dose increments should be given time to take effect – and ideally should not be made more than once weekly. **Regular re-assessment** of ‘as required’ (or ‘prn’) medication and its potential to raise the total daily dose of antipsychotic above the high-dose threshold is required<sup>1</sup>.

**During Rapid Tranquillisation**, the use of HDT should be circumvented or minimised by the use of alternative strategies such as: de-escalation techniques, use of benzodiazepines (instead of antipsychotics), allowing sufficient time for a clinical response between doses, and transferring a patient to a suitable environment (with sufficient numbers of adequately skilled staff). If, however, HDT has to be used – then routine monitoring of a sedated patient should include regular checks of pulse, BP, respiration, hydration, and temperature. ECGs should be carried out frequently during dose escalation, if and when possible and especially, if parenteral administration of antipsychotic has been implemented<sup>1</sup>. (See CG 52 Pharmacological Management of Acutely Disturbed Behaviour)

## **2.6 Guidance on the use of Clozapine**

### **2.6.1 Indications**

Clozapine is indicated for patients with treatment resistant schizophrenia, who have not obtained satisfactory clinical improvement despite the sequential use of the recommended doses for 6–8 weeks of at least two antipsychotic drugs, at least one of which should be an atypical. Currently, all patients must be commenced or re-titrated on clozapine as inpatients. Some patients in the North may be initiated in the community following liaison with the Clozapine clinic.

### **2.6.2 Treatment**

- Advantages
  - 30% of patients who have previously been refractory to treatment improve significantly after 6 weeks’ treatment with clozapine, and up to 60% respond after 1 year
  - Effective in negative symptomatology
  - Clozapine is associated with an extremely low incidence of EPSEs
- Disadvantages
  - 3% of patients develop neutropenia, necessitating a regular full blood count
  - Higher incidence of seizures compared to other antipsychotics, especially above 600mg daily
  - Orthostatic hypotension is common on initiation necessitating gradual dose titration, and close monitoring
  - Significant risk of weight gain
  - Night-time salivation can cause severe discomfort

- Increased risk of myocarditis (1000-fold), and cardiomyopathy (5-fold)
- A wide range of other adverse effects

### 2.6.3 Choice of proprietary brand

Clozapine is available in three proprietary brands, “Zaponex”, “Clozaril” and “Denzapine”. Each has its own database for monitoring blood-tests, ZTAS, CPMS, and DMS respectively. **EPUT patients in Essex should be started on “Clozaril”, and those in Luton and Bedfordshire on “Denzapine”** unless pharmacy advise that they are to continue on another brand.

### 2.6.4 Prescriber Registration

**Before prescribing**, the clinician responsible for treatment must be registered with the relevant clozapine database – ZTAS/DMS/CPMS. . Registration forms may be downloaded from [www.clozaril.co.uk](http://www.clozaril.co.uk); [www.ztas.co.uk](http://www.ztas.co.uk), [www.denzapinesupport.co.uk](http://www.denzapinesupport.co.uk). Once registered, prescribers will be sent information detailing how to access the relevant on-line database.

### 2.6.5 Patient Registration and Initiation

Before using clozapine, the doctor must contact the clozapine clinic nurse and mental health pharmacist with the patient’s name, date of birth, race, ward, and any available information about previous use of clozapine. The clozapine clinic staff/pharmacist/consultant will then register the patient, and once a satisfactory baseline blood test result has also been received, the clozapine clinic staff/pharmacist will advise the consultant that it is safe to commence treatment. Clozapine should NOT be written on the prescription card until the consultant has been informed that the registration process has been completed and the blood result is valid.

### 2.6.6 Routine Blood Tests (full blood count)

The routine blood test required when taking clozapine is a **full blood count (FBC)**. Tests are taken weekly for the first 18 weeks of treatment, fortnightly for the next 34 weeks, then every 4 weeks after one year. Routine blood tests should be completed at clozapine clinics using Pochi machines to facilitate one stop service. That is, medication supply will be provided to patients at the same appointment on obtaining a valid blood result (green or amber). Where blood samples need to be sent to a laboratory for analysis (e.g. inpatient settings), samples should be taken early in the week, preferably on Monday or Tuesday unless alternative arrangements are made with the Clozapine clinic.

In an emergency or if an urgent test is required, blood should be sent to the local pathology laboratory for immediate analysis, and not posted.

Results are assigned a traffic light style colour code according to the white blood cell (WBC), neutrophil and platelet counts: “Green” indicates a normal count, “Amber” indicates a lower count than normal, and “Red” indicates a very low count.

It is recognised that nursing staff may occasionally need to take blood against the patient’s consent if they are detained under the mental health act. This is a necessary part of treatment and the Mental Health Act Commission has given approval.

In the event of a late, amber or red blood result, ZTAS/DMS/CPMS will send an email alert to the registered consultant and the pharmacist. The pharmacist will act on late or amber warnings automatically by forwarding to appropriate clozapine clinic staff although it is prudent for the consultant or their secretary to contact the pharmacist or clozapine clinic staff to ensure the email has been received. In the event of a red blood result, the pharmacist will contact the clozapine clinic nurse and consultant as soon as the alert is received to discuss the course of action. Blood test results requiring urgent action include:

- “Red” result: Stop treatment and seek advice from pharmacy. Repeat blood test urgently at clinic or local laboratory.
- “Amber” result: Repeat blood test within 2-3 days at clinic or local laboratory. Clozapine treatment should continue, but blood test to be repeated twice a week until “green” result obtained.

### 2.6.7 Management Following a Red Alert Result

Clozapine can cause serious blood disorders which may be life threatening if not detected. On receiving a red result, clozapine treatment must be stopped immediately in order to ensure the minimisation of harm to the service user experiencing the red. Guidance on the management of a red alert result can be found in [Appendix 6](#).

### 2.6.8 Plasma Clozapine Assays (additional cost involved)

Plasma clozapine assays are **NOT** the routine blood tests required for treatment maintenance. However, plasma levels of clozapine and norclozapine can be useful to optimise treatment and to check compliance. Consider requesting assay if it suspected levels are not within desired range or if individual’s circumstances change. Monitoring blood clozapine levels for **toxicity** is now advised<sup>12</sup> in certain clinical situations such as when:

- a patient stops smoking or switches to an e-cigarette
- concomitant medicines may interact to increase blood clozapine levels
- a patient has pneumonia or other serious infection
- poor (reduced) clozapine metabolism is suspected
- toxicity is suspected

Assays can only be analysed by a specialist laboratory such as [ASI Laboratory](#), [Viapath](#) and Magna Laboratories, and should not be sent to a local pathology laboratory.

- The dose should be adjusted to give plasma clozapine levels in the range 350 – 500 micrograms per litre although some patients may require higher or lower levels for optimum response

- Seizure activity may be more frequent if plasma clozapine levels rise above 800 micrograms per litre and prophylactic valproate should be considered in patients for whom a dose reduction is not appropriate.
- Results are available online 2 days after assay received for Beds and Luton online <http://www.kingspath.co.uk/results.php>

**Assays will only be done at the request of a consultant or senior doctor. Every request for a plasma clozapine assay must be co-ordinated by Pharmacy or the clozapine clinic.**

- An assay can be requested in the following way:
  - Contact the clozapine clinic for advice
  - Contact a mental health pharmacist for advice
  - Obtain a Magna ( South Essex), CPMS (North Essex) or DMS yellow plasma (Bedfordshire & Luton) blood test kit and patient's barcode labels
  - Take blood 12 hours (+/- 1 hour) after the night time dose (trough sample)
  - The day before the assay, move any afternoon / evening dose of clozapine to 10pm
  - On the day of the assay, postpone any morning dose of clozapine and take blood sample (at least 2ml) between 9am and 11am. The patient should then take their morning dose and continue as usual.
  - Complete documentation in kit
  - Attach completed patient's barcode labels to blood tube and form
  - Complete time and date of previous dose, time and date sample taken and current dose
  - Post as directed by laboratory

### **2.6.9 Medication Supply**

Tablets are dispensed by the pharmacy and delivered in advance of clinic date. Medication supplied should be quarantined and released after obtaining a valid blood result (green and amber). Amber results should be followed up as stated above (2.6.6). Supply should be crosschecked by clozapine clinic staff against prescription before handing over to patient. Under no circumstances should there be a break in treatment except for reasons of a "red" result or under specific medical advice. Every effort must be made to ensure a blood result is obtained before a patient's treatment becomes "prohibited".

### **2.6.10 Treatment breaks**

A treatment break, whether deliberate patient choice, gastric upset, or medically advised (e.g. surgery) is not clinically significant if **less than 48 hours** duration, and treatment can continue as before with the dose unchanged.

A break of **greater than 48 hours** is clinically significant in that the patient is at risk of profound hypotension if treatment resumes at full dose. Such a break should be followed by an increasing dosage titration whereby the patient receives 12.5mg on day 1, and has returned to their original dose after 7 to 10 days. The monitoring frequency may also change depending on the duration of the break.

The mental health pharmacist and consultant must be informed of any break that is greater than 48 hours so that advice can be given and the records held by ZTAS/DMS/CPMS can be updated. Re-titration should occur in an inpatient environment (see 2.6.1).

### **2.6.11 Admitting a Patient on Clozapine**

Before any clozapine is prescribed or administered, the pharmacy must be informed when any clozapine patient is admitted or transferred from another unit. The pharmacist will then check that the patient is currently registered for clozapine treatment, they have a valid blood result and that no treatment break has occurred. The records held by ZTAS/DMS/CPMS will also be updated.

**Clozapine must not be prescribed or administered until it is confirmed that the blood result is current and that no treatment break has occurred.** If the patient is admitted out of pharmacy hours, the doctor, community team or on-call pharmacist may help to confirm these details.

The relevant clozapine clinic team should be informed of admission of their clozapine patient.

### **2.6.12 Discharging a Patient on Clozapine**

The amount of clozapine supplied on a discharge note must correspond to the patient's monitoring frequency as the pharmacy can only supply medication for the duration of the current valid blood result. Inpatient clinical team need to engage and liaise with relevant clozapine clinic team from time of admission till discharge. Clozapine clinic staff will amongst other things, advice and/or facilitate necessary documentation such as prescriptions, next available outpatient clinic date and medication supply to ensure appropriate follow up plan is in place prior to discharge. Planning should also involve inpatient mental health pharmacist and the patient's community care-coordinator.

### **2.6.13 Transferring a Patient on Clozapine to another Unit**

The doctor must inform the mental health pharmacist when any clozapine patient is transferred to another unit so that a continuous supply of medication can be arranged and the records held by ZTAS/DMS/CPMS can be updated. Appropriate clozapine clinic(s) should be informed as the patient could be transferred from one clozapine clinic to another on discharge.

### **2.6.14 Transferring a Clozapine Patient to another Consultant**

If a clozapine patient is transferred to the care of a different consultant, the new consultant should inform the mental health pharmacist and clozapine clinic as soon as possible so the records held by ZTAS/DMS/CPMS can be updated. This

is essential so that any alerts sent by ZTAS/DMS/CPMS are sent to the correct consultant.

### **2.6.15 Discontinuing Clozapine Treatment**

In the event that clozapine treatment is to be discontinued, the doctor must inform the mental health pharmacist and clozapine clinic. The pharmacist or clinic nurse will cancel the patient's clozapine prescription (if an outpatient) and contact ZTAS/DMS/CPMS to change the patient's treatment status to "discontinued". The patient must continue to have blood tests at their regular monitoring interval for four weeks after they stop taking clozapine.

### **2.6.16 Outpatient Prescriptions**

Outpatient prescription forms are held by pharmacy and should be ordered by clozapine clinic staff or doctors by scanning completed order forms to pharmacy. Completed prescription forms are held by the clozapine clinic and a scanned copy of the original is held in the dispensary for 6 dispensing episodes. After this time, a new prescription is requested from the clozapine clinic.

### **2.6.17 Making Doses Changes in Outpatient Clinics**

Dose changes require a new prescription to be written and scanned to the Pharmacy at Chelford Court. This should be facilitated by clozapine clinic staff.

### **2.6.18 Collection of Clozapine Tablets from Community Teams**

Clozapine is regularly dispensed and sent to clozapine clinics (e.g. Grays Hall, Taylor Centre) for collection. If medication is not collected within one week of dispensing, the mental health pharmacist or supplying dispensary must be informed. Clinic staff must ensure any medication that is given to a patient at any time is not in excess of that permitted by the blood result.

The date of dispensing is printed on all pharmacy labels and clozapine clinic should keep a record of all medication it receives, including the date of dispensing and the date of collection. Medication should be checked against prescription before handing supply to patient. Wherever possible, checks should be completed prior to running the clinic so discrepancies can be highlighted and addressed with pharmacy.

### **2.6.19 Smoking**

Hydrocarbons contained in cigarette smoke induce CYP1A2, the main enzyme responsible for clozapine metabolism. **Smoking can reduce clozapine plasma levels by as much as 70%.** If someone taking clozapine stops smoking, it is expected that their plasma clozapine level will increase dramatically, possibly resulting in toxicity.

The use of **nicotine replacement therapy has no effect on enzyme activity**, so the effect on plasma clozapine levels will be the same as in a patient who is not prescribed NRT. It takes approximately five to seven days for the enzymes to adjust to the change in smoking habits.

When a clozapine patient stops smoking, either by choice or on admission to a smoke-free ward, a clozapine assay should be conducted as soon as possible. Due to the possibility that the patient may not have been fully compliant prior to

admission, this test should then be repeated seven days later. These results, together with any previous assay results, should then be used to determine the desired plasma level for the individual patient.

Doses should then be adjusted and assays should be repeated regularly until the plasma clozapine level has stabilised at the desired level. Please contact pharmacy for advice

## **2.6.20 Inpatient initiation of clozapine**

Inpatients with treatment resistant schizophrenia may be considered for clozapine initiation if certain criteria are fulfilled:-

- Clozapine treatment will be initiated by a consultant psychiatrist with the agreement of the inpatient ward. Baseline investigations and registration should be undertaken prior to admittance when possible. (see Appendix 5)
- Only patients likely to be adherent with oral medication should be considered.
- The patient must understand the need for, and agree to undergo regular blood tests and daily physical monitoring during the early dose-titration phase.
- Baseline blood test results and ECG must be within normal limits before clozapine is started (specialist examination is recommended if there are cardiac abnormalities or a history of heart disease. Clozapine is contra-indicated in patients with severe cardiac disorders).
- Many adverse effects of clozapine are dose-dependent and associated with the speed of titration. To minimise these problems it is important to start at a low dose and increase slowly (see Appendices 3a and 3b).

### **Consultant's Checklist:**

1. Discuss with patient/family/carers:-
  - Realistic expectations of treatment including time frames
  - How to recognise adverse reactions and side effects of clozapine (tiredness; dizziness; postural hypotension; hypersalivation; raised temperature/cough/signs of infection; tachycardia; fitting)
  - What to do if adverse events occur
  - Smoking and clozapine interaction
2. Patient to give informed consent
3. Full medical history review
4. Full medication review – caution in patients taking sedatives or benzodiazepines, anticholinergics, antihypertensives, alcohol. Bone-marrow suppressants (e.g. Carbamazepine, depot antipsychotics) should be withdrawn before starting clozapine

5. Full physical examination
6. Perform baseline tests (see [Appendix 5](#))
7. Register patient directly. Pharmacy or clozapine clinic staff can provide guidance as needed – clozapine may only be started once the patient has been registered and has a valid blood result taken in the last 10 days
8. Patient will be reviewed medically once a week as a minimum during the first 4 weeks of treatment

### **Dosing**

Usually the dose titration should be according to the suggested guidelines for inpatient initiation (see [Appendix 3a](#)). Reasons for variation from this regimen should be documented in the medical notes

Clozapine levels are lower in males, smokers and younger adults.

### **Switching from other antipsychotics**

- The switching regimen will be largely dependent on the patient's mental state. Consider additive side-effects of the antipsychotics (e.g. effect on QTc)
- Consider drug interactions (e.g. risperidone may increase clozapine levels).
- All depots should be stopped before clozapine is started.
- **Risperdal Consta** should be stopped several weeks before starting clozapine. This would normally be 3 – 4 weeks.
- Other antipsychotics and clozapine may be cross-tapered with varying degrees of caution.

### **Suggested titration regimen – clozapine inpatients**

*See Appendix 3 – Clozapine Initiation Prescription Charts.*

### **Monitoring by the ward in the early dose-titration phase (see [Appendix 3a](#)).**

Blood pressure (BP), temperature and pulse. After the first dose, monitor BP, temperature and pulse 1-3 hours afterwards. (This may not be necessary if the first dose is given at bedtime.) Thereafter, the patient should be seen at least once a day, and all three parameters should be monitored before and after the morning dose. Appendix 4 should be used for record keeping. Standing and supine BP should be monitored daily for three weeks for patients with Parkinson's Disease.

- Continue daily monitoring for 2 weeks and at least until there are no unacceptable adverse effects. Alternate day monitoring may then be

undertaken until a stable dose is reached. Thereafter monitor at time of blood testing.

- Side effects should be monitored and documented after every dose
- Weight, lipids, plasma glucose, LFTs and cardiac function should be monitored at baseline and then regularly throughout treatment. (appendix 4)
- The ward should inform the prescriber (or duty doctor out of hours):-
  - **If temperature** rises above **38°C** (this is very common and is not a good reason, on its own, for stopping clozapine)
  - **If pulse is >100 bpm** (also common but may rarely be linked to myocarditis)
  - **If BP Postural drop of > 30 mmHg (systolic)**. If necessary measure blood pressure standing and sitting.
  - **If patient is clearly over-sedated**
  - **If any other adverse effect is intolerable.**

#### **Additional monitoring requirements after the first month (see Appendix 5)**

Where available, consider also use of ECG (benefit not established).

#### **Adverse effects**

- **Sedation and orthostatic hypotension (with or without syncope)** are common at the start of treatment. These effects can usually be managed by reducing the dose or slowing down the rate of titration.
- Many **other adverse effects** associated with clozapine can also be managed by dose reduction.
- Patients may experience ECG changes, including ST depression, flattening of T waves, which normalise after discontinuation of Clozapine. The clinical significance is unclear but may be related to myocarditis.
- Isolated cases of cardiac arrhythmias, pericarditis/pericardial effusion and myocarditis have been reported, some of which have been fatal. Myocarditis has usually occurred in the first two weeks of treatment, whereas cardiomyopathy has tended to be later.
- Patients, who have **persistent tachycardia** at rest, especially during the first 2 months of treatment, should be closely observed for other signs or symptoms of myocarditis or cardiomyopathy. These include shortness of breath, palpitations, arrhythmia, symptoms mimicking myocardial infarction, chest pains and other unexplained symptoms of heart failure (unexplained fatigue, dyspnoea, tachypnoea). Flu-like symptoms may also occur. Eosinophilia may accompany myocarditis and pericarditis/pericardial effusion. In patients with suspected clozapine-induced myocarditis or cardiomyopathy, the drug must be stopped and the patient referred to a

cardiologist. If clozapine-induced myocarditis or cardiomyopathy is confirmed, the patient must not be re-exposed to clozapine.

### **2.6.21 Clozapine re-challenge**

*Information pertaining to the re-introduction of clozapine after a 'red' result can be found in [Appendix 7](#).*

### **2.6.22 Community Clozapine Initiation (North Essex)**

In North Essex, clozapine may also be initiated in the community setting either in the patient's own home or a day care setting. The patient should be registered with CPMS and have all baseline assessments completed as for inpatient initiation above.

Community initiation requires a slower, flexible titration schedule. An example dosing schedule can be found in The Maudsley Prescribing Guidelines in Psychiatry. This or another titration schedule should be used and prescribed on the community initiation chart (Appendix 3b).

The clozapine clinic nurse should be the lead on the practicalities of community initiation. Once the decision to use community initiation has been made, a copy of the community initiation chart should be scanned to the dispensary at Chelford Court. A supply will be made for each day up to the validity of the prescription. This should be taken to the patient each day and signed for on the community initiation chart to provide an audit trail. This includes medication left with the patient for evening doses.

Arrangements for monitoring must be made and agreed with the patient prior to initiation of clozapine. Blood monitoring is required as for inpatient initiation. Observation monitoring is suggested as follows:

- Day 1 – pulse, temperature and lying/standing blood pressure pre-dose then hourly for 6 hours post-dose
- Day 2 – pulse, temperature and lying/standing blood pressure pre-dose then 2 and 6 hours post-dose
- Day 3 – pulse, temperature and lying/standing blood pressure pre-dose then 6 hours post-dose. FBC to be taken.
- Days 4 - 14 – pulse, temperature and lying/standing blood pressure at least once a day. FBC to be taken on day 10.

Adverse effect monitoring should occur at least weekly with the prescriber informed if any effects or observations are noted as above. The patient should be seen by a doctor at least weekly during initiation. After two weeks, patients should be assessed for their need to continue on initiation or be transferred to the outpatient clozapine clinic on a regular dose.

## **2.7 Risperidone Long-Acting Injection (RISPERDAL CONSTA®)**

### **2.7.1 Indications**

Risperidone long acting injection (RLAI) is indicated for the maintenance treatment of schizophrenia in patients currently stabilised with oral antipsychotics. It is not indicated for treatment resistant schizophrenia. RLAI should not be prescribed for patients who have shown little or no response to oral risperidone. For further information relating to patient selection and inclusion criteria for the use of RLAI please see [Appendix 8](#) (guidelines for the use of Risperidone long acting injection)

## 2.7.2 Treatment

As it is not possible to give a test dose of RLAI, patients must be prescribed oral risperidone for several days before RLAI is initiated to assess tolerability (that is, to rule out hypotension or EPSE (extra-pyramidal side-effects)). The starting dose should normally be 25mg, although if a patient is taking more than 4mg per day of oral risperidone, RLAI may be started at 37.5mg. **RLAI is to be administered fortnightly.**

Oral risperidone (or other current oral antipsychotic) must be continued at the same dose for at least four to six weeks following the first injection, and then tapered off over the next two weeks. RLAI releases only small amounts of drug during the first three weeks. The main release starts in week four and peaks in weeks five to six.) Further supplementation of RLAI with oral antipsychotics should only occur in exceptional circumstances and must be kept under close review.

**The dose of RLAI should not be increased for at least six (to eight) weeks as steady state will not have been reached and therefore assessment of response will not be possible.**

At this point, it may be increased by 12.5mg (if considering above 50mg, 62.5mg can be achieved by using 25mg and 37.5mg injections) and a further six to eight weeks should elapse before any further increase. RLAI may only be initiated by Consultants. Other grades may not initiate therapy or adjust doses without direct instruction from their consultant.

If there is no significant improvement after six months of treatment with RLAI, consideration should be given to withdrawing it.

Prior to commencing consultants are reminded that before commencing RLAI an initiation form ([Appendix 8](#)) needs to be completed and forwarded to pharmacy.

## 2.7.3 Discontinuation

When discontinuing RLAI, the plasma level due to the last injection will not have declined significantly until 7-8 weeks after its administration. This must be considered when starting a new medication and is especially relevant if initiating clozapine.

## 2.7.4 Storage

RLAI packs must be refrigerated at 2-8°C. Storage at 8-25°C reduces the shelf life to 7 days. Packs must not be exposed to temperatures in excess of 25°C. After reconstitution, RLAI should be administered immediately. If not used immediately, it is considered suitable for use for a maximum of 6 hours, if stored below 25°C.

## 2.7.5 Reconstitution of high dose RLAI

Instead of giving two injections or a large volume injection each time a dose is due, the following procedure may be followed, although this is also outside the license:-

1. Make up one 37.5mg injection, and draw it up in the syringe.
2. Use this solution to make up the 2nd 37.5mg injection, and then draw it all up into the syringe. (25mg & 50mg injections could be used to achieve the 75mg injection and 25mg & 37.5mg injections could be used to achieve 62.5mg.)
3. You now have a syringe containing 75mg (or 62.5mg) in a little more than 2mls.
4. Give the injection in the usual way.

**If you have any doubts or questions about this, please contact pharmacy.**

Patient Status	Action
Compliant with oral risperidone.	Continue with oral risperidone.
No previous history of treatment with risperidone.	Assess tolerability by prescribing oral risperidone for several days at a dose of at least 2mg daily.
Documented previous history of treatment with risperidone. Well tolerated.	Consider RLAI 25mg every 2 weeks (if effective oral dose is less than or equal to 4 mg daily).
Patient currently prescribed oral risperidone but non-compliant.	If current oral dose is 4mg per day or less, consider RLAI 25mg every 2 weeks. If current oral dose is above 4mg per day, consider RLAI 37.5mg every 2 weeks.
Patient currently prescribed another oral atypical antipsychotic but non-compliant.	Assess tolerability by prescribing oral risperidone for several days at a dose of at least 2mg daily. Consider RLAI 25mg every 2 weeks.
Patient currently prescribed depot typical antipsychotic.	Assess tolerability by prescribing oral risperidone for several days at a dose of at least 2mg daily. Consider RLAI 25mg every 2 weeks. Administer first dose one week before depot is due and give last dose of typical depot on the due date.
Elderly (over 65 years)	The licensed dose is 25mg every 2 weeks for oral doses less than or equal to 4 mg daily. For doses in excess of 4 mg daily, administration of RLAI 37.5 mg should be considered.

## 2.8 Paliperidone Long-Acting Injection (XEPLION®)

### 2.8.1 Indications

Paliperidone LAI 1-monthly (PLAI1) is indicated for maintenance treatment of schizophrenia in adult patients stabilised with paliperidone or risperidone. (Oral paliperidone remains non-formulary)

In selected adult patients with schizophrenia and previous responsiveness to oral paliperidone or risperidone, PLA11 may be used without prior stabilisation with oral treatment if psychotic symptoms are mild to moderate and a long-acting injectable treatment is needed.

For further information relating to patient selection and inclusion criteria for the use of PLA11 please see [Appendix 8](#).

### 2.8.2. Treatment

As it is not possible to give a test dose of PLA11, patients must be prescribed oral risperidone for several days before PLA11 is initiated to assess tolerability (that is, to rule out hypotension or EPSE (extra-pyramidal side-effects)). The starting dose should normally be 150mg on day 1, 100mg on day 8 followed by a maintenance dose of 75mg one month after day 8. **PLA11 is to be administered monthly.**

If there is no significant improvement after six months of treatment with PLA11, consideration should be given to withdrawing it.

Prior to commencing, consultants are reminded that before commencing PLA11 an initiation form ([Appendix 8](#)) needs to be completed and forwarded to pharmacy.

### 2.8.3 Discontinuation

When discontinuing PLA11, the plasma level due to the last injection will not have declined significantly until several weeks after its administration. This must be considered when starting a new medication and is especially relevant if initiating clozapine.

### 2.8.4 Storage

PLA11 packs must be kept at room temperature and not refrigerated. Packs must not be exposed to temperatures in excess of 30°C<sup>6</sup>.

**If you have any doubts or questions about this, please contact pharmacy.**

Patient Status	Action
Compliant with oral risperidone.	Continue with oral risperidone.
No previous history of treatment with risperidone.	Assess tolerability by prescribing oral risperidone for several days at a dose of at least 2mg daily.
Documented previous history of treatment with risperidone. Well tolerated.	Consider PLA11 150mg on day 1, 100mg on day 8 and maintenance dose 75mg one month later. Maintenance doses to be given every month
Patient currently prescribed oral risperidone but non-compliant.	Consider PLA11 150mg on day 1, 100mg on day 8 and maintenance dose 75mg one month later. Maintenance doses to be given every month
Patient currently prescribed another oral atypical antipsychotic but non-compliant.	Assess tolerability by prescribing oral risperidone for several days at a dose of at least 2mg daily. Consider PLA11 75mg once a month
Patient currently prescribed depot typical antipsychotic.	Assess tolerability by prescribing oral risperidone for several days at a dose of at least 2mg daily. Consider PLA11 75mg once a month
Elderly (over 65 years)	Efficacy and safety in elderly > 65 years have not been established.

## 2.9 Paliperidone Long-Acting Injection 3-monthly (TREVICTA®)

### 2.9.1 Indications

Paliperidone LAI 3-monthly (PLAI3) is indicated for the maintenance treatment of schizophrenia in adult patients who are clinically stable on 1-monthly Paliperidone LAI.

Patients who are adequately treated with 1-monthly Paliperidone LAI (preferably for four months or more) and do not require dose adjustment may be switched to Paliperidone LAI 3-monthly.

For further information relating to patient selection and inclusion criteria for the use of PLAI3, see [Appendix 8](#).

## 2.9.2 Treatment

Paliperidone LAI 3-monthly should be initiated in place of the next scheduled dose of 1-monthly paliperidone LAI ( $\pm 7$  days). The dose should be based on the previous 1-monthly paliperidone LAI using a 3.5-fold higher dose shown in the following table:

Paliperidone LAI 3-monthly doses for patients adequately treated with 1-monthly Paliperidone LAI	
If the last dose of 1-monthly Paliperidone LAI is	Initiate Paliperidone 3-monthly LAI at the following dose
50 mg	175 mg
75 mg	263 mg
100 mg	350 mg
150 mg	525 mg

Following the initial dose, Paliperidone LAI 3-monthly should be administered by intramuscular injection once every 3 months ( $\pm 2$  weeks). If doses are missed, refer to detailed instructions in the SPC.

If needed, dose adjustment can be made every 3 months in increments within the range of 175 mg to 525 mg based on individual patient tolerability and/or efficacy. Due to the long-acting nature of this LAI the patient's response to an adjusted dose may not be apparent for several months.

### *Switching from other antipsychotic medicinal products*

Paliperidone LAI 3-monthly is to be used only after the patient has been adequately treated with 1-monthly Paliperidone LAI, preferably for four months or more.

## 2.9.3 Treatment review

Treatment should be reviewed every 3 months. If there is no sustained clinical stability, consideration should be given to withdrawing treatment.

## 2.9.4 Discontinuation

When discontinuing PLAI3, its exceptionally prolonged release characteristics must be considered, when planning a switch to another medicine. This is especially relevant if planning clozapine treatment. Refer to pharmacy for advice

on the time taken for complete clearance after treatment with repeated doses of PLA13.

### 2.9.5 Storage

PLA13 packs must be kept at room temperature and not refrigerated. Packs must not be exposed to temperatures in excess of 30°C <sup>6</sup>.

**If you have any doubts or questions about this, please contact pharmacy.**

## 2.10 Aripiprazole Long-Acting Injection (ABILIFY MAINTENA®)

### 2.10.1 Indications

Aripiprazole long acting injection (ALAI) is indicated for the maintenance treatment of schizophrenia in patients currently stabilised with oral antipsychotics. It is not indicated for treatment resistant schizophrenia. ALAI should not be prescribed for patients who have shown little or no response to oral aripiprazole. For further information relating to patient selection and inclusion criteria for the use of LAI please see [Appendix 8](#) (guidelines for the use of Aripiprazole long acting injection).

### 2.10.2 Treatment

As it is not possible to give a test dose of ALAI, patients must be prescribed oral aripiprazole for several days before ALAI is initiated to assess tolerability (that is, to rule out adverse drug reaction or EPSE (extra-pyramidal side-effects)). **ALAI is to be administered monthly on the same date of each month. Please note this is not every 28 days.** To provide flexibility in administration, for example at weekends, the interval between injections can be 26 days but no less.

Oral aripiprazole must be continued at the same dose for 14 days at a dose of 10 –20mg daily following the first injection. ALAI releases only small amounts of drug during the first few weeks and requires supplementation during this initial period. The main release starts after the initial two week period.

The starting dose of ALAI is 400mg once a month. This may be reduced, should side effects be problematic, to 300mg once a month. The dose cannot be increased further than 400mg once a month as there is no evidence to suggest efficacy. ALAI is not recommended for those over 65 years of age.

If there is no significant improvement after six months of treatment with ALAI, consideration should be given to withdrawing it.

Consultants are reminded that before commencing a LAI, an initiation form ([Appendix 8](#)) needs to be completed and forwarded to pharmacy.

### 2.10.3 Discontinuation

When discontinuing ALAI, the plasma level due to the last injection will not have declined significantly until 7-8 weeks after its administration. The terminal elimination half-life of a 400mg Maintena dose is 45 days<sup>6</sup>. This must be considered when starting new medication and is especially relevant if initiating clozapine.

## 2.10.4 Storage

ALAI packs must be kept at room temperature and not refrigerated. Packs must not be exposed to temperatures in excess of 25°C. After reconstitution, ALAI should be administered immediately. If not used immediately, it is considered suitable for use for a maximum of 4 hours, if stored below 25°C<sup>6</sup>.

**If you have any doubts or questions about this, please contact pharmacy.**

Patient Status	Action
Compliant with oral aripiprazole.	Continue with oral aripiprazole.
No previous history of treatment with aripiprazole.	Assess tolerability by prescribing oral aripiprazole for several days at a dose of at least 10mg daily.
Documented previous history of treatment with aripiprazole. Well tolerated.	Consider ALAI 400mg once a month .
Patient currently prescribed oral aripiprazole but non-compliant.	Consider ALAI 400mg once a month .
Patient currently prescribed another oral atypical antipsychotic but non-compliant.	Assess tolerability by prescribing oral aripiprazole for several days at a dose of at least 10mg daily. Consider ALAI 400mg once a month.
Elderly (over 65 years)	Aripiprazole LAI is not recommend for those over 65 years of age

**Dose adjustments of Abilify Maintena in patients who are taking concomitant strong CYP2D6 inhibitors, strong CYP3A4 inhibitors, and/or CYP3A4 inducers for more than 14 days<sup>6</sup>**

	Adjusted dose
<b>Patients taking 400 mg of Abilify Maintena</b>	
Strong CYP2D6 or strong CYP3A4 inhibitors	300 mg
Strong CYP2D6 and strong CYP3A4 inhibitors	200 mg
CYP3A4 inducers	Avoid use
<b>Patients taking 300 mg of Abilify Maintena</b>	
Strong CYP2D6 or strong CYP3A4 inhibitors	200 mg
Strong CYP2D6 and strong CYP3A4 inhibitors	160 mg
CYP3A4 inducers	Avoid use

## 2.11 Olanzapine Long Acting Injection (Zypadhera®)

Olanzapine LAI remains non-formulary. Prior to prescribing, an 'Olanzapine Long Acting Injection (Zypadhera®) Named Patient Request Form' (See Appendix 10) must be completed and approved by the chair of the Medicines Management Group. This form outlines plans for immediate and long-term monitoring. There should also be confirmation that the patient has agreed to the stringent monitoring following each dose.

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<http://guidance.nice.org.uk/CG120>
9. NICE CG 178. February 2014. Psychosis and schizophrenia in adults: treatment and management.
10. Nice QS 88 June 2015 Personality Disorders: Borderline and Antisocial Personality disorders: borderline and antisocial | Introduction | Guidance and guidelines | NICE
11. NICE NG181. Rehabilitation for adults with complex psychosis. Published date: 19 August 2020. Accessed 16.9.2020.
12. Drug Safety Update volume 14, issue 1: August 2020: 8. Page 5, "Clozapine and other antipsychotics: monitoring blood concentrations for toxicity".

**Appendix 1**  
**Physical Health Monitoring of Adults (*Children and Adolescents*) taking Antipsychotics (except clozapine)**

Name:	D.O.B:	NHS number:	Ward:
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Parameter	Baseline	1 month	3 months	6 months	9 months	12 months	Then...	
Date								
Weight (BMI & waist size)							Annually	
LFTs							Annually	
Fasting plasma glucose							6 monthly for olanzapine, annually for all others	
U&Es							Annually	
Fasting blood lipids							Annually	
FBC							Annually	
TFTs							Annually	
Prolactin							Annually	
BP/pulse		Before starting antipsychotic medication & during significant dose changes, see SPC of individual drug for full guidance						Annually
ECG		Recommended pre-treatment and at dose increase for typical antipsychotics, high dose treatment (>BNF maximum) and combination treatment with more than one antipsychotic						Annually

Blank (un-shaded) boxes indicate monitoring required

Physical health monitoring of those taking antipsychotic drugs should be based on the schedule above **in addition** to any specific SPC/NICE requirements. More frequent monitoring should be conducted if there are clinical symptoms or changes detected are appropriately actions taken/cascaded

Perform a **full physical examination** before starting antipsychotic therapy. Record **BP and pulse** and, before starting antipsychotic medication, offer all in-patient service users with schizophrenia (and related disorders) an electrocardiogram (ECG).

**References**

1. South London & Maudsley NHS Foundation Trust Prescribing Guidelines 12<sup>th</sup> edition, Informa Healthcare, 2010

**Appendix 2**

**HIGH DOSE AND COMBINATION ANTIPSYCHOTIC TREATMENT  
MONITORING FORM**

Patient's name:		Date of Birth:	
NHS Number		Ward:	
Consultant		Date	

This form is to be completed **prior** to commencing an antipsychotic drug where doses prescribed by all routes either exceed 100% of the BNF maximum recommended dose (including PRN) OR involve more than one antipsychotic drug prescribed on a regular and/ or PRN basis, where the combined doses by all routes exceed 100% of the BNF maximum recommended dose.

**HIGH DOSE OR COMBINATION ANTIPSYCHOTIC TREATMENT SHOULD BE REVIEWED AT INTERVALS OF TWO WEEKS OR LESS AND DISCONTINUED IF NO ADDITIONAL CLINICAL BENEFIT IS OBSERVED.**

<b>Current Medication</b>		
Drug name and formulation	Current total daily dose	Planned maximum daily dose

<b>Previous Antipsychotic Medication</b>		
Drug name and formulation	Total daily dose	Reason for stopping

<b>Reasons for High Dose / Combination Antipsychotics</b>

		YES	NO
1. Has this patient been prescribed clozapine?  If NO, please state reason(s) for not prescribing If YES, please state reason(s) for discontinuation			
2. Has the patient shown signs of adverse effects to antipsychotic drugs or is there evidence of drug interactions?  If YES, please give details			
3. Is the patient subject to Section 58 (consent to treatment) requirements?  If YES, has the patient either given informed consent to high dose treatment and T2 been amended accordingly, or SOAD consent has been obtained on Form T3?  (Answer must be YES)			

Monitoring required prior to commencing high dose treatment								
	ECG	FBC	U&Es	LFTs	TFTs	Glucose	Lipids	
Date								
Normal / Abnormal								

Monitoring required after commencing high dose treatment (repeated at a minimum of every three months)								
Date	ECG (Norm/Abn)	FBC (Norm/Abn)	U&Es (Norm/Abn)	LFTs (Norm/Abn)	TFTs (Norm/Abn)	Glucose (Norm/Abn)	Lipids (Norm/Abn)	

Consultant Name:	Signature:
Date of commencing High Dose Treatment:	

## Clozapine Inpatient Initiation Chart (page1)

Affix Addressograph Label Here				Consultant			
Forename				Ward/Unit			
Surname				Date Chart Started			
Date of Birth				Date Chart Finished			
NHS No.						Clozapine Number	

**Notes**

1. This chart should only be used for patients starting treatment with clozapine in Inpatient units.
2. Attach this chart to the main prescription chart, which must be endorsed "Clozapine as per Clozapine Initiation Chart" in one of the prescription boxes in the "regular medication" section.
3. The CONSULTANT should sign this chart for the start of week 1. Subsequent prescriptions may be signed by any appropriate prescriber.
4. The nurse administering the clozapine should sign in the "Given By" box beside each dose.
5. Once the maintenance dose has been reached all unused boxes should be crossed out and initialled by the prescriber. The maintenance dose of clozapine should then be prescribed on the main drug chart.

**MONITORING**

Baseline assessment and physical monitoring should be done according to the guidelines in the Trust's Formulary and prescribing Guidelines (section 2) and using relevant monitoring forms. See Trust Intranet>Teams>Pharmacy & Medicines Management>Formulary and Prescribing Guidelines MH>Section 2 "Treatment of Psychosis">Guidelines for the Use of Clozapine.

<b>Week 1</b>		<b>Consultant's signature .....</b> <b>Date .....</b> <b>Print Name .....</b> <b>Tel/Bleep.....</b>				
<b>Day</b>	<b>Total Daily Dose (mg)</b>	<b>Date</b>	<b>Morning Dose</b>	<b>Given By (nurse sign)</b>	<b>Evening Dose</b>	<b>Given By (nurse sign)</b>
1	12.5mg		xxxxxxxx	xxxxxxx	Clozapine 12.5mg	
2	25mg		Clozapine 12.5mg		Clozapine 12.5mg	
3	50mg		Clozapine 25mg		Clozapine 25mg	
4	50mg		Clozapine 25mg		Clozapine 25mg	
5	75mg		Clozapine 25mg		Clozapine 50mg	
6	75mg		Clozapine 25mg		Clozapine 50mg	
7	100mg		Clozapine 50mg		Clozapine 50mg	
<b>Pharmacy</b>	Week 1 17x25mg	Screened by..... Date .....	Dispensed by..... Date .....	Checked by..... Date .....		

**BLOOD TESTS**

**Pre-treatment sample:** Date sample taken ..... Signature .....

Green result confirmed ; Date ..... Signature .....

Date Clozapine started: .....(must be within 10 days of pre-treatment sample)

**Second blood sample:** Date sample taken .....(within 7 days of the pre-treatment sample)

Green result confirmed ; Date ..... Signature.....

Second sample taken; Date ..... Signature.....



## Clozapine Community Initiation Prescription Chart

<b>Forename</b>		<b>Surname</b>	
<b>DOB</b>		<b>NHS Number</b>	
<b>Consultant</b>			

**Notes:**

1. This chart is for community initiation of clozapine only
2. The prescription for the first week should be signed by the consultant. Thereafter, prescriptions can be signed by an appropriate prescriber
3. Titrations should start on a Monday, with prescriptions and supply organised the previous week
4. Administration/supply should be signed by the registered nurse in the “given by” box next to the dose
5. Once the target maintenance dose is reached, clozapine should be prescribed on an outpatient clozapine prescription
6. Ensure pre-treatment baseline assessment is completed
7. Clozapine can only be given to patients registered with CPMS and with a ‘green’ blood result. Please document CPMS number and date of 1<sup>st</sup> green result below to confirm.

<b>CPMS Number</b>		<b>Date of 1<sup>st</sup> green result</b>	
--------------------	--	--	--

**Monitoring:**

Complete the following on a track and trigger form and record on Paris (Remedy):

Day	Monitoring
1	Pulse, temperature and lying/standing blood pressure pre-dose and hourly for 6 hours post-dose
2	Pulse, temperature and lying/standing blood pressure pre-dose, 2 and 6 hours post-dose
3	Pulse, temperature and lying/standing blood pressure pre-dose and 6 hours post-dose. FBC to be taken
4-14	Pulse, temperature and lying/standing blood pressure at least once a day. FBC to be taken on day 10

FBC (to include differential white cell count):

Week	Frequency	Validity (if green)
1-18	Weekly	10 days
19-52	Fortnightly	21 days
53 onwards	Monthly	42 days

Forename		Surname	
DOB		NHS Number	
Consultant			

**Week 1**

<b>CLOZAPINE</b>	Consultant signature					
<b>Pharmacy</b>  Screened by:  Ordered by:  Supply received by:	Print name			Date		
	<b>Day</b>	<b>Date</b>	<b>0900</b>	<b>Given by</b>	<b>1800</b>	<b>Given by</b>
	1					
	2					
	3					
	4					
	5					
	6					
	7					

**Week 2**

<b>CLOZAPINE</b>	Prescriber signature					
<b>Pharmacy</b>  Screened by:  Ordered by:  Supply received by:	Print name			Date		
	<b>Day</b>	<b>Date</b>	<b>0900</b>	<b>Given by</b>	<b>1800</b>	<b>Given by</b>
	8					
	9					
	10					
	11					
	12					
	13					
	14					

**Week 3**

<b>CLOZAPINE</b>	Prescriber signature					
<b>Pharmacy</b>  Screened by:  Ordered by:  Supply received by:	Print name			Date		
	<b>Day</b>	<b>Date</b>	<b>0900</b>	<b>Given by</b>	<b>1800</b>	<b>Given by</b>
	15					
	16					
	17					
	18					
	19					
	20					
	21					

**NOW TRANSFER TO AN OUTPATIENT CLOZAPINE PRESCRIPTION**

**Clozapine Inpatient Monitoring Record**

See section 2.6.19 for further information

Name:	D.O.B:	NHS number:	Ward:
-------	--------	-------------	-------

**PHYSICAL:**

Date														
Time														
Completed By														
Blood Pressure														
Pulse														
Temperature (°C)														

**SIDE EFFECTS:**

Restlessness														
Blurred Vision														
Confusion														
Diarrhoea														
Dry Mouth														
Excessive Sweating														
Excessive Salivation														
Muscle Spasm														
Nausea or Vomiting														
Sedation														
Tremor														
Other														

**KEY: 0= none    1= minor    2= moderate    3=severe**

**Clozapine Physical Monitoring Record**

(See section 2.6.19 of EPUT formulary for further information)

Name:	D.O.B:	NHS number:	Ward:
-------	--------	-------------	-------

	Baseline	1 month	3 months	6 months	12 months	Ongoing
<b>Date</b>						
<b>Weight (BMI &amp; waist size)</b>						Annually
<b>Fasting lipid profile</b>						Annually
<b>Blood glucose random/fasting</b>						Annually
<b>Liver function</b>						Annually
<b>ECG</b>	Clozapine may cause cardiomyopathies and myocarditis. Check ECG when maintenance dose is reached. Check annually if high dose (>600mg daily)					
<b>Urea &amp; Electrolytes</b>						Annually
<b>Full blood count</b>	As per clozapine protocol. Weekly for 18 weeks, then fortnightly for up to 1 year, then 4-weekly. Additional monitoring may be required if appropriate					
<b>Prolactin</b>	Hyperprolactinaemia is rare with clozapine - check serum prolactin if symptoms occur (menstrual disturbance, galactorrhoea, gynaecomastia, sexual dysfunction). Consider other possible causes.					
<b>BP and Pulse</b>	Daily during titration See appendix 4					Annually

Blank (un-shaded) boxes indicate monitoring required

**ECG comment:-****Notes**

## MANAGEMENT FOLLOWING A CLOZAPINE RED ALERT RESULT

### INTRODUCTION

If a patient's WBC is less than  $3.0 \times 10^9/L$  and/ or the neutrophil count is less than  $1.5 \times 10^9/L$  then this is known as a **RED ALERT**.

When the Clozaril Patient Monitoring Service (CPMS) or Denzapine Monitoring Service (DMS) detects a red alert, a registered contact will be notified. The registered contact would normally be the consultant psychiatrist or nominated deputy, or a designated pharmacist or their deputy.

The registered contact must arrange for this procedure to be carried out without delay.

The following people must also be made aware:

- Consultant psychiatrist or nominated deputy
- Team leader/ward manager or deputy
- Clozapine pharmacist or designated deputy
- The service user's GP
- Crisis Resolution and Home Treatment Teams (CRHTTs) if appropriate

The service user must be advised to stop taking clozapine until further notice (remove the tablets as soon as possible).

Management of a red result is under the clinical leadership of the service user's consultant psychiatrist. The consultant psychiatrist must liaise with either the relevant monitoring service i.e. CPMS or DMS.

The implications and the procedure to be followed should be explained in full to the service user/ carer(s).

The information which the service user/ carer(s) are given must meet the individual's communication needs.

The service user and carer(s) must be kept informed of progress.

The mental state of the service user must be monitored on an on-going basis as a psychotic relapse can occur following sudden withdrawal of clozapine.

Healthcare professionals must carry out daily checks as a minimum on the service user's temperature, BP, pulse rate and respiratory rate.

The risk assessment should be kept up to date and all results and events should be recorded on the electronic patient record as soon as possible, in order that the information is readily available to healthcare professionals.

The consultant psychiatrist or deputy/ nurse in charge must arrange to take follow-up blood samples on the 2 days following the date of the red alert sample. Arrangements for receiving the result of the test (in or out of working hours) must be in place.

If either of these follow up blood counts is in the red range, then the red alert is confirmed and the patient must not restart clozapine treatment.

If the red alert is confirmed then follow up full blood counts with differential should be performed daily whilst the blood counts remain in the red range, and the patient must be observed closely for signs of infection, such as a sore throat or fever. Other physical signs are flu-like symptoms e.g. rapid pulse and respiration, hypotension, mouth ulcers, swollen and tender gums and skin infections.

If the patient's neutrophil count has fallen to less than  $1.0 \times 10^9/L$  or the WBC falls to less than  $2.0 \times 10^9/L$ , or if the patient develops a fever, it is extremely important to contact a haematologist, or failing this, a general medical physician, for advice regarding appropriate treatment for the patient. This may include transferring the patient to a ward with facilities for the care of neutropenic patients.

If antipsychotic medication is considered essential, a drug with a low potential to cause neutropenia should be considered, and depot preparations should be avoided. All other medication should be reviewed and consideration given to stopping any drugs which may reduce WBC and/ or neutrophil counts. If necessary a more appropriate alternative should be introduced.

If neither follow up sample is red, then the red alert is unconfirmed and the patient may resume clozapine treatment. This may be at the normal dose if the break in treatment is less than 48 hours, or with re-titration from 12.5mg, if over 48 hours.

Following an unconfirmed red, additional monitoring is needed as a precaution if the follow up results are either amber or green, but still low for that patient, whether clozapine is restarted or not. In the case of an unconfirmed red, CPMS or DMS should be contacted to provide specific advice on additional monitoring, frequency and duration.

Blood results should be reported to the CPMS or DMS as soon as they are available.

Clozapine re-challenge is contraindicated in any patients who have experienced a red alert. All patients with a confirmed red result will be entered onto the Central Non-rechallenge Database to ensure that they are not inadvertently re-exposed to clozapine from alternative suppliers.

## **PATIENTS WITH BENIGN ETHNIC NEUTROPENIA**

Patients with diagnosed benign ethnic neutropenia (BEN) may be considered for treatment with clozapine, with the agreement of a haematologist. The CPMS and DMS colour-coded ranges are all decreased by  $0.5 \times 10^9/L$  for these patients, hence a red alert for a patient with BEN is WBC  $<2.5 \times 10^9/L$  and/ or neutrophils  $<1.0 \times 10^9/L$ .

Any patients who develop a red or amber alert within the modified ranges will be treated as per standard RED ALERT procedures.

## **EFFECT OF SUDDEN DISCONTINUATION OF CLOZAPINE**

When a patient has a red alert it is essential to stop clozapine immediately. Careful psychiatric monitoring of the patient is essential since symptoms may recur quickly.

Stopping clozapine suddenly can lead to physical and mental withdrawal effects which may occur within 2-3 days, and usually within the first 2 weeks. Patients may experience a rapid deterioration in their mental state with rebound psychosis. In addition, abrupt withdrawal of clozapine has been associated with symptoms such as nausea, vomiting, diarrhoea, headache, restlessness, agitation, and sweating; and it has been suggested that these are a result of cholinergic rebound since clozapine has strong cholinergic action. Discontinuation of clozapine for reasons other than a red alert, or other serious side-effect, should be done gradually to minimise the risk of withdrawal effects.

### **ADDITIONAL GUIDANCE IF THE SERVICE USER IS BEING MANAGED IN THE COMMUNITY**

A member of the community team must visit at least daily. In the event of needing weekend monitoring, community teams must arrange with support teams who operate 7 day services to provide cover.

The service user must have a full blood count with differentials every day until the results are within the normal recommended range. This may include transportation of the service user to have their blood sample taken, especially if the service user lives alone or does not have transport. In the event of this not being possible, taxi services may need to be provided - approved by the CMHT manager or deputy.

The community team must liaise with consultant psychiatrist or designated deputy on a daily basis and inform the service user's GP in relation to blood results and service user's physical health observations.

## Clozapine re-challenge after a 'red' blood result

### Procedure for clozapine re-challenge after a 'red' blood result – unlicensed use

1. Before considering clozapine re-challenge in a patient who has had a 'red' blood result, alternative drug treatments should be considered. The Maudsley Prescribing Guidelines 12<sup>th</sup> Edition contains a table listing alternatives to clozapine for refractory schizophrenia.
2. If these options have been tried without success, or if they are not considered appropriate, the possibility of re-starting the patient on clozapine should be discussed within the clinical team and with senior colleagues. These discussions should take into account the patient's current mental status and their previous response to clozapine.
3. If there is agreement that re-challenge with clozapine is justified, the patient's consultant should discuss the case with the local consultant haematologist.
4. If the haematologist agrees that it is safe to proceed with a re-challenge, the patient's consultant should contact the manufacturer of clozapine
5. The company will issue a 'Patient Re-challenge Request' form which the consultant must complete and return
6. On receipt of this form, the company will issue the following documents:
  - A standard clozapine patient registration form
  - A 'Patient Re-challenge Agreement' form
  - A 'Off-label Treatment Agreement' form
7. These forms must be completed by the consultant and returned **before the re-challenge** can proceed. It is important to note that the 'Off-label Treatment Agreement' is a disclaimer which states that the manufacturer does not recommend the prescribing of clozapine for re-challenge and that the consultant accepts full clinical responsibility for the decision to proceed with this.
8. Once a proposed starting date for the re-challenge has been agreed, **the hospital Pharmacy** (and, if necessary, the local haematologist), should be notified. In addition, the chair of the **Medicines Management Group** should be notified
9. The rationale for proceeding with clozapine re-challenge, and the subsequent discussions with haematologists and the manufacturer, should be fully documented in the patient's notes. The patient and/or their representative(s) should be informed of the unlicensed nature of this treatment and its associated risks, and this discussion should be recorded in the notes. Informed consent should also be obtained.

## Guidelines for the Use of Long Acting Injections (Risperdal Consta® / Xeplion® / Trevicta® / Abilify Maintena®)

### 1. Introduction

Risperidone, Paliperidone and Aripiprazole are effective atypical antipsychotics used in the treatment of schizophrenia and are currently recommended as first line atypical oral antipsychotics (paliperidone is non-formulary), due to their lower acquisition costs than others in the class. Long Acting Injections (LAIs) are a slow release injectable form of the same drug, the acquisition cost of which is very high compared with other depot antipsychotics.

#### Patient Selection Criteria

Patients who are unlikely to consistently take oral medication should be considered for a depot or long-acting injection. As non-adherence with oral treatment is the main reason for switching to a depot it does not necessarily follow that a patient prescribed oral aripiprazole or risperidone should automatically be switched to a the equivalent LAI.

- A first generation antipsychotic depot injection should be considered before Risperidone, Paliperidone or Aripiprazole LAI unless there are contra-indications. Patients suffering side effects on conventional depot injections despite dose reduction, where appropriate, should be considered for these second generation preparations.
- Patients who are responding well and not experiencing intolerable side effects of conventional depot injections **should not** be transferred to Risperidone, Paliperidone or Aripiprazole LAI. Patients who have shown little or no response to oral aripiprazole/risperidone **should not** be transferred to Risperidone, Paliperidone or Aripiprazole LAI.
- Risperidone, Paliperidone or Aripiprazole LAI are not indicated for Treatment Resistant Schizophrenia – such patients should always be considered for clozapine.
- The patient should have a demonstrated tolerance to the oral drug, and stabilisation of their symptoms on the oral drug, prior to switch to the LAI.
- In selected adult patients with schizophrenia and previous responsiveness to oral paliperidone or risperidone, Paliperidone LAI (monthly) may be used without prior stabilisation with oral treatment if psychotic symptoms are mild to moderate and a long-acting injectable treatment is needed.
- Patients stabilised on Paliperidone 1-monthly LAI may only be switched to Paliperidone 3-monthly LAI after initial stabilisation for at least 4 months. The Paliperidone 3-monthly LAI initiation form must be completed **before** making the switch.

Clinicians wishing to initiate Risperidone, Paliperidone (1-monthly) or Aripiprazole LAI must complete the relevant initiation form. Note that there is a separate initiation form for Paliperidone 3-monthly LAI.

### 2. Initiation Doses

#### Fortnightly / monthly LAIs

Fortnightly/ monthly LAIs have a unique release profile and it must be remembered that there is virtually no release of active ingredient for the first few weeks following administration. It therefore follows that there will be no response during this period and alternative treatment e.g. oral risperidone/ paliperidone/ aripiprazole or alternative depot needs to be continued (see the Trust Formulary and Prescribing Guidelines).

Dose equivalence should be taken into account in determining the starting dose, therefore a patient who has been stable on 6mg of risperidone may be started on a dose of 37.5mg RLAI providing all other criteria have been met. All other patients should start on a dose of 25mg. For aripiprazole, the usual starting dose is 400mg. For paliperidone patients should be given 150mg on day 1, 100mg on day 8, and transferred to a maintenance dose of 75mg one month after day 8.

### **3-monthly LAI (Paliperidone)**

Dose as per SPC. There is no need to supplement with oral doses.

**INITIATION OF RISPERIDONE/PALIPERIDONE/ARIPRAZOLE LONG ACTING INJECTION (LAI)**  
**(RISPERDAL CONSTA® / XEPLION® / ABILIFY MAINTENA®)**

(NB: Authorisations for Paliperidone 3-monthly TREVICTA® should **not** be completed on this form, use the separate form).

This authorisation form needs to be completed prior to initiating risperidone/ paliperidone/ aripiprazole long acting injections (as agreed by the Medicines Management Group in September 2017).

A new form is required for each treatment episode. Incorrect or partially completed forms along with requests for LAI without the requisite form will be referred back to the prescribing consultant and may cause unnecessary delay in drug supply.

<b>Patient's name:</b>		<b>NHS Number:</b>	
<b>Date of Birth:</b>		<b>Ward / Team:</b>	
<b>Name of LAI to be initiated</b>			

1. <b>Is the patient suffering from treatment resistant schizophrenia?</b> <i>(treatment resistant schizophrenia is not a licensed indication and clozapine should be considered)</i>	Y / N
2. <b>Has a first generation antipsychotic (FGA) depot injection been tried prior to considering LAI?</b> <i>(non-adherence with oral therapy is the main reason for switching to a depot injection; it does not necessarily follow that a patient prescribed oral risperidone/aripiprazole should automatically be switched to LAI)</i>	Y / N
3. <b>Did the patient respond well to FGA depot injections?</b>	Y / N
4. <b>Did the patient experience intolerable side effects despite dose reduction?</b> <i>(patients who are responding well and not experiencing intolerable side effects of conventional depot injections should not be transferred to LAI)</i>	Y / N

**Please provide details of your reasons for wishing to use LAI in this patient:**

Consultant Name:	Signature:
Date:	Contact Tel:

**Return to Pharmacist for clinical ratification**

Pharmacist Name:	Signature:	Date:
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**INITIATION OF PALIPERIDONE 3-MONTHLY LONG ACTING INJECTION (LAI) (TREVICTA®)**

This authorisation form needs to be completed prior to initiating paliperidone 3-monthly long acting injection (as agreed by the Medicines Management Group in June 2019).

A new form is required for each treatment episode. Incorrect or partially completed forms along with requests for LAI without the requisite form will be referred back to the prescribing consultant and may cause unnecessary delay in drug supply.

<b>Patient's name:</b>		<b>NHS Number:</b>	
<b>Date of Birth:</b>		<b>Ward / Team:</b>	
<b>Name of LAI to be initiated</b>	<b>PALIPERIDONE 3-MONTHLY LAI (TREVICTA®)</b>		

1. <b>Is this for the maintenance treatment of schizophrenia (not treatment resistant)?</b>	Y / N
2. <b>Is the patient now clinically stable on Paliperidone 1-monthly LAI?</b> <i>(Paliperidone 3-monthly LAI is indicated for the maintenance treatment of schizophrenia in adult patients who are clinically stable on 1-monthly paliperidone LAI.)</i>	Y / N
3. <b>Has the patient been clinically stabilised on Paliperidone 1-monthly LAI for at least 4 months (including the 4 months up to the date of this form)?</b> <i>(Patients who are adequately treated with 1-monthly paliperidone LAI (preferably for four months or more) and do not require dose adjustment may be switched to TREVICTA.)</i>	Y / N
4. <b>Did the patient comply with the Paliperidone 1-monthly injections?</b>	Y / N
5. <b>Did the patient tolerate Paliperidone 1-monthly LAI?</b> <i>(patients who are not tolerating paliperidone 1-monthly LAI should not be transferred to 3-monthly LAI.)</i>	Y / N
<b>Please provide details of your reasons for wishing to use Paliperidone 3-monthly LAI in this patient:</b>	

<b>Consultant Name:</b>	<b>Signature:</b>
<b>Date:</b>	<b>Contact Tel:</b>

**Return to Pharmacist for clinical ratification**

<b>Pharmacist name:</b>	<b>Signature:</b>	<b>Date:</b>
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## Switching from Quetiapine XL to Quetiapine IR

### Advice for Health Professionals

The following advice has been developed to aid clinicians switch patients from quetiapine extended release (XL) to quetiapine immediate release (IR).

Switching from XL to IR is recommended across the health economy to maximize the cost savings available. Switching however, is **NOT** mandatory and clinicians are reminded to consider individual patient circumstances before attempting a switch as remaining on quetiapine XL may be in the best clinical interests of some patients. There is little published evidence to guide clinicians on the best method of switching between quetiapine XL and quetiapine IR tablets. Any switch should be fully discussed with the individual patient and carer, combined with increased monitoring for adverse events.

- In general a straight swap from once daily XL to twice daily IR is appropriate<sup>1</sup> but may be associated with a slightly higher risk of sedation and postural hypotension following the switch.
- If sedation and postural hypotension are a concern clinicians may wish to consider giving a larger dose in the evening (see table 1).
- Although other pharmacokinetic parameters are similar the peak plasma concentration differ; quetiapine XL = 5-6hours vs. IR = 1 hour.
- For details comparison between Quetiapine XL vs. IR clinicians are encouraged to visit the relevant SPC

**Table1: Switching between quetiapine XL and IR. Suggested dosing changes**

Current daily Dose of XL formulation	Dosing Options (quetiapine IR)	
	For those who are tolerating quetiapine well and <b>do not</b> have compliance concerns	For those who are (or are at <b>risk</b> of) experiencing sedation or postural hypotension following the switch*
Quetiapine XL 100mg OD	Quetiapine 50mg BD	Quetiapine 25mg OM, 75mg ON
Quetiapine XL 200mg OD	Quetiapine 100mg BD	Quetiapine 50mg OM, 150mg ON
Quetiapine XL 300mg OD	Quetiapine 150mg BD	Quetiapine 100mg OM, 200mg ON
Quetiapine XL 400mg OD	Quetiapine 200mg BD	Quetiapine 150mg OM, 250mg ON
Quetiapine XL 600mg OD	Quetiapine 300mg BD	Quetiapine 200mg OM, 400mg ON
Quetiapine XL 800mg OD	Quetiapine 400mg BD	Quetiapine 300mg OM, 500mg ON

\*Those at increased risk of experiencing sedation or postural hypotension following the switch to quetiapine IR may include: the elderly, those with learning disabilities, adolescents, concurrent cardiac medication, and/or concurrent CNS depressants.

**Table 2: Current licensed indications<sup>2</sup> (see current BNF for more information)**

Formulation	Current manufacturer license	Number of daily doses
Quetiapine <b>XL</b>	<ul style="list-style-type: none"><li>• Schizophrenia including prevention.</li><li>• Mania or depression in bipolar disorder</li><li>• Prevention of relapse in bipolar disorder</li><li>• Add on treatment (to an antidepressant) in major depressive episodes.</li></ul>	Once daily
Quetiapine <b>IR</b>	<ul style="list-style-type: none"><li>• Schizophrenia including prevention</li><li>• Mania in bipolar disorder</li><li>• Prevention of relapse in bipolar disorder</li></ul>	Twice daily
	<ul style="list-style-type: none"><li>• Depression in bipolar disorder</li></ul>	Once daily

\*Although unlicensed in schizophrenia as a once daily preparation there are 3 small, short term studies supporting quetiapine IR once daily and this is occasionally done in practice<sup>3,4,5</sup>

### **Please contact pharmacy for further information**

#### **Reference**

1. Figueroa C et al (2009) Pharmacokinetic profiles of extended release quetiapine fumarate compared with quetiapine immediate release. *Progress in Neuro-Psychopharmacology and Biological Psychiatry* 33: 199-204.
2. Seroquel (Quetiapine) Summary of Product Characteristics last updated on the eMC: Feb 2012. Astra Zeneca. Electronic Medicines Compendium: <http://emc.medicines.org.uk/>
3. Chengappa et al (2003) A random-assignment, double-blind, clinical trial of once vs twice daily administration of quetiapine fumarate in patients with schizophrenia or schizoaffective disorder: A pilot study. *Can J Psychiatry*; 48: 187-194
4. Ohlsen et al (2004) Clinical response after switching from twice to once daily quetiapine in first episode schizophrenic patients. *Schizophrenia research*:. 67(1Suppl S): 169-70, Abs 336B
5. Tauscher-Wisniewski et al (2002) Quetiapine: an effective antipsychotic in first episode schizophrenia despite only transiently high dopamine 2 receptor blockade. *J Clin Psychiatry*: 63; 992-997

**Olanzapine Long Acting Injection (Zypadhera®)  
Named Patient Request Form**

Patient name		NHS No.	
DOB		Ward	
Diagnosis			
Consultant name			
Reason for prescribing olanzapine LAI			
Other information to support this request: e.g. record of admissions over last 2 years, identified adherence concerns.			

**Before this request can be approved the following criteria must be met and confirmed:**

**(Requesting consultant to initial boxes to confirm)**

1. The patient has successfully responded to oral olanzapine treatment and has been stabilised during acute treatment.
2. The patient has been assessed as having significant adherence problems with oral olanzapine therapy that may compromise on-going therapeutic benefits.
3. Long term arrangements have been made, (and agreed with the patient), for every injection to be administered in healthcare premises and for a doctor or nurse to be available to observe the patient on site for a minimum of three hours after every injection.
4. All nurses and doctors who will be administering the injection have undergone, or will be undergoing, specific training on product administration.
5. All nurses and doctors who will be providing the three hour post-injection observation of the patient have undergone, or will be undergoing, specific training on the identification and management of post-injection syndrome.

**Supporting signatures must be completed overleaf before this request can be processed.**

### **Confirmatory / Supporting signatures**

I confirm the information provided overleaf, that appropriate training and long-term monitoring arrangements are in place, and that olanzapine long-acting injection will only be used in accordance with Trust guidance and within the terms of the Product Licence.

#### **Initiating Consultant**

Name: _____ Signature: _____ Date: _____
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This application for use of long-acting olanzapine injection is supported by the undersigned who confirm that training and long-term monitoring requirements have been agreed and appropriately addressed.

#### **Clinical Pharmacist (Community MH&LD Lead)**

Name: _____ Signature: _____ Date: _____
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#### **Consultant taking long-term responsibility (if not initiating)**

Name: _____ Signature: _____ Date: _____
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#### **Manager of community-based team responsible for patient's treatment after discharge from ward**

Name: _____ Signature: _____ Date: _____
<b>Healthcare premises where olanzapine LAI will be administered/ monitored after discharge from ward:</b>

**If olanzapine LAI will be administered/ monitored on ward after discharge, ward manager to sign below:**

Name: _____ Signature: _____ Date: _____
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#### **Care co-ordinator**

Name: _____ Signature: _____ Date: _____
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#### **Chair of MMG**

Name: _____ Signature: _____ Date: _____
--

This form is to be completed and sent to the MMG Chair prior to commencing treatment. If approved, a signed copy to be returned to the ward to be filed in the patient's healthcare record and sent to the relevant pharmacy team.