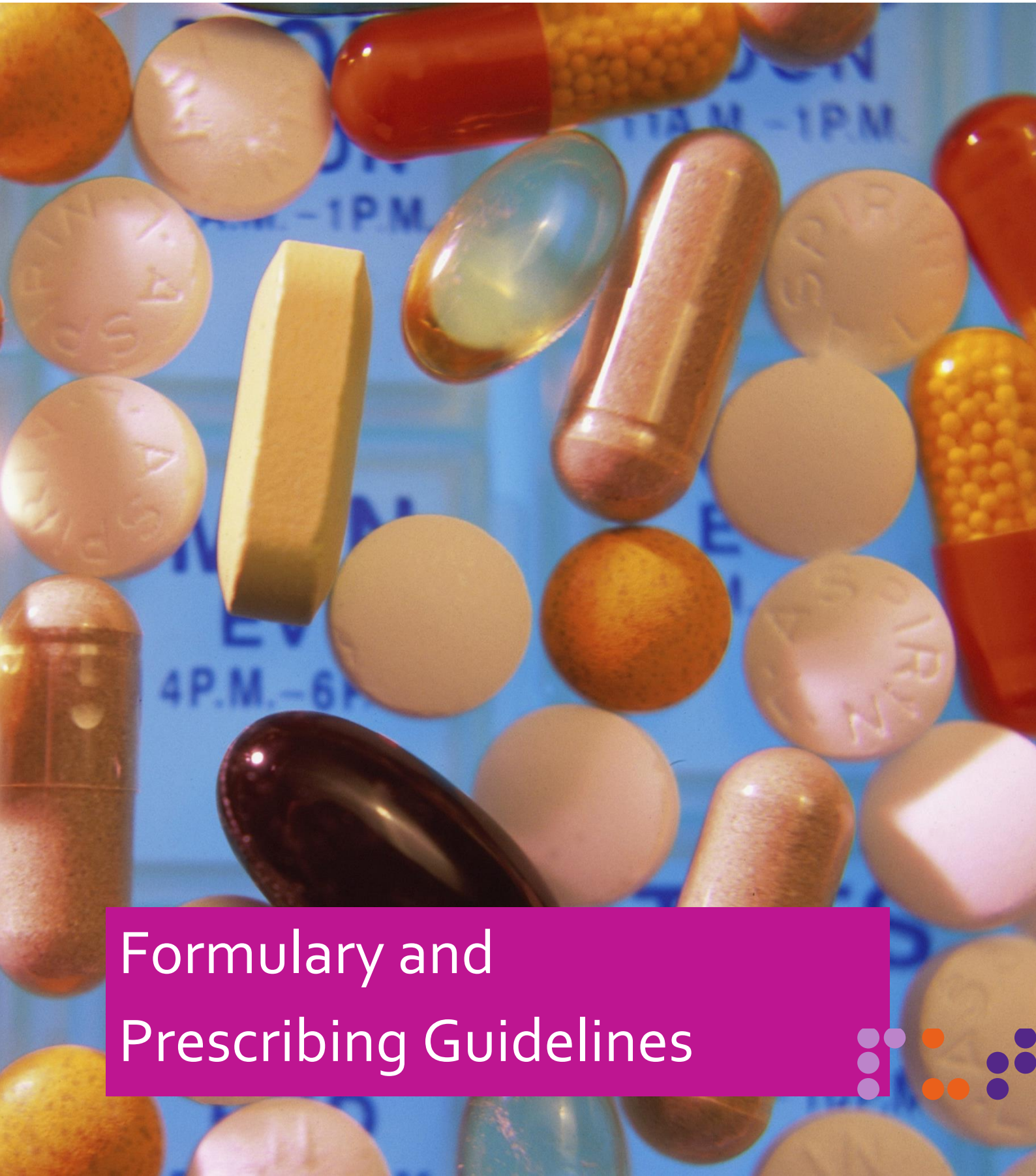
Essex Partnership University
NHS Foundation Trust

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. Due to evidence of reduced relapse and improved long term outcomes consider early prescription of long acting antipsychotic injections (depots).

'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.

All patients prescribed antipsychotics should have an annual review with a prescriber.

Toxicity and antipsychotics

Blood level monitoring of clozapine is advised[12] 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) however the clinical relevance of these is uncertain and routine monitoring is not advised.

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[1]	Formulation[2]	Comments
Typical Antipsychotics (First Generation Antipsychotics (FGA))		
Haloperidol	Tabs 1.5mg, 5mg, 10mg, Liquid 2mg/ml, 5mg/5ml 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[1]	Formulation[2]	Comments
Atypical Antipsychotics (Second Generations Antipsychotics (SGA))		
Risperidone	**Tabs 0.25mg, 0.5mg, 1mg, 2mg, 3mg, 4mg, 6mg** Liquid 1mg/ml Orodispersible tablet s 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 Injection 7.5mg/ml (immediate release)	
Clozapine	Tabs 25mg, 100mg	(**Consultant initiation only**)
Lurasidone	**Tabs 18.5mg, 37mg, 74mg**	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.
Olanzapine	**Tabs 2.5mg, 5mg, 7.5mg, 10mg, 15mg, 20mg** 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

Drug[1]	Formulation[2]	Comments
Quetiapine	**Tabs 25mg,100mg, 150mg, 200mg, 300mg** XL tabs 50mg, 200mg, 300mg, 400mg.	Patients should be discharged on standard release
Depot Injections		
Flupentixol decanoate	Injection 20mg/ml, 40mg/2ml, 50mg/0.5ml, 100mg/ml, 200mg/ml	
Fluphenazine decanoate (unlicensed)	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)	
Zuclopenthixol decanoate	Injection 200mg/ml, 500mg/ml	
Paliperidone	Paliperidone (monthly) 50mg, 100mg, 150mg PFS	
	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. Consultant initiation Initiation form to be completed and sent to pharmacy

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/ICBs that suitable service users should be transferred to standard release formulations as highlighted in Appendix 9.

Clozapine orodispersible tablets and liquid are non-formulary and can only be used if approved via the non-formulary process

Clozapine intramuscular injection is unlicensed and non-formulary and can only be used if approved via the non-formulary process

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 druq 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 ≥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 ≥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.

Aripiprazole 2-monthly Long-Acting Injection (ABILIFY MAINTENA®) 960mg or 720mg is available for the maintenance treatment of schizophrenia in patients currently stabilised with oral aripiprazole or clinically stable on the 1-monthly aripiprazole long acting injection. It is non-formulary and can only be used if approved via the non-formulary process.

2.3 NICE Clinical Guidelines

NICE CG178, Feb 2014. Schizophrenia in ADULTS[9]

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:

1. The patient has a specific cardiovascular risk (including elevated BP), or an established personal history of cardiovascular disease;
2. the service user is being admitted as an inpatient
3. 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. Doses above the maximum effective doses (which may be considerably lower than the maximum licensed dose) for individual antipsychotics should only be exceeded after an adequate trial and where the patient is tolerating the antipsychotic well. **Record (with justification)** the use of an unlicensed dosage(s) range outside that specified in the BNF/SPC (See CLP13 SOP 4 – Prescribing antipsychotic medication above recommended maximum daily doses).

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 an effectivedose 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[8]

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[9] (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[9] in managing 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[11]

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:

1. an antipsychotic, for example aripiprazole for schizophrenia and related psychoses and/or

2. a mood stabiliser for psychosis with significant affective symptoms and/or

3. 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 maximum effective doses, 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)[5]

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 itis less thorough than the LUNSERS. The GASS-C is a specifically adapted version of the GASS for use in patients prescribed clozapine. Additional tools such as the Abnormal Involuntary Movement Scale (AIMS), or the Simpson Angus Scale may be necessary if there is evidence of akathisia or 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 or a LUNSERS if on a Long Acting Injection (LAI) 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 or the medicine switched to alleviate side effects, it is important to recognise that the plasma-drug concentration may not fall for some time after reducing the dose or stopping. 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). The Choice and Medication Website provides visual aids and a range of leaflets to help patients chose between medication including when looking at clozapine or LAIs as options.

Where more than one drug is appropriate, and the patient has no preference, an antipsychotic of low acquisition cost should be chosen.

The table below compares common side effects however the list is not exhaustive. 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, 14th 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	++	+	+++	+	+	+	+++
Haloperidol	+	+/-	+++	+	+	+	+++
Lurasidone	-	-	+	-	+	-	-
Olanzapine	+	+++	+/-	+	++	+++	+
Paliperidone	+	+	+	++	+	++	+++
Perphenazine	+	+/-	+++	+	+	+	+++
Quetiapine	+	++	--	++	++	++	-
Risperidone	+	+	+	++	+	++	+++
Sulpiride	-	+	+	--	-	+	+++
Trifluoperazine	+/-	+/-	+++	+	+	+	+++
Zuclopenthixol	++	+	++	+	++	++	+++

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

2.4 Physical Health Monitoring of Adults taking Antipsychotics[4]

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)[1]

The prescribing of high dose antipsychotics occurs in two ways:

1. A single antipsychotic (including PRN, and by all routes) prescribed at a dose in excess of the maximum BNF recommended dose

2. 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%.

Whilst not HDT the prescription of two regular antipsychotics is also associated with increased risks and the principles of HDT should be followed.

High dose antipsychotic therapy should be prescribed following the guidance in CLP13 SOP04 using the monitoring tool in that 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[4]**	**Range of values[4]**	**Maximum dose[2]**
FGAs – oral			
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
SGAs – oral			
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)
Depot			
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 in may prove effective[1]. 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.

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) and often achieve higher plasma levels when prescribed the same dose
- 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[1] (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 reach steady-state take effect – and ideally should not be made more than once weekly for oral antipsychotics. **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[1].

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[1].(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. It is also licensed in the treatment of psychosis associated with Parkinson's disease. Currently, all patients must be commenced on clozapine as inpatients however re-titrations can take place in an inpatient or community (Home First) setting.

Use of clozapine for any other indication would be considered off-label and should follow the process required with the clozapine monitoring service. The patient and family/carer where appropriate should be informed of the off-label use and rational for use within their specific condition and this should be documented in the patient's clinical notes.

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, diabetes and hyperlipidaemia
- Night-time hypersalivation 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; www.ztas.co.uk, 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 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.

A completed clozapine initiation checklist (appendix 2) must be completed before initiation

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 Use of Intramuscular Clozapine

Intramuscular (IM) clozapine 25mg/ml is an unlicensed product made in the Netherlands by Broacacef and imported by Durbin PLC which at present is not approved for use within EPUT but has been used to support titration or re-titration of clozapine in patients who are currently refusing oral clozapine. Before applying for approval of non-formulary use the following criteria must be met

1. Patient must be an adult aged over 18 years who is eligible for clozapine treatment
2. They must be under a treatment section of the Mental Health Act and lack capacity to consent and treatment with intramuscular clozapine is in their best interest
3. They must be refusing oral clozapine despite attempts and support to administer medicines orally
4. If the patient is under consent to treatment legislation a SOAD must be requested as soon as possible however intramuscular clozapine can be administered under a Section 62 whilst awaiting SOAD approval

5. The patient must be Registered with a clozapine monitoring system as per 2.6.5

Before administering each injection, the patient should always be offered clozapine orally. If they accept oral clozapine, IM clozapine should not be administered. However, if they continue to refuse oral, then IM clozapine can be administered. Under no circumstances should the patient be administered both IM clozapine and oral clozapine on the same day. NB: the oral bioavailability is approximately half that of the IM injection. For example, 100mg of oral clozapine is approximately equivalent to 50mg of IM clozapine. Nursing staff must clearly record dose and route of administration on the clozapine IM titration chart (appendix 4c).

Clozapine injection should be used for the shortest duration possible with the aim to switch to oral. Patient must be switched to oral clozapine prior to discharge from the ward. In general, the injection should be used for no longer than two weeks at initiation stage. The need for ongoing intramuscular treatment must be reviewed regularly by the MDT.

In exceptional cases, the injection may be used for longer than two weeks if deemed appropriate by the medicines management group.

Full blood count and physical health monitoring is done in the same was as for oral clozapine (see below)

2.6.7 Routine Blood Tests (full blood count)

The routine blood test required when taking clozapine is a **full blood count (FBC)**. Tests are normally taken weekly for the first 18 weeks of treatment, fortnightly for the next 34 weeks, then every 4 weeks after one year but tests may be taken more frequently if advised by the clozapine monitoring service. 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 and document the reason for requesting an assay in the patients' medical record. Monitoring blood clozapine levels for **toxicity** is now advised[12] in certain clinical situations such as when:

- a patient stops smoking or switches to an e-cigarette

- concomitant medicines that may interact to increase blood clozapine levels are started

- a patient has pneumonia or other serious infection

- poor (reduced) clozapine metabolism is suspected

- toxicity is suspected

Assays can only be analysed at the appropriate designated laboratory.

- The dose should be adjusted to give plasma clozapine levels in the range 350 – 600 micrograms per litre although some patients may require higher or lower levels for optimum response. See table 1 below for further guidance.

- Seizure activity may be more frequent if plasma clozapine levels rise above 800 micrograms per litre and prophylactic antiepileptic cover should be considered in patients for whom a dose reduction is not appropriate. **Valproate should not be used as a prophylactic antiepileptic**. .

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 the relevant blood test kit plus patient barcode labels and post to ASI labs (Essex) or DMS yellow plasma (Bedfordshire & Luton). Forms for ASI are available at: FORMS (asilab.co.uk). It can take up to 5 working days to obtain the result
    - 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

  If patients have been newly initiated on clozapine, plasma levels should be taken once the patient reaches a maintenance dose or a dose off 300mg per day, whichever is lower. When a clozapine assay level is received, the following steps should be taken:

  - Document the result in the patient's medical record
  - Document any actions required including:
    - Level within range – no action required
    - Level low or high – actions taken
    - Discussion with other professionals such as the patients' consultant

  Clozapine assay results are presented with both clozapine and norclozapine levels. The importance of norclozapine levels is not established but clozapine/norclozapine ratio can be useful in order to establish recent compliance, saturation, change in smoking status or ultra-rapid metabolism.

  The following table can be used as a guide for suggested actions following receipt of clozapine levels.

Table 1

Trough clozapine (mg/l)	Clinical response	Suggested action
< 0.35	Good	Repeat at six months, then annually unless response deteriorates or side effects become troublesome
	Poor or incomplete	Increase dose cautiously, aiming for a level between 0.35 and 0.5mg/l. (Note – doses above 450mg per day have increased risk of side effects such as seizures)
0.35 to 0.60	Good	Repeat at six months, then annually unless response deteriorates or side effects become troublesome. If side effects persist or are serious, consider cautious dose reduction of 25mg/week but note there may be a possible loss of response
	Poor or incomplete	Consider augmentation of clozapine.
0.61 to 0.99	Good with no clinical features of toxicity	Slowly reduce dose (e.g. 25mg in week 1, then 25mg in week 2 and then recheck level) to get within 0.35-0.5mg/l. Consider augmentation of clozapine. Consider use of prophylactic anticonvulsant if level above 0.6mg/l. Recheck level after one week on new dose and 3 monthly thereafter
	Poor, incomplete or reduced and/or with clinical features of toxicity	Consider a cautious dose reduction to bring the clozapine level to below 0.6 mg/l. Monitor the patients mental state and repeat assay after one week on the new dose.
>1.0	Any	Review urgently. Check for clinical signs of toxicity e.g. severe sedation, falls, seizures. Withhold clozapine for 24 hours and reintroduce at a lower dose (e.g. 25% lower). Add anticonvulsant, reduce clozapine dose to reduce level below 1mg/l and consider reducing further down to 0.6mg/l. Consider augmenting clozapine. Recheck level again after 3 months once in range.

2.6.8.1 Additional considerations when reviewing clozapine plasma levels

Please note that clozapine assay levels should not be viewed in isolation. The following points may need to be considered:

- A review of side effects to clozapine such as tachycardia, borderline or high QTc interval, constipation, seizures or pre-cursors of seizures such as myoclonic jerks

- A consultant review following raised clozapine levels (see table above)

- An urgent referral to cardiologist where the patient has ECG changes from baseline or persistent tachycardia (see section below on tachycardia)

- An urgent referral to a neurologist if there are signs of seizures or

- An urgent abdominal assessment if rising levels are associated with signs of constipation.

- Any trend in levels particularly where they are not associated with dose changes or do not follow doses changes even where these levels are not out of the normal range. This suggests that something else may be altering the metabolism of clozapine and more frequent monitoring of clozapine is advised.

2.6.9 Medication Supply to community clozapine clinics

Clozapine for patients having blood test monitoring undertaken using a point of care testing machine (Pochi) is dispensed by the pharmacy and delivered in advance of clinic dates. Medication supplied should be quarantined and released after obtaining a valid blood result (green and amber) using the Pochi. Amber results should be followed up as stated above (2.6.6). Where patients are unable to access the Pochi machine, a valid blood test will be required prior to the release of clozapine from the pharmacy.

Supply should be crosschecked by clozapine clinic staff against prescription before handing over to patient. Every attempt should be made to avoid 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 FBC 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 can occur in a community or inpatient environment depending on the risk of the individual patient (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 Dose 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 Changes in Clozapine monitoring frequency in Outpatient Clinics

The Clozapine monitoring service will alert the clozapine clinic when a patient has a change in their monitoring frequency. If a change in the supply quantity is required, a new prescription should be written and scanned to the Pharmacy at Chelford Court. This should be facilitated by clozapine clinic staff.

2.6.19 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.

2.6.20 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, the following procedure should be followed:

- a clozapine assay should be conducted as soon as possible in order to obtain a baseline.
- Reduce the dose by 25% over one week once a patient stops smoking, then recheck the level after 1 week on the new dose, adjusting to clinical response. Initiate smoking cessation therapy if required.
- Where it is discovered that the patient has stopped smoking, decrease the dose of clozapine by 25% and check the clozapine level after 1 to 2 weeks

When a patient starts smoking, levels should be monitored as per the advice the advice when stopping smoking and doses should be adjusted according to plasma levels in order to ensure the level does not become sub-therapeutic.

assays should be repeated regularly until the plasma clozapine level has stabilised at the desired level.

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 1)

- The patients GP and practice manager should be informed of the initiation of clozapine so that it can be added to the patient's primary care record. See appendix 3.

- 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 4a-c).

Consultant's Checklist see appendix 2:

1. Discuss with patient/family/carers:
    - Realistic expectations of treatment including time frames
    - How to recognise and manage adverse reactions and side effects of clozapine (tiredness; constipation, weight gain, dizziness; postural hypotension; hypersalivation; raised temperature/cough/signs of infection; tachycardia; fitting)
    - What to do if adverse events occur
    - Monitoring requirements and lifestyle advice
    - The importance of adherence and not to stop taking clozapine suddenly without medical advice
    - Smoking and clozapine interaction
    - The use of prophylactic laxatives
    - Off label use (where applicable)
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 1)

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 4a). Reasons for variation from this regimen should be documented in the medical notes

Clozapine levels are lower in males, smokers and younger adults and therefore higher maintenance doses are often required. Clozapine is metabolised by cytochrome P450 enzymes and will be metabolised differently in fast or slow metabolisers and if the expected effect is not achieved then a plasma level should be used to guide dose adjustments.

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 4a-c – Clozapine Initiation Prescription Charts.

Monitoring in the early dose-titration phase (see Appendix 4a).

Blood pressure (BP), temperature and pulse.

- For days 1-7 monitor, BP, temperature and pulse before the first dose and at 30 mins and 1 hour afterwards.

- Thereafter, the patient should be seen at least once a day for BP, temperature and pulse monitoring.

- Appendix 5 should be used for record keeping.
- Standing and supine BP should be monitored daily for three weeks for patients with Parkinson's Disease.

o Continue daily monitoring for 2 weeks and at least until completion of the titration. Thereafter monitor at time of blood testing or when clinically indicated.

Other monitoring

o Side effects should be monitored and documented after every dose

o A stool chart should be in place and patients should be asked directly about changes in bowel habits. (see adverse effects below)

o Weight, lipids, plasma glucose, LFTs and cardiac function should be monitored at baseline and then regularly throughout treatment. (appendix 1)

When to refer

o 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 **systolic BP below 100 mmHg** and /or **diastolic below 60 mmHG**
- **If** patient is clearly **over-sedated**
- If any warning signs of **constipation** occur (see below)
- **If** any other **adverse effect is intolerable**.

Do not administer clozapine if these are pre-treatment observations

Additional monitoring requirements after the first month (see Appendix 1**)**

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

2.6.21 Clozapine and Constipation

o **Constipation** is a very common but potentially serious adverse effect which can lead to paralytic ileus and even death. Constipation can increase clozapine levels which can further worsen constipation, consider investigating plasma clozapine levels particularly in chronic or difficult to manage constipation.

o Constipation should be managed prior to starting clozapine, asked about routinely and proactively managed if signs and symptoms of constipation occur.

- Patients with any warning signs should be urgently reviewed to rule out intestinal obstruction. Patients in the community should be referred urgently to Accident and Emergency services

    1. Medium to severe abdominal pain or discomfort lasting over an hour
    2. Swollen or distended stomach (also known as 'clozapine belly')
    3. Overflow diarrhoea (particularly if there is blood in the stools)
    4. Sickness or vomiting (particularly if it smells of stool)
    5. Absent bowel sounds
    6. Symptoms of sepsis

    If there are no warning signs or concerns about potential faecal impaction, treat with

    - Stimulant laxatives, (e.g. senna or bisacodyl) plus a stool softener (e.g. docusate)
    - Osmotic laxatives (e.g. lactulose or macrogols) can be added if needed however it is important to ensure adequate fluid intake if prescribing osmotic laxatives.
    - Ensure a stool chart is in use and review regularly
    - Optimise treatment with the initial laxatives before adding in further laxatives
    - Do not routinely use bulk forming laxatives e.g. ispaghula husk, as they can increase the risk of impaction if fluid intake isn't sufficient

- Prophylactic laxatives should be considered and their prescription discussed with all patients as there is evidence of benefit. Laxatives must be prescribed for patients with a history of constipation or with risk factors for developing constipation.

- Constipation can increase clozapine levels which in turn can worsen constipation, monitor any patient with constipation for other signs of high clozapine levels and consider taking a plasma level if any concerns (see section 2.6.8).

- For further information on management of clozapine induced constipation and patient information:

    7. Managing constipation in people taking clozapine – SPS - Specialist Pharmacy Service – The first stop for professional medicines advice
    8. Printable leaflets (choiceandmedication.org)

2.6.22 Clozapine re-challenge

Information pertaining to the re-introduction of clozapine after a 'red' result can be found in Appendix 7.

2.6.23 Community Clozapine Re-Initiation

Clozapine may be restarted in the community setting either in the patient's own home or a day care setting after a treatment break. The patient must have valid registration with CPMS and have all assessments completed as for inpatient initiation above.

For re-initiation a flexible titration schedule can be used based on tolerance and adverse effects experience with any previous clozapine titration. The first two days should be dosed as per the inpatient initiation (appendix 4a) however then can be adjusted based on the length of the treatment break and any prior clozapine titrations. Increases in daily doses should not exceed a maximum of 50mg per day. Pharmacy staff should be contacted for advice on any re-titrations. The titration schedule should be used and prescribed on the blank initiation chart (Appendix 4b).

Suitability for clozapine re-titration in the community should be agreed between the community team, home first team and a member of the senior pharmacy team. Patients who are unable to be managed in the community, have limited support at home, have previously needed extra monitoring during clozapine titration, have poorly tolerated clozapine or have uncontrolled or new physical health conditions would not normally be considered for titration in the community.

Once the decision to use community initiation has been made, a copy of the blank initiation chart (Appendix 4b) 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 and will also depend on the length of the treatment break. Observation monitoring is suggested as follows:

- Day 1 – 7 - pulse, temperature and lying/standing blood pressure pre-dose and 30 minutes and 1 hour post dose.

- Day 8 until completion of titration– pulse, temperature and lying/standing blood pressure at least once per day

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.

Please refer to the protocol for re-titration of clozapine in the community for further information.

2.6.24 Withholding treatment

If the patient appears to be heavily sedated, looks drowsy or experiencing any others side-effects i.e. flu like symptoms, the prescriber should be informed because the

clozapine dose may need to be reduced or withheld. Out of hours the on-call doctor should be contacted for advice.

If any of the following observations are recorded then a doctor needs to be called to review the patient. Do not administer clozapine if any of the following pre-treatment observations are present:

- Temperature of patient is ≥ 38˚C
- Pulse rate is ≥ 100 beats per minute
- Lying and standing blood pressure shows a postural drop of >30 mmHg
- Systolic BP below 100mmHg and /or diastolic below 60 mmHg,

Note that for some patients there may be an alteration in the thresholds for individual patients for administering clozapine or contacting a doctor and if these are in place they should be clearly documented and referred to by team caring for the patient.

If the patient collapses, experiences breathing problems or has a seizure an ambulance should be called immediately.

2.6.25 Adverse effects

Side Effect	Management
If patient has a **raised temperature, sore throat or other infection,** this may be a sign of a low white cell count caused by clozapine	The patients' responsible clinician should be informed straight away and the patient examined. A blood test should be taken immediately and analysed locally. If the blood result is satisfactory and the temperature is under 38.5°C, clozapine can be continued. If the temperature is over 38.5°C, consider withholding clozapine until the fever subsides. Paracetamol may be prescribed to treat the fever if the FBC is within range.
Blood dyscrasias - occur in 4 % patients. These can affect the patient's ability to fight infection. Some other drugs can cause blood dyscrasias, so should not be taken with clozapine e.g. carbamazepine or antipsychotics (particularly long lasting depots)	Blood to be routinely monitored by the relevant Patient Monitoring Service. Patient must stop clozapine immediately if they have a "**RED**" blood result.
Can cause **hypotension**	Clozapine has to be initiated gradually. Blood pressure both lying and standing should be monitored. Patient should be advised to stand up slowly to avoid associated dizziness.

Side Effect	Management
Can cause **constipation** (see section 2.6.21 for further information)	Encourage prophylactic use of laxative, advise on diet, fluid intake and exercise. Ensure that a bowel chart is in place at initiation and any pre-existing constipation is managed before clozapine is started Advise patient on the importance of reporting changes in bowel habits and seeking support immediately if any warning signs are seen Prescribe a stimulant plus stool softener (e.g. senna and docusate) as a prophylactic or if constipation develops, optimise doses of these before adding an additional laxative Avoid bulk laxatives as they can worsen impaction. A patient information leaflet is available https://www.choiceandmedication.org/eput/generate/handyfactsheetclozapineandconstipationuk.pdf
Sedation – the patient must be advised not to drive if affected (and not at all during initial titration)	Consider adjusting the dose so that a higher proportion of the dose is taken at bedtime, initial sedation may improve over time however if sedation is new or worsening consider taking a plasma level of clozapine.
Hypersalivation	Hyoscine hydrobromide at a dose of 150mcg – 300mcg up to three times daily can help (off-label use). These may cause drowsiness and constipation. Pirenzepine tablets (unlicensed medicine) and atropine eye drops used sublingually (off label use) are alternatives that may be used if hyoscine is ineffective or not tolerated. Medicines used to manage hypersalivation are highly anticholinergic which can worsen side effects such as constipation so monitor carefully and review treatments for hypersalivation at regular intervals There is a choice and medication leaflet for more information on medicines and non-pharmacological options https://www.choiceandmedication.org/eput/generate/handyfactsheethypersalivationuk.pdf
Weight gain	Counsel on the risk of weight gain and importance of diet and exercise on initiation. Ensure that weight is monitored in line with guidance in appendix 1 and refer to the prescriber if there are concerns around weight gain. A patient information leaflet is available https://www.choiceandmedication.org/eput/generate/handyfactsheetweightgainantipsychoticsuk.pdf

Side Effect	Management
Dry mouth	Sugar-free chewing gum, or citrus fruit or low calorie drinks may help. An artificial saliva mouth spray is available. Ensure that they are attending regular dental checks and have good dental hygiene. A choice and medication leaflet is available to support dental health https://www.choiceandmedication.org/eput/generate/handyfactsheetdentalhealthuk.pdf
Fast heart beat	Monitor pulse in line with appendix 1 and initiation guidance. Doctor must be informed if pulse >100bpm. See section below on tachycardia, myocarditis and cardiomyopathy
Headache	Paracetamol can be prescribed if no other physical cause is evident, ensure that there is no fever or other signs that could suggest agranulocytosis.
Neuroleptic Malignant Syndrome – symptoms include hyperthermia or fever, severe muscle rigidity, with two or more of: diaphoresis, dysphagia, tremor, incontinence, tachycardia, altered BP, altered consciousness, raised Creatinine Kinase level	Doctor must be called urgently to review patient and perform bloods including Creatinine Kinase levels immediately. If concerns that NMS is present seek advice from a general hospital and stop clozapine. Note NMS may present atypically in patients who are prescribed clozapine or other atypical antipsychotics where muscle rigidity and /or hyperthermia may not be present. NMS is a rare complication with all antipsychotics but is more frequently seen with older antipsychotics or where high doses are use.
*** Diabetes, Lipid changes and metabolic syndrome** Impaired glucose tolerance and/or development or exacerbation of diabetes mellitus. On very rare occasions, severe hyperglycaemia, sometimes leading to ketoacidosis/ hyperosmolar coma Metabolic syndrome is the group of	Check fasting plasma glucose and HbA_{1C} at baseline and then at 3 months and annually thereafter. Monitor more frequently in those with risk factors or existing diabetes. Note that in some patients the use of clozapine may be associated with an improvement in diabetic control as the patient's mental state improves. Monitor plasma lipids at baseline, at 3 months and then annually **Metabolic syndrome** is a RARE but important side-effect, hence has been included in this list to ensure its awareness and monitoring. A patient information leaflet is available https://www.choiceandmedication.org/eput/generate/handyfactsheetmetabolicsyndromeuk.pdf

Side Effect	Management
symptoms that include weight gain, diabetes, high blood pressure and altered lipid levels.	
Seizures	Risk of seizures is higher with clozapine than many other antipsychotics, patients with pre-existing epilepsy must be well controlled before starting clozapine and should be monitored for any change in seizure activity. If new seizures or activity such as myoclonic jerks occur the patient should be reviewed urgently. The risk of seizures is dose related and therefore a clozapine level is advised and where possible a reduction in the dose of clozapine. If prophylaxis is required for seizures valproate (including sodium valproate, and semi-sodium valproate) should not be prescribed and an alternative anticonvulsant such as lamotrigine should be considered.
Hypertension	Often occurs within the first 4 weeks and is transient, consider reducing the dose and slowing the titration If it persists follow hypertension guidelines to manage

2.6.26 QTc prolongation, tachycardia, myocarditis and cardiomyopathy

2.6.26.1 QTc prolongation

The QT interval broadly relates to the duration of cardiac repolarisation. Some antipsychotics are linked to prolongation of the cardiac QT interval, a risk factor for the ventricular arrhythmia torsade de pointes, which is often fatal. Overall risk is probably dose-related. Medicine interactions (involving enzyme inhibition) are important (See current BNF for details).

See Appendix 12 for risk factors for QT prolongation.

See table below for Management of QT prolongation in patients receiving antipsychotic medicines where other causes are not suspected or have been ruled out.

QTc	Action	Refer to cardiologist
<440msec (men) or <470msec (women)	None unless abnormal T-wave morphology	Consider if in doubt
>440msec (men) or >470msec (women), but <500msec	Consider referral to specialist to reduce dose or switching to a medicine of lower effect; repeat ECG	Consider referral if remains elevated or unable to reduce the dose or switch

QTc	Action	Refer to cardiologist
	If unable to reduce the dose or switch, monitor closely and seek cardiology advice	
>500msec	Repeat ECG. Stop suspected causative medicine(s) and refer to specialist to switch to a medicine of lower effect	Immediately – same day
Abnormal T-wave morphology	Review treatment. Refer to specialist to consider reducing dose or switching to a medicine of lower effect.	Immediately – same day
Correct electrolyte disturbances (potassium and magnesium) if present		

2.6.26.2 Tachycardia

Tachycardia is defined as a heart rate greater than 100 bpm. It occurs in 10-25% of clozapine-treated patients and is believed to be due to the anticholinergic effect of clozapine, although in some cases it may be a compensatory response to hypotension. It usually occurs in the first 4 weeks of treatment and in some patients it can persist beyond this time.

Guidelines suggest contacting prescriber if pulse >100 but in certain patients a different level may be advised and this should be clearly documented in the patients notes.

Additionally if the prescriber is aware of a pulse above 100 and has considered and or investigated possible causes, the threshold of notification may be adjusted. It is worth noting that a sustained tachycardia can in some instances cause cardiomyopathy.

Tachycardia is usually dose-related and often occurs when dose escalation is rapid. The lowest possible maintenance dose of clozapine should be used in order to minimise the incidence of tachycardia. If it occurs, reducing the dose of clozapine, if possible, is often effective. During a titration the dose could be reduced or stabilised for a few days before slowly increasing again. Decreasing smoking and caffeine intake should also be beneficial although changes in clozapine plasma levels as a result of this should be considered (see section on smoking).

Patients who develop tachycardia should be considered for an ECG in order to exclude other arrhythmias or cardiac abnormalities. Performing a clozapine plasma concentration should be considered in order to exclude excessive concentrations. Myocarditis should be considered (see below).

If clozapine-induced tachycardia does not improve following dose reduction then consultation with a physician or cardiologist is recommended. If other caused are ruled out (see below) and the tachycardia is prolonged (greater than 4 weeks) occasionally, a small dose of a cardioselective beta-blocker such as bisoprolol may be considered appropriate by the cardiologist. However, it is important to ensure there are no contraindications to a beta-blocker and that the patient's blood pressure is carefully monitored in the early days of the beta-blocker treatment.

2.6.26.3 Differentiating between benign tachycardia, myocarditis and cardiomyopathy

Myocarditis should be suspected if a patient develops persistent tachycardia at rest, palpitations, arrhythmias, chest pain, signs and symptoms of heart failure (unexplained fatigue, dyspnoea or tachypnoea), symptoms mimicking myocardial infarction, dysuria, GI symptoms or flu-like symptoms.

Sometimes a tachycardia may be the only sign of myocarditis

Cardiomyopathy should be suspected in any patient showing signs of heart failure which should provoke stopping the clozapine immediately and a cardiology referral. Presentation can vary with symptoms of palpitations, chest pain, syncope, sweating, decreased exercise capacity or breathing difficulties being seen and any of these symptoms should prompt review. Cardiomyopathy tends to present later (average onset around 9 months) however can present at any time.

Things to consider when trying to differentiate a benign tachycardia from a tachycardia associated with myocarditis (limited evidence to back this up):

1. Baseline resting pulse
2. A benign tachycardia usually starts around day 3. It is usually 10-20 bpm above baseline
3. The following are more likely to be associated with myocarditis and require further investigation
    - An earlier heart rate rise of 20-30 bpm is more concerning, and although probably still benign it warrants further investigation.
    - A sudden increase in pulse between day 10-21 of titration as this is when myocarditis incidence peaks
    - Persistently raised pulse and associated with fever
    - A tachycardia persisting for weeks
    - A tachycardia that does not improve on decreasing dose or stabilising dose of clozapine during titration. (Myocarditis is a hypersensitivity reaction thus not dose dependent)
4. If myocarditis is suspected, withhold clozapine. Take bloods for CRP and troponin and consult with a cardiologist ASAP.
5. If myocarditis is confirmed clozapine should be stopped and rechallenge is not normally appropriate. A clear entry should be made into the patients notes and it should be added as a serious adverse reaction to the patients chart and medical records.
6. If decision is made that tachycardia is benign; stabilise or reduce the dose to be administered, then consider a slower titration.

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 long acting injections)

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 RLA I 37.5 mg should be considered.

2.8 Paliperidone Long-Acting Injection

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, PLAI1 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 PLAI1 please see Appendix 8 . An initiation form is no longer required for initiation of paliperidone 1 monthly LAI.

2.8.2. Treatment

As it is not possible to give a test dose of PLAI1, patients must be prescribed oral risperidone for several days before PLAI1 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. **PLAI1 is to be administered monthly**.

If there is no significant improvement after six months of treatment with PLAI1, consideration should be given to withdrawing it.

2.8.3 Discontinuation

When discontinuing PLAI1, 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

PLAI1 packs must be kept at room temperature and not refrigerated. Packs must not be exposed to temperatures in excess of 30°C[6].

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 PLAI1 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 PLAI1 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 PLAI1 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 PLAI1 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®) and 6-monthly (BYANNLI®)

2.9.1 Indications

Paliperidone LAI 3-monthly (PLAI3) and Paliperidone LAI 6-monthly (PLAI6) are indicated for the maintenance treatment of schizophrenia in adult patients who are clinically stable on 1-monthly Paliperidone LAI for PLAI3 and PLAI6 or on PLAI3 if switching to PLAI6.

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 or Paliperidone LAI 6-monthly and those treated with one cycle of Paliperidone LAI 3-monthly may be switched to Paliperidone LAI 6-monthly.

For further information relating to patient selection and inclusion criteria for the use of PLAI3 and PLAI6, 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 (± 7 days) or 3-monthly. The dose should be based on the previous paliperidone LAI shown in the following table:

Paliperidone LAI 3-monthly doses and LAI 6-monthly doses for patients adequately treated with 1-monthly Paliperidone LAI		
1-monthly Paliperidone LAI dose	**Paliperidone 3-monthly LAI dose**	**Paliperidone 6-monthly LAI dose**
50 mg	175 mg	No Equivalent
75 mg	263 mg	
100 mg	350 mg	700mg
150 mg	525 mg	1000mg

Following the initial dose, Paliperidone LAI 3-monthly or LA1 6-monthly should be administered by intramuscular injection once every 3 or 6 months (± 2 weeks). If doses are missed, refer to detailed instructions in the SPC.

If needed, dose adjustment can be made every 3 months or 6 months in increments within the range in the table above 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 or LAI 6-monthly are to be used only after the patient has been adequately treated with 1-monthly or 3-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 PLAI3.

2.9.5 Storage

PLAI3 packs must be kept at room temperature and not refrigerated. Packs must not be exposed to temperatures in excess of 30°C [6].

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 long acting injections). An initiation form is no longer required before starting aripiprazole LAI.

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.

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[6]. 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[6].

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[6]

	Adjusted dose
Patients taking 400 mg of Abilify Maintena	
Strong CYP2D6 or strong CYP3A4 inhibitors	300 mg
Strong CYP2D6 and strong CYP3A4 inhibitors	200 mg
CYP3A4 inducers	Avoid use
Patients taking 300 mg of Abilify Maintena	
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.

2.12 Use of two long-acting antipsychotic injections concomitantly

Please see section 2.5 and CLP13 SOP04 for general guidance on the use of high dose or combined antipsychotic therapy.

The use of two LAIs together is outside of normal practice with very limited evidence, would be considered off-label use and should only be considered where all other options including clozapine have been exhausted.

Long acting injections remain in the system for extended periods therefore if there are any adverse effects it will take time for these to be removed from the body which can prolong any reactions that the patient experiences. The use of two antipsychotics together may also lead to additive adverse effects which may be more severe than with either antipsychotic used alone. Before considering the use of two LAIs together the patient should be trialled on each antipsychotic individually and on the combination of antipsychotics, usually as one LAI and one oral medicine, to ensure that they tolerate the combination.

Requests for two LAAIs must be made by the consultant psychiatrist, agreed with the MDT, with the community team for patients not treated in secure settings, and agreed with the Director of Pharmacy and the Chair of the MMG, using the form in appendix 11.

Monitoring should follow CLP13 SOP04 even if the combination of LAIs does not exceed 100% BNF maximum.

References

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3. NICE CG178 , March 2014. Psychosis and schizophrenia in adults: prevention and management Clinical guideline [CG178]

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11. NICE NG181. Rehabilitation for adults with complex psychosis. Published date: 19 August 2020. Accessed 16.9.2020.

Drug Safety Update volume 14, issue 1: August 2020: 8. Page 5, "Clozapine and other antipsychotics: monitoring blood concentrations for toxicity".

Appendix 1

Minimum Physical Health Monitoring recommendations for Adults (*Children and Adolescents)* taking Antipsychotics

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

Parameter	Baseline	1 month	3 months	6 months	9 months	12 months	Then…
Date							
Weight (BMI & waist size)		*See below					Annually
LFTs							Annually
Fasting plasma glucose							Annually
U&Es							Annually
Fasting blood lipids							Annually
FBC (clozapine see below)**							Annually
TFTs							Annually
Prolactin				*** See below			Annually
BP/pulse**							Annually
Side Effects***							Annually and after each dose change
ECG		Recommended pre-treatment and at dose increase for typical antipsychotics, clozapine, high dose treatment (>BNF maximum) and combination treatment with more than one antipsychotic					Annually

Blank (un-shaded) boxes indicate monitoring required
* Weight should be monitored weekly for the first 6 weeks and then at 3 months and 12 months
** There are specific requirements for FBC monitoring, with clozapine, please see section 2.6.7 for full information on FBC monitoring and appendix 5 for initial monitoring guidance. Check
*** Baseline prolactin should be offered to all patients starting antipsychotics however routine monitoring at 6 months is only recommended for patients on antipsychotics likely to elevate prolactin levels.
**** This is the minimum requirements for all antipsychotics however see SPC of individual drug for full guidance and appendix 5 for specific guidance on BP/ pulse monitoring during titration of clozapine
***** This should be done using an accredited rating scale, see section 2.3.1

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: NICE Guideline (CG178) Psychosis and schizophrenia in adults: prevention and management. Published 12 Feb 2014. Accessed online via https://www.nice.org.uk/Guidance/CG178 on 30.11.23

Appendix 2

Initiation of clozapine checklist

	YES	NO	SIGNATURE	COMMENTS
Does the patient have a diagnosis of treatment Resistant Schizophrenia?				
Has the patient had a trial of two antipsychotics for an appropriate time period?				NICE (2014) guidance states clozapine can only be commenced if Service User has had a trial of two different antipsychotics.
Will the patient be adherent to clozapine and the mandatory blood tests?				
Has a multidisciplinary team meeting been arranged with the patient? (The care coordinator and Trust pharmacist should be present at the meeting)				The service user needs to understand the risks and benefits of taking clozapine. The Service user should be given a patient information leaflet on clozapine?
Does the patient agree to initiating clozapine?				
Has the patient's General Practitioner been informed about the clozapine initiation?				See appendix 3
Is the patient's physical health stable for initiating clozapine?				
Have the following baseline tests been completed? U & E's including eGFR,				

	YES	NO	SIGNATURE	COMMENTS
Blood lipids (ideally fasting), BMI (weight/height), fasting blood glucose, LFT's , Blood pressure and ECG				
Has the patient had a consultation including the pros and cons of clozapine and the adverse effects including the monitoring involved and when to seek help				» Printable leaflets (choiceandmedication.org)
Is the patient registered with the Clozaril Patient monitoring service (CPMS)?				Please record the CPMS number here……
Has the appropriate prescription chart been completed and clozapine ordered from pharmacy				
Are any monitoring charts in place 1. Clozapine initiation monitoring record 2. Clozapine physical monitoring record 3. NEWS 4. Stool Chart (if required) 5. GASS-C				

Appendix 3

Clozapine letter to GP Practice

Date

GP Address 1

GP Address 2

GP Address 3

Pharmacy Department

Units E & F Chelford Court

37 Robjohns Road

Widford Industrial Estate

Chelmsford

Essex, CM1 3AG

Dear Doctor,

RE: patient name, NHS number, date of birth

Task for GP practice – Ensure that clozapine is added to the patient's record as a hospital only medicine

Whilst EPUT is responsible for the prescribing and supply of clozapine, please ensure your prescribing system shows that this patient is on clozapine so that this information is readily available to anyone during a consultation or on admission to hospital. If clozapine is not recorded on your prescribing system for this patient, normal safety alerts will not appear when a drug with a potentially significant interaction is co-prescribed with clozapine. When adding clozapine to a patient record, please ensure it is done so in a way that doesn't allow inadvertent dispensing by a community pharmacy. Some practices report difficulties adding drugs they do not prescribe to their prescribing systems. If your practice is having difficulties, please contact the ICB prescribing team for advice.

Important information about clozapine and potentially fatal side effects

The above patient is on clozapine (Clozaril®).

In addition to the adverse effects associated with other antipsychotics, serious (though relatively rare) risks of clozapine are:

4.0 Agranulocytosis

4.1 Clozapine has caused fatalities but the incidence has decreased with the institution of a strict prescribing protocol and rigorous regimen for blood tests

4.2 Refer any patient prescribed clozapine with unexplained sore throat, fever or signs of infection for an urgent Full Blood Count

5.0 Myocarditis and cardiomyopathy

5.1 Most often occurs in the first two months of clozapine treatment and has been associated with fatalities

6.0 Impairment of intestinal peristalsis

6.1 This effect can range from constipation, which is very common, to very rare intestinal obstruction, faecal impaction and paralytic ileus

6.2 Patients are asked to report constipation immediately and any constipation should be actively investigated and treated

6.3 Fatalities have been reported with clozapine due to intestinal obstruction

Clozapine and constipation

Clozapine has been associated with varying degrees of impairment of intestinal peristalsis which is sometimes overlooked. This effect can range from constipation, which is very common, to very rare intestinal obstruction, faecal impaction and paralytic ileus. (Clozapine is contraindicated in patients with paralytic ileus.)

All patients initiated on clozapine are asked to report constipation immediately before taking their next dose of clozapine and should be given information about appropriate diet and advised to seek help from their GP or pharmacist if they become constipated.

It is vital that constipation is recognised early and actively treated. If the patient presents to you with symptoms of constipation please ensure:

- An abdominal examination is performed to exclude intestinal obstruction.
- Where intestinal obstruction has been excluded, both a stimulant and stool-softening laxative should be started (for example senna and docusate). Bulk-forming laxatives are not effective in slow-transit constipation and therefore should be avoided.
- The mental health team are informed.
- Prescribing of any other medication that may cause constipation as an adverse effect is avoided (for example antimuscarinic/anticholinergic medicines, such as some antipsychotics, antidepressants and antiparkinsonian treatments), particularly in patients with a history of colonic disease or lower abdominal surgery and those aged 60 years and older.

Clozapine and interactions

Certain medicines are contra-indicated with the use of clozapine; a table of those more commonly prescribed can be found enclosed. The manufacturer's Summary of Product Characteristics (SPC) for Clozaril® should referred to at www.medicines.org.uk for a full list of cautions, contra-indications and interactions.

Concomitant use with drugs known to prolong the QT interval may increase the risk of ventricular arrhythmias, including Torsades de pointes, therefore concomitant use of these products is not recommended. Examples include certain antipsychotics (phenothiazines, pimozide and haloperidol) and certain tricyclic antidepressants (such as amitriptyline). This list is not exhaustive. Depot antipsychotics, carbamazepine and chemotherapy agents that can potentiate the risk of agranulocytosis are contraindicated with clozapine. Drugs such as SSRIs and tricyclic antidepressants can alter plasma clozapine levels

Clozapine and smoking

If the patient either starts smoking (i.e. cigarettes, cigars, rolled tobacco) or decides to stop smoking, please inform the mental health team. This also applies if the patient goes from smoking to vaping or smoking to NRT and vice versa. When smoking status changes, this can very significantly affect plasma levels of clozapine and clozapine plasma level monitoring may be needed to ascertain if any changes to the dose are required. Dose increases for smokers of up to 70% are sometimes needed, whilst the average patient who stops smoking needs to reduce their dose by at least one quarter to

avoid serious adverse effects developing. If it is considered that a clozapine assay (clozapine plasma level monitoring) is required, please contact the mental health team who will be able to organise this.

Yours sincerely,

Pharmacy Department

Enc. Summary of common interactions with clozapine

The most common drug interactions with clozapine

Drug	Interactions	Comments
Bone marrow suppressants (e.g. carbamazepine, chloramphenicol), sulphonamides (e.g. co-trimoxazole), pyrazolone analgesics (e.g. phenylbutazone), penicillamine, cytotoxic agents and long-acting depot injections of antipsychotics	Interact to increase the risk and/or severity of bone marrow suppression.	Clozapine **must not be used** concomitantly with other agents having a well-known potential to suppress bone marrow function.
Benzodiazepines	Concomitant use may increase risk of circulatory collapse, which may lead to cardiac and/or respiratory arrest.	Caution advised if using together. Respiratory depression and collapse more likely to occur at start of this combination or when clozapine is added to an established benzodiazepine regimen.
Anticholinergics	Clozapine potentiates action of these agents through additive anticholinergic activity.	Observe patients for anticholinergic side-effects, e.g. constipation, especially when using to help control hypersalivation.
Antihypertensives	Clozapine can potentiate hypotensive effects of these agents due to sympathomimetic antagonistic effects.	Caution is advised. Patients should be advised of the risk of hypotension, especially during the period of initial dose titration.
Alcohol, MAOIs, CNS depressants, including narcotics and benzodiazepines	Enhanced central effects. Additive CNS depression and cognitive and motor performance interference when used in combination with these substances.	Caution is advised if clozapine is used concomitantly with other CNS active agents. Advise patients of the possible additive sedative effects and caution them not to drive or operate machinery.
Highly protein bound substances (e.g. warfarin and digoxin)	Clozapine may cause increase in plasma concentration of these substances due to displacement from plasma proteins.	Patients should be monitored for the occurrence of side effects associated with these substances, and doses of the protein bound substance adjusted, if necessary.

Drug	Interactions	Comments
Phenytoin	Addition of phenytoin to clozapine regimen may cause a decrease in the clozapine plasma concentrations.	If phenytoin must be used, the patient should be monitored closely for a worsening or recurrence of psychotic symptoms.
Lithium	Concomitant use can increase the risk of development of neuroleptic malignant syndrome (NMS).	Observe for signs and symptoms of NMS.
CYP1A2 inducing substances (e.g. omeprazole)	Concomitant use may decrease clozapine levels	Potential for reduced efficacy of clozapine should be considered.
CYP1A2 inhibiting substances (e.g. fluvoxamine, caffeine, ciprofloxacin)	Concomitant use may increase clozapine levels	Potential for increase in adverse effects. Care is also required upon cessation of concomitant CYP1A2 inhibiting medications as there will be a decrease in clozapine levels.

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

- This chart should only be used for patients starting treatment with clozapine in Inpatient units.
- 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.
- The CONSULTANT should sign this chart for the start of week 1. Subsequent prescriptions may be signed by any appropriate prescriber.
- The nurse administering the clozapine should sign in the "Given By" box beside each dose.
- 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.

Week 1		**Consultant's signature ..... Date ..... Print Name ..... Tel/Bleep.....**				
Day	**Total Daily Dose (mg)**	**Date**	**Morning Dose**	**Given By (nurse sign)**	**Evening Dose**	**Given By (nurse sign)**
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**	

Pharmacy	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 Inpatient Initiation Chart (page2)

Forename											Surname	
NHS No.											Ward/Unit	

Week 2		Prescriber's signature ..... Date ..... Print Name ..... Tel/Bleep.....				
Day	**Total Daily Dose (mg)**	**Date**	**Morning Dose**	**Given By (nurse sign)**	**Evening Dose**	**Given By (nurse sign)**
8	**125mg**		**Clozapine 50mg**		**Clozapine 75mg**	
9	**150mg**		**Clozapine 75mg**		**Clozapine 75mg**	
10	**175mg**		**Clozapine 75mg**		**Clozapine 100mg**	
11	**200mg**		**Clozapine 100mg**		**Clozapine 100mg**	
12	**225mg**		**Clozapine 100mg**		**Clozapine 125mg**	
13	**250mg**		**Clozapine 125mg**		**Clozapine 125mg**	
14	**275mg**		**Clozapine 125mg**		**Clozapine 150mg**	

Pharmacy	Week 2 20x25mg 9x100mg	Screened by ..... Date	Dispensed by ..... Date	Checked by ..... Date .....

BLOOD TESTS

Third blood sample: **Date sample should be taken: ..... (7 days after second blood sample)**

Date sample taken ..... Signature .....

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

Week 3 onwards: After initiation, prescribe maintenance dose of clozapine on the main drug chart. NB. Cross out unused prescription boxes on this drug chart.

Blank Clozapine 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

- This chart is for community or inpatient initiation or retitration of clozapine where an individualised titration is required
- The prescription for the first week should be signed by the consultant. Thereafter, prescriptions can be signed by an appropriate prescriber
- For community titrations should start on a Monday, with prescriptions and supply organised the previous week
- Administration/supply should be signed by the registered nurse in the "given by" box next to the dose
- Once the target maintenance dose is reached, clozapine should be prescribed on an inpatient chart or outpatient clozapine prescription
- Clozapine can only be given to patients registered with CPMS and with a 'green' blood result. Please document CPMS number and date of 1st green result below to confirm.

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.

Week 1		**Consultant's signature ..... Date ..... Print Name ..... Tel/Bleep.....**				
Day	**Total Daily Dose (mg)**	**Date**	**Morning Dose**	**Given By (nurse sign)**	**Evening Dose**	**Given By (nurse sign)**
1						
2						
3						
4						
5						
6						
7						

Pharmacy	Week 1 ……. 25mg ……. 100mg	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.....

Blank Clozapine Inpatient Initiation Chart (page2)

Forename											Surname	
NHS No.											Ward/Unit	

Week 2		**Prescriber's signature ..... Date ..... Print Name ..... Tel/Bleep.....**				
Day	**Total Daily Dose (mg)**	**Date**	**Morning Dose**	**Given By (nurse sign)**	**Evening Dose**	**Given By (nurse sign)**
8						
9						
10						
11						
12						
13						
14						

Pharmacy	Week 2 ……. 25mg ……. 100mg	Screened by ..... Date	Dispensed by ..... Date	Checked by ..... Date .....

Week 3		**Prescriber's signature ..... Date ..... Print Name ..... Tel/Bleep.....**				
Day	**Total Daily Dose (mg)**	**Date**	**Morning Dose**	**Given By (nurse sign)**	**Evening Dose**	**Given By (nurse sign)**
15						
16						
17						
18						
19						
20						
21						

Pharmacy	Week 3 ……. 25mg ……. 100mg	Screened by ..... Date	Dispensed by ..... Date	Checked by ..... Date .....

<u>BLOOD TESTS</u>

Third blood sample: **Date sample should be taken: ..... (7 days after second blood sample)**

Date sample taken ..... Signature .....

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

Week 4 onwards: After initiation, prescribe maintenance dose of clozapine on the main drug chart (inpatient or outpatient clozapine chart). <u>NB.</u> Cross out unused prescription boxes on this drug chart.

Intramuscular 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

- This chart should only be used for patients starting treatment with clozapine in Inpatient units who have been approved to use Intramuscular (IM) clozapine.
- IM clozapine is only given once a day therefore titration for patients who may require IM clozapine should be titrated using a once a day schedule. Intramuscular clozapine dose is given as half the oral clozapine dose
- 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.
- The CONSULTANT should sign this chart for the start of week 1. Subsequent prescriptions may be signed by any appropriate prescriber.
- Oral clozapine should always be offered before administering clozapine intramuscularly.
- The nurse administering the clozapine should sign in the "Given By" box beside each dose.
- 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.

Week 1		**Consultant's signature ..... Date ..... Print Name ..... Tel/Bleep.....**				
Day	**Clozapine oral Dose (mg)**	**Clozapine IM dose (mg)**	**Time Due**	**Route given**	**Given By (nurse sign)**	**Restraint required**
1	**12.5mg**	**6.25mg (0.25ml)**				
2	**25mg**	**12.5mg (0.5ml)**				
3	**50mg**	**25mg (1 ml)**				
4	**50mg**	**25mg (1 ml)**				
5	**75mg**	**37.5mg (1.5 ml)**				
6	**75mg**	**37.5mg (1.5 ml)**				
7	**100mg**	**50mg (2 ml)**				

Pharmacy		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.....

Intramuscular Clozapine Inpatient Initiation Chart (page2)

Forename											Surname	
NHS No.											Ward/Unit	

Week 2		**Consultant's signature ..... Date ..... Print Name ..... Tel/Bleep.....**				
Day	**Clozapine oral Dose (mg)**	**Clozapine IM dose (mg)**	**Time Due**	**Route given**	**Given By (nurse sign)**	**Restraint required**
8						
9						
10						
11						
12						
13						
14						

Pharmacy	Week 2	Screened by ..... Date	Dispensed by ..... Date	Checked by ..... Date .....

BLOOD TESTS

Third blood sample: **Date sample should be taken: ..... (7 days after second blood sample)**

Date sample taken ..... Signature .....

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

Week 3 onwards: After initiation, prescribe maintenance dose of clozapine on the main drug chart. NB. Cross out unused prescription boxes on this drug chart.

If clozapine is to be given intramuscularly from week three onwards further approval from the medicines management group is required

Appendix 5

Clozapine Initiation 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

Appendix 6

MANAGEMENT FOLLOWING A CLOZAPINE RED ALERT RESULT

INTRODUCTION

If a patient's WBC is less than 3.0 x 10^9/L and/ or the neutrophil count is less than 1.5 x 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
- Home First Teams (HFT) 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 x 10^9/L or the WBC falls to less than 2.0 x 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. The blank initiation chart (Appendix 3b) can be used to adjust re-titrations

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 x 10^9/L for these patients, hence a red alert for a patient with BEN is WBC <2.5 x 10^9/L and/ or neutrophils <1.0 x 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 the 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.

Appendix 7

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 12th 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.

Appendix 8

Guidelines for the Use of Long Acting Injections (Risperdal Consta® / Xeplion®/ Trevicta® / Byannli®) 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.

1. 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.
2. 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.
3. Risperidone, Paliperidone or Aripiprazole LAI are not indicated for Treatment Resistant Schizophrenia – such patients should always be considered for clozapine.
4. 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.
5. 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.
6. 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 LAI or paliperidone 3 monthly or 6 monthly LAIs, must complete the relevant initiation form.

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 and 6 monthly LAI (Paliperidone)

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

Essex Partnership University
NHS Foundation Trust

INITIATION OF RISPERIDONE (LAI)
(RISPERDAL CONSTA®

(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 long acting injections (as agreed by the Medicines Management Group in September 2023).

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.

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

• **Is the patient suffering from treatment resistant schizophrenia?** *(treatment resistant schizophrenia is not a licensed indication and clozapine should be considered)*	Y / N
• **Has a first generation antipsychotic (FGA) depot injection been tried prior to considering LAI?** *(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)*	Y / N
• **Did the patient respond well to FGA depot injections?**	Y / N
• **Did the patient experience intolerable side effects despite dose reduction?** *(patients who are responding well and not experiencing intolerable side effects of conventional depot injections should not be transferred to LAI)*	Y / N
Please provide details of your reasons for wishing to use Risperidone LAI in this patient:	

Consultant Name:	Signature:
Date:	Contact Tel:

Return to Pharmacist for clinical ratification

Pharmacist Name:	Signature:	Date:

Essex Partnership University
NHS Foundation Trust

INITIATION OF PALIPERIDONE 3-MONTHLY OR 6-Monthly LONG ACTING INJECTION (LAI) (TREVICTA® / BYANNLI®))

This authorisation form needs to be completed prior to initiating paliperidone 3-monthly or 6-monthly long acting injection (as agreed by the Medicines Management Group in September 2023).

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.

Patient's name:		**NHS Number:**	
Date of Birth:		**Ward / Team:**	
Name of LAI to be initiated (indicate)	**PALIPERIDONE 3-MONTHLY LAI (TREVICTA®)** **PALIPERIDONE 6-MONTHLY LAI (BYANNLI®)**		

• **Is this for the maintenance treatment of schizophrenia (not treatment resistant)?**	Y / N
• **Is the patient now clinically stable on Paliperidone 1-monthly LAI?** *(Paliperidone 3-monthly/ 6-monthly LAI is indicated for the maintenance treatment of schizophrenia in adult patients who are clinically stable on 1-monthly paliperidone LAI.)*	Y / N
• **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)?** *(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/BYANNLI.)*	Y / N
• **Did the patient comply with the Paliperidone 1-monthly injections?**	Y / N
• **Did the patient tolerate Paliperidone 1-monthly LAI?** *(patients who are not tolerating paliperidone 1-monthly LAI should not be transferred to 3-monthly/ 6-monthly LAI.)*	Y / N
Please provide details of your reasons for wishing to use Paliperidone 3-monthly/ 6 monthly LAI in this patient:	

Consultant Name:	Signature:
Date:	Contact Tel:

Return to Pharmacist for clinical ratification

Pharmacist name:	Signature:	Date:

Appendix 9

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[1] 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

	Dosing Options (quetiapine IR)	
Current daily Dose of XL formulation	For those who are tolerating quetiapine well and **do not** have compliance concerns	For those who are (or are at **risk** 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[2] (see current BNF for more information)

Formulation	Current manufacturer license	Number of daily doses
Quetiapine **XL**	• Schizophrenia including prevention. • Mania or depression in bipolar disorder • Prevention of relapse in bipolar disorder • Add on treatment (to an antidepressant) in major depressive episodes.	Once daily
Quetiapine **IR**	12. Schizophrenia including prevention 13. Mania in bipolar disorder 14. Prevention of relapse in bipolar disorder	Twice daily
	• Depression in bipolar disorder	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[3,4,5]

Please contact pharmacy for further information

Reference

1. Figueroa C et al (2009) Pharmacokinetic profiles of extended release queitiapine 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 pisode schizophrenia despite only transiently high dopamine 2 receptor blocade. J Clin Psychiatry: 63; 992-997

Appendix 10

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

Patient name		NHS No.	
DOB		Ward	
Diagnosis			

Consultant name			
Reason for prescribing olanzapine LAI			
Has olanzapine LAI been used previously? If yes what was the outcome and reason for stopping			
Please indicate if the following have been prescribed	Previously or currently prescribed		Outcome or reason for not prescribing
Clozapine	Yes	No	
Aripiprazole	Yes	No	
Flupentixol	Yes	No	
Haloperidol	Yes	No	
Risperidone	Yes	No	
Paliperidone	Yes	No	
Zuclopenthixol	Yes	No	
Other information to support this request: e.g. record of admissions over last 2 years, identified adherence concerns. **Include other medicines tried**			

Before this request can be approved the following criteria must be met and confirmed:
(Requesting consultant to initial boxes to confirm)

- The patient has successfully responded to oral olanzapine treatment and has been stabilised during acute treatment. ☐
- The patient has been assessed as having significant adherence problems with oral olanzapine therapy that may compromise on-going therapeutic benefits. ☐

- The patient is happy to continue olanzapine long acting injection in the community ☐

- 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. ☐

- All nurses and doctors who will be administering the injection have undergone, or will be undergoing, specific training on product administration. ☐

- 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: _____

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 (Lead Pharmacist or Deputy Chief Pharmacist)

Name: _____ Signature: _____ Date: _____

Consultant taking long-term responsibility (if not initiating)

Name: _____ Signature: _____ Date: _____

Manager of community-based team responsible for patient's treatment after discharge from ward

Name: _____ Signature: _____ Date: _____

Healthcare premises where olanzapine LAI will be administered/ monitored after discharge from ward:

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

Name: _____ Signature: _____ Date: _____

Care co-ordinator

Name: _____ Signature: _____ Date: _____

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.

Appendix 11

Use of Two Long Acting Antipsychotic Injections
Named Patient Request Form

Patient name		NHS No.	
DOB		Ward/ Team	
Diagnosis			

Consultant name		
What are the proposed antipsychotics and target doses		
Reason for prescribing two long acting injections		
Has clozapine been used previously? Please provide details of previous use or reasons for not initiating clozapine		
Please indicate if the following have been prescribed	Please circle if prescribed	Outcome or reason for not prescribing
Aripiprazole LAI	Oral LAI	
Flupentixol LAI	Oral LAI	
Haloperidol LAI	Oral LAI	
Risperidone LAI	Oral LAI	
Paliperidone LAI	Oral LAI	
Zucloenthixol LAI	Oral LAI	
Others		
	Oral LAI	
	Oral LAI	
	Oral LAI	
Have both the proposed LAIs been prescribed individually in the past		
Has the patient been prescribed the antipsychotics together (orally, or oral plus LAI)		
Is the use of two depots covered by the appropriate consent to treat form (T3/T2) where applicable		
Is the High Dose and Combined antipsychotic form completed		
Other information to support this request: e.g. record of admissions over last 2 years, identified adherence concerns.		

Evidence to support this specific combination	

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 been assessed as having significant adherence problems with oral therapy that may compromise on-going therapeutic benefits. ☐

2. The patient is happy to continue two long acting injection in the community ☐

3. If use includes olanzapine injection - please complete the following
    1. Long term arrangements have been made, (and agreed with the patient), for every injection to be administered in healthcare premises and for a doctor ornurse to be available to observe the patient on site for a minimum of three hours after every injection. ☐

    2. All nurses and doctors who will be administering the injection have undergone,or will be undergoing, specific training on product administration. ☐

    3. 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 two injections will be used in accordance with Trust guidance. I will provide follow up information if requested by the MMG on the outcome of the patient.

Initiating Consultant

Name: _____ Signature: _____ Date: _____

This application for use of two long-acting injections is supported by the undersigned who confirm that training and long-term monitoring requirements have been agreed and appropriately addressed.

Clinical Pharmacist (Lead Pharmacist or Deputy Chief Pharmacist)

Name: _____ Signature: _____ Date: _____

Consultant taking long-term responsibility (if not initiating)

Name: _____ Signature: _____ Date: _____

Manager of community-based team responsible for patient's treatment after discharge from ward

Name: _____ Signature: _____ Date: _____

If applicable: healthcare premises where olanzapine LAI will be administered/ monitored after discharge from ward:

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

Name: _____ Signature: _____ Date: _____

Care co-ordinator

Name: _____ Signature: _____ Date: _____

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.

Appendix 12

Risk factors for QT prolongation

Effects of antipsychotics on QTc interval		
High effect	A medicine/combination of medicines exceeding the 100% BNF limits	Extensive average QTc prolongation (usually > 20msec at normal clinical doses).
Moderate effect	Amisulpride Chlorpromazine Haloperidol Levomepromazine Quetiapine Ziprasidone	Observed to prolong QTc by > 10msec on average when given at normal clinical doses or where ECG monitoring is officially recommended in some circumstances.
Low effect	Clozapine Flupentixol Fluphenazine Perphenazine Prochloperazine Olanzapine Paliperidone Risperidone Sulpiride	Severe QTc prolongation has been reported only following overdose or where only small average increases (<10msec) has been observed at clinical doses.
No effect	Aripiprazole	QT prolongation has not been reported either at therapeutic doses or in overdose.
Unknown effect	Loxapine Pipothiazine Trifluoperazine Zuclopenthixol	
Non-psychotropics associated with QT prolongation		
Antibiotics	Erythromycin, clarithromycin, ampicillin, co-trimoxazole, pentamidine, some 4-quinolones	
Antimalarials	Chloroquine, mefloquine, quinine	
Antiarrthythmics	Quinidine, disopyramide, procainamide, sotolol, amiodarone, bretylium	
Others	Amantadine, cyclosporin, diphenhydramine, hydroxyzine, methadone, nicardipine, tamoxifen	
Physiological risk factors		
Cardiac	Long QT syndrome Bradycardia Ischaemic heart disease, Myocardial infarction Myocarditis Left ventricular hypertrophy	
Metabolic	Hypokaleamia Hypomagnesaemia Hypocalcaemia	
Others	Extreme physical exertion Stress or shock Anorexia nervosa Extremes of age Female gender	