

Clozapine Policy

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1. **Introduction**
	1. Clozapine is an atypical antipsychotic that is indicated in treatment-resistant schizophrenia or the management of psychosis during the course of Parkinson’s disease. Clozapine can rarely cause neutropenia and agranulocytosis, which has led to the MHRA mandating that the drug may only be used in combination with a strict blood test monitoring regime. Three brands of clozapine are currently used within ELFT; **Zaponex**, **Denzapine** and **Clozaril.** It is important that prescriptions clearly state which brand of clozapine is being prescribed as they each have their own separate monitoring service.
	2. These together with other aspects of clozapine’s adverse effect profile have led to it being a hospital only prescribed drug within many trusts including ELFT. Consequently its initiation and maintenance spans both inpatient and outpatient services. Treatment often involves many members of the ELFT MDT in addition to other healthcare providers including the service user’s GP.
	3. The Clozapine Clinics exist to ensure that the many statutory and clinical requirements for treatment with this drug are coordinated and undertaken whilst providing advice, support and consultancy to service users, their carers and all healthcare professionals involved in their care. For information on the operational elements of this clinic, please refer to the [Clozapine Clinic Standard Operating Procedure.](http://elftintranet/download/315b5eac-26b1-4002-8a6c-9bbb8db778ef/f/Clozapine_Clinic_Standard_Operating_Procedure_V50_May_2013.pdf)
2. **Aim of this Policy**
	1. To set out the requirements for the initiation, maintenance and monitoring of clozapine in inpatient and outpatient settings throughout ELFT.
3. **Inclusion and exclusion criteria for treatment with clozapine**

**3.1** **Inclusion Criteria**

3.11 Service users with a confirmed diagnosis of schizophrenia who:

* Have not responded to two antipsychotics of which one is an atypical antipsychotic medication.
* Experience unacceptable side effects/ intolerance to typical or atypical antipsychotics
* Experience tardive dyskinesia.
	1. Service users who have severe, untreatable neurological adverse reactions to other antipsychotics including atypical psychotic disorders occurring during the course of Parkinson’s disease in cases where standard treatment has failed.

3.13 Service users with other diagnoses (for example bipolar disorder) may be considered for treatment with clozapine. Clinicians should refer to the ELFT [Unlicensed Medicine Policy](http://elftintranet/download/488cb5d8-a486-4712-9d73-8f7811172292/f/Unlicensed_Medicines_Policy_V30_November_2012.pdf) for further information.

**3.2 Exclusion Criteria**

3.21 Hypersensitivity to the active substance or to any of the excipients.

3.22 Service users unable to undergo regular blood tests.

3.23 Service users unable to attend the Clozapine Clinic (the Clozapine Clinic can not undertake home visits)

3.24 Impaired bone marrow function, history of toxic or idiosyncratic granulocytopenia/agranulocytosis (with the exception of from previous chemotherapy), or history of clozapine induced agranulocytosis.

3.25 Uncontrolled epilepsy.

3.26 Alcoholic and other toxic psychoses, drug intoxication, comatose conditions.

3.27 Circulatory collapse and/or CNS depression of any cause.

3.28 Severe renal or cardiac disorders (e.g. myocarditis). Active liver disease associated with nausea, anorexia or jaundice; progressive liver disease, hepatic failure.

* 1. Paralytic ileus.
	2. Clozapine must not be started concurrently with substances known to have a substantial potential for causing agranulocytosis; Depot antipsychotics, carbamazepine, chloramphenicol (excluding eye or ear drops) and sulphonamides should be avoided. Any concurrent treatment with any of these substances will require authorisation via appendix 3 of the [ELFT Unlicensed Medicines Policy](http://elftintranet/download/488cb5d8-a486-4712-9d73-8f7811172292/f/Unlicensed_Medicines_Policy_V30_November_2012.pdf).

 In those service users established on clozapine who then require chemotherapy it may be possible to continue both concurrently. However, this will require pre-treatment authorisation by a consultant oncologist, haematologist and psychiatrist. The unlicensed use procedure would need to be followed according to the brand of clozapine been prescribed and appendix 3 of the [ELFT Unlicensed Medicines Policy](http://elftintranet/download/488cb5d8-a486-4712-9d73-8f7811172292/f/Unlicensed_Medicines_Policy_V30_November_2012.pdf) must also be completed. Before treatment starts there must be a clear plan in place regarding monitoring of the WBC and responsibilities for action if it drops. Clinicians should contact the Clozapine Clinic for further information.

3.31 For a full and up to date list of the indications, cautions, contraindications and any other information regarding clozapine the clinician should refer to the summary of product characteristic (SPC) of the brand of clozapine being prescribed.

# 4.0 Adverse Effects of Clozapine Requiring Mandatory Monitoring in ELFT

**4.1 Agranulocytosis/Neutropenia**

4.11 The cumulative risk of agranulocytosis is approximately 0.8%, although 70% of all cases occur within the first 18 weeks of treatment. The incidence of neutropenia is approximately 3%. The clinical signs and symptoms of agranulocytosis/neutropenia may include flu like symptoms, sore throat and raised temperature and all clinical staff should be aware of these. Routine blood monitoring is mandatory and will identify sub-clinical cases 1 2.

4.12 Benign Ethnic Neutropenia (BEN)

Approximately 25% to 50% of persons of African descent and other Middle Eastern groups have BEN resulting in low leukocyte and neutrophil counts. This may have been identified during the referral/registration process for starting clozapine. If a diagnosis of BEN is suspected it is essential that a haematologist reviews the service user before starting treatment. A successful diagnosis of BEN will result in lowered white blood cell level requirements preventing blood test management problems and false amber and red results in the future 2 3.

4.13 Required Monitoring:

The service user will require regular full blood count (FBC) and differentials for as long as they are treated with clozapine. This is mandatory in the UK and clozapine cannot be supplied without this. The frequency will be as follows:

* Weekly for the first 18 weeks of treatment.
* Fortnightly during weeks 18-52
* Four weekly thereafter for as long as the service user remains on clozapine treatment. In some cases it may be deemed clinically necessary to undertake a FBC more frequently, e.g. in those service users who continue to produce multiple red then amber/green results (see below).

Blood tests will be categorised as follows;

|  |  |  |  |
| --- | --- | --- | --- |
| **Category** | **White Blood Cell Count** | **Absolute Neutrophil Count** | **Platelet Count** |
| **GREEN** | Normal pt≥ 3500 ( 3.5x109) BEN pt≥ 3000 ( 3.0x109)  | Normal pt≥ 2000 ( 2.0x109) BEN pt≥ 1500 ( 1.5x109 | Normal and BEN pt ≥50 000/mm3 (50x109/L) |
| **AMBER** | Normal pt3000-3500 (3.0x109- 3.5x109)BEN pt2500-3000 (2.5x109- 3.0x109) | Normal pt1500-2000 (1.5x109 - 2.0x109)BEN pt1000-1500 (1.0x109- 1.5x109) | Normal and BEN pt> 50 000/mm3 (50x109/L) |
| **RED** | Normal pt< 3000 (< 3.0x109)BEN pt< 2500 (< 2.5x109) | Normal pt< 1500 (< 1.5x109)BEN pt< 1000 (< 1.0x109) | Normal and BEN pt<50 000/mm3 (50x109/L) |

4.14 Management of Blood Results/Side Effects

If the result is **GREEN**:

Continue clozapine and take blood sample at the next planned blood test date.

If result is **AMBER**:

* If the service user is clinically well and not experiencing any signs of neutropenia (flu like symptoms, sore throat and raised temperature) clozapine can still be administered.
* However the service user will have to have twice weekly full blood counts (FBC), in addition to physical observations until the result is ‘green’.
* Where blood tests are carried out using Point Of Care Haematology i100 (PoCHi100), clinic staff will be aware immediately of the result. Pharmacist and clinic staff are notified by the clozapine monitoring system usually via telephone call and Consultants are notified by fax.
* The service user should be advised to attend GP or A&E if they begin to feel unwell or experience signs or symptoms of neutropenia or agranulocytosis (sore throat, high temperature, flu like symptoms), between blood tests.

If result is **RED:**

* The service user must be informed and **CLOZAPINE STOPPED.**
* **No clozapine** should be given to service user.
* All physical observations should be carried out and staff should check if the service user is experiencing any flu like symptoms, high temperature, and sore throat. If the service user is experiencing any of these symptoms they should be advised to present at their local A+E service. Clinic staff will contact the A+E service to inform them of the relevant details and implications.
* Where possible, service user to be reviewed by the Responsible Consultant (RC) or a senior doctor from his/her team, for review of mental and physical health and medication.
* Service user will need to have daily blood tests until two consecutive GREEN results are obtained. The service user will be advised to attend A+E or GP if physical health deteriorates.
* RC, clinic staff and pharmacist are notified by the respective clozapine monitoring system via telephone call of RED result. (PoCHi 100 sites are aware of the result).
* Red Alert Guidelines and Adverse Events forms are faxed by clozapine monitoring system to RC. These are to be completed by RC and returned back to them.
* If service user has an AMBER result after RED, two consecutive GREEN results MUST be obtained to restart Clozapine. However, service user will need to be re-titrated back on clozapine.
* If service user has two consecutive RED results, the service user will NOT be able to restart Clozapine and their name will be added to the clozapine non-rechallengable list. Service user must be seen immediately by a psychiatrist.
* If a service user is concerned about signs of infection outside working hours, they should immediately attend their local A&E Department or Walk-in clinic, stating that they had been taking clozapine 2.

**4.2 Acute Intestinal Obstruction and Constipation**

4.21 Clozapine has an anti-cholinergic effect, which may produce problems for service users treated with clozapine. Its anti-cholinergic properties may cause varying degrees of impairment or slowing of intestinal peristalsis, ranging from constipation to intestinal obstruction, faecal impaction and paralytic ileus that may be fatal. Acute obstruction is a medical emergency.

At the earliest opportunity the service user should be counselled about constipation and that it is important that they report any constipation lasting more than two days to a healthcare professional as a matter of priority. They should also be counselled on methods to avoid constipation including maintaining an adequate fluid balance and eating a high fibre diet, which includes fruit and vegetables (‘five a day’).

Particular care is necessary in service users who are receiving concomitant medications known to cause constipation: especially those with anti-cholinergic properties such as other antipsychotic medications, antidepressants, and anti-parkinsonian treatments. Hyoscine Hydrobromide (Kwells®) and pirenzapine are commonly prescribed for the treatment of clozapine induced hypersalivation and are anti-cholinergic in nature. They can therefore compound the problem. Careful management of this aspect of the Service User’s care is advised and it should be addressed during medical reviews and CPA meetings as it is on each attendance at the Clozapine Clinic. Service users who have a history of colonic disease or a history of lower abdominal surgery should be carefully monitored as this may exacerbate the risk of constipation 2.

4.22 Required monitoring:

* Whilst on the ward the service user will be asked daily whether they have opened their bowels/are constipated.
* At every clinic visit staff will enquire as to whether they have opened their bowels/are constipated.
* Clinical staff should also be alert for the symptoms of acute intestinal obstruction. These include abdominal distension, loss of appetite, pain, nausea/vomiting and faecal overflow (service users will report this as diarrhoea).

4.23 Management of Constipation8

Advice/action should follow that set out in figure 1.

Bulk forming laxatives (fybogel) are not effective in slow transit constipation and should be avoided.

Osmotic laxatives (macrogol) should be considered early.

Lactulose an osmotic laxative **should not be used**, as the non-absorbable sugars in it can ferment within the colon exacerbating bloating and distention.

Stimulant laxatives (senna) can be used.

**Figure 1: Constipation Decision Making Algorithm**

**4.3 Myocarditis and Cardiomyopathy**

4.31 Although very rare (<1/10,000), the use of clozapine is associated with an increased risk of myocarditis(especially during first two months) and cardiomyopathy 3.

4.32 Required Monitoring:

* Troponin level weekly for first 4 weeks of treatment. A troponin result twice the usual reference range can be an indicator of myocarditis or cardiomyopathy.
* CRP weekly for first four weeks of treatment.
* Pre and post clozapine BP and pulse whilst service user remains on titration. Daily BP and pulse thereafter on the ward.
* BP and pulse to be monitored at every visit to the clozapine clinic.
* Clinical staff should be alert to symptoms of myocarditis or cardiomyopathy. These include palpitations, arrhythmias, chest pain and other signs and symptoms of heart failure (e.g. unexplained fatigue, dyspnoea, tachypnea, peripheral oedema), or symptoms that mimic myocardial infarction. Other symptoms which may be present in addition to the above include flu-like symptoms.

4.33 Management of Cardiomyopathy/Myocarditis

If myocarditis or cardiomyopathy is suspected, clozapine should be promptly stopped and the service user immediately referred to a cardiologist/A+E.

 Service users with clozapine-induced myocarditis or cardiomyopathy should not be re-exposed to clozapine 2.

**4.4 Orthostatic hypotension and hypertension**

4.41 Orthostatic hypotension, with or without syncope, can occur at any point of clozapine treatment. However, it is far more likely to become an issue during the initial titration of this drug, or when dose escalation is too rapid. For this reason clozapine initiation in ELFT follows three standardised titrations, depending on whether the service user is an inpatient, day patient, or community based patient. Outside of clozapine titrations, dose increases are limited to a maximum of 50mg per day. The risk of hypotension is enhanced by the concomitant use of benzodiazepines or any other psychotropic agents, so these need to be used with caution.

4.42 Hypertension can also occur commonly in the first four weeks of treatment with clozapine, although in some cases this may last longer 2.

4.43 Required Monitoring

* Pre and post clozapine sitting and standing BP whilst service user remains on titration. Daily BP thereafter on the ward.
* Sitting and standing BP to be monitored at every visit to the clozapine clinic.

4.44 Management of hypotension

If a service user develops hypotension during clozapine titration, it may be advisable to slow down the titration or in extreme cases stop it all together. The service user should be offered standard advice to deal with hypotension including advising them to take time to stand up and ensuring adequate fluid intake 2.

4.45 Management of hypertension

If a systolic reading of greater than 140 mmHg or a diastolic reading of greater than 90mmHg is recorded then the ward doctor should be notified (if inpatient) or the service user’s GP, RC and mental health team (if they are an outpatient). Hypotensive therapy is sometimes required 1.

**4.5 Tachycardia**

4.51 Tachycardia is very common in the early stages of clozapine treatment and usually benign. However, together with chest pain, symptoms of heart failure or flu like symptoms may be indicative of cardiomyopathy or myocarditis.

4.52 Required Monitoring:

* ECG prior to initiation
* Pre and post clozapine pulse whilst service user remains on titration. Daily manual pulse thereafter on the ward.
* Manual pulse to be monitored at every visit to the clozapine clinic.

4.53 Management of Tachycardia

If tachycardia occurs in combination with chest pain, shortness of breath or symptoms that resemble a Myocardial Infarction, staff should refer to section 4.3 on myocarditis and cardiomyopathy. A heart rate above 120 bpm or an increase in heart rate greater than 30 bpm are considered risk markers for clozapine-induced myocarditis

 Any long-standing tachycardia MUST be referred by psychiatry to be investigated further by a cardiologist. The GP, RC and mental health team should also be informed of the referral for community patients. If found to be a benign sinus tachycardia, it may be possible to treat this with a beta-blocker 2.

**4.6 Pyrexia**

4.61 Mild hyperthermia occurs in approximately 5% of service users, typically early in treatment and is usually not significant. However, pyrexia may also be indicative of an infection, NMS, myocarditis and rarely neutropenia or agranulocytosis 3.

4.62 Required Monitoring:

* Daily temperature whilst on titration and during inpatient stay.
* Temperature will be measured at clinical discretion of clozapine clinic staff whilst an outpatient, if service user appears unwell or there is cause for concern.

4.63 Management of Pyrexia

Any pyrexia should be medically examined and a full blood count should be performed as soon as possible. If the body temperature exceeds 38.50 C, the ward doctor/service user’s consultant should be notified and the clozapine monitoring service should be contacted for advice, a high temperature could require clozapine to be stopped 2.

**4.7 Diabetes and Impaired Glucose Tolerance**

4.71 Clozapine has been strongly linked to hyperglycaemia and impaired glucose tolerance with as many as a third of patients developing diabetes after 5 years of treatment. There are also rare reports of diabetic ketoacidosis.

Many cases of diabetes are noted in the first 6 months. Diabetes associated with clozapine is not necessarily linked to obesity or to a family history of diabetes. However standard risk factors still apply and these include the above in addition to poor diet, lack of exercise, increased age and existing cardiovascular disease.

Use of clozapine in those with already established diabetes may also de-stabilise blood sugar control 1 2. Therefore, ELFT staff should closely monitor blood glucose levels following initiation of clozapine in diabetic service users.

4.72 Required Monitoring and Management of Suspected Diabetes or Glucose Intolerance

For service users screened as non-Diabetes Mellitus

* Random Blood Glucose (using glucometer) should be monitored at every scheduled blood test for the duration of clozapine treatment. Normal blood glucose levels are between 4mmol/L to 6 mmol/l before meals and less than 8.0 mmol/L two hours after meals. The GP should be notified of any abnormal results falling outside of the target range and a note placed on RIO.
* If the service user refuses a random blood glucose test, clozapine can still be issued to them. However, a capacity assessment for that decision should take place and documented on the progress notes accordingly. If the service user refuses random glucose test and more than six months have elapsed since the last one, the GP/Diabetes specialist nurse and Consultant Psychiatrist should be informed.
* A fasting blood glucose test and HbA1c/IFCC should be taken at baseline, and subsequently every six months. The GP/Diabetes specialist nurse should be notified of abnormal results (>48 mmol/mol / 6.5%), depending on whether the service user is an inpatient or outpatient respectively. If the Hba1c/IFCC is between 42 and 47mmol/mol, they should be considered pre-diabetic (at high risk of developing diabetes). Abnormal findings should be communicated directly from clinician to clinician and concerns not left to the service user to raise.

For service users with a diagnosis of Diabetes Mellitus,

* A monitoring/treatment plan should be formed in conjunction with the Diabetes specialist nurse whilst an inpatient. There is a need for a shared clinical plan with the GP for monitoring and treating DM on discharge. The mental health team should not be treating DM.
* Blood glucose levels should be monitored in line with the service user’s normal schedule whilst on the ward.
* The clozapine clinic will perform three monthly random blood glucose checks using a glucometer, and Hba1c/IFCC testing six monthly whilst service users are in the community. The GP should be notified of abnormal Hba1c/IFCC results (>48 mmol/mol / 6.5%).
* For service users with Type 1 Diabetes Mellitus
	+ Blood glucose target ranges are 5.0 – 7.0mmol/L when fasting, and 4.0 – 7.0mmol/L before meals and at any other times of the day.
	+ If blood glucose is ≥ 13mmol/L, a capillary blood sample should be tested for ketones using the specific test strips in the glucometer, and results acted upon as per below table:

|  |
| --- |
| **Blood b- Ketone Result Guide (CareSens Dual blood glucometer)** |
| **Results** | **Meaning** | **Action Plan** |
| < 0.6 mmol/L | Normal Range | Document on RiO |
| 0.6 mmol/L – 1.5 mmol/L | Slightly increased risk of Diabetic Ketoacidosis | Test again in 2 hoursInform GP / Diabetes Specialist Nurse |
| 1.6 mmol/L – 2.9 mmol/L | Risk of Diabetic Ketoacidosis | Liaise with GP / Diabetes Specialist Nurse immediately |
| > 3.0 mmol/L | Very High Risk of Diabetic Ketoacidosis | Send service user to A&E |

* For service users with Type 2 Diabetes Mellitus
	+ If random blood glucose is ≥ 17mmol/L this information should be alerted to the GP by telephone call. Clinicians should ascertain if service user has just had any sugary food/drinks, and if so contact the doctor or diabetes specialist nurse for advice.
	+ If random blood glucose is ≥ 20.0mmol/L, clinicians will assess if service user is asymptomatic or showing diabetic symptoms, e.g. feeling thirsty, tired, passing a lot of urine, etc. Should this be the case, then the service user will be directed to A&E.
	+ If service user is showing diabetes symptoms, a capillary blood sample should be tested for ketones using the specific test strips in the glucometer, and results acted upon as per below table:

|  |
| --- |
| **Blood b- Ketone Result Guide (CareSens Dual blood glucometer)** |
| **Results** | **Meaning** | **Action Plan** |
| < 0.6 mmol/L | Normal Range | Document on RiO |
| 0.6 mmol/L – 1.5 mmol/L | Slightly increased risk of Diabetic Ketoacidosis | Test again in 2 hoursInform GP / Diabetes Specialist Nurse |
| 1.6 mmol/L – 2.9 mmol/L | Risk of Diabetic Ketoacidosis | Liaise with GP / Diabetes Specialist Nurse immediately |
| > 3.0 mmol/L | Very High Risk of Diabetic Ketoacidosis | Send service user to A&E |

* + If random blood glucose is ≥ 25.0mmol/L (or Hi Hi on the glucometer), the service user should be directed to A&E even if asymptomatic, as they might be at risk of slowly developing Hyperosmolar Hyperglycaemic State (HHS).
* Any abnormal findings should be communicated directly from clinician to clinician and concerns not left to the service user to raise.
* If the service user refuses a random blood glucose test, clozapine can still be issued to them. However, a capacity assessment for that decision should take place and documented on the progress notes accordingly. If the service user refuses random glucose test and more than three months have elapsed since the last one, the GP/Diabetes specialist nurse and Consultant Psychiatrist should be informed.

All service users should be monitored for symptoms of diabetes. These include rapid weight loss (5kg in one month), excessive thirst or increased urinary output. These symptoms should prompt an immediate random blood glucose and referral to the service user’s GP.

**Figure 2: Diabetes Decision Making Algorithm Following Random Blood Glucose**

**4.8 Weight Gain**

4.81 Weight gain following clozapine is common and may be significant for some service users. Most weight gain tends to occur within the first year of treatment. This is extremely important as obesity is a risk factor for cardiovascular disease and the development of diabetes mellitus. Early intervention is important as this has been shown to prevent or mitigate weight gain 1. Service users need to be counselled from an early stage (preferably before starting treatment) regarding this adverse effect and standard advice applies.

4.82 Required monitoring:

* Weekly weight and BMI whilst on titration and an inpatient.
* Weight and BMI at every clinic appointment.

4.84 Management of Weight Gain

All service users whose BMI exceeds 30, or who are rapidly gaining weight should be referred to their GP for further investigation and/or treatment.

A referral to a Dietician may also be of use. It is often reported by Service Users that an increase in appetite occurs in the evening/after administration of night-time dose of clozapine. However, it does also occur during the day. A frank discussion with the Service User and their carer if possible needs to take place regarding their diet and how best to manage their increased appetite. Snacking using fruit and vegetables is recommended as they are low in calorific value and are nutritious.

**4.9 Seizures**

4.91 Clozapine can lower the seizure threshold and this is a dose related side effect. The incidence of seizures increases with doses of clozapine greater than 600mg daily. However this can occur in doses under 600mg daily and staff should always be aware of this gain 1.

Some 2% of patients taking clozapine develop **myoclonus**, mostly orofacial myoclonus though it can occur in other parts of the body in particular the hands/lower arms 4.

Myoclonus is a sudden, involuntary jerking of a muscle or group of muscles. Myoclonic twitches or jerks usually are caused by sudden muscle contractions. The twitching cannot be controlled by the person experiencing it. In its simplest form, myoclonus consists of a muscle twitch followed by relaxation. These movements may represent myoclonic seizures, and increase the risk of the service user experiencing grand mal convulsions 5.

4.92 Required Monitoring:

* Service user will be visually observed by staff whilst an inpatient.
* Clozapine clinic staff will enquire and also observe for any symptoms that resemble seizures/myoclonus at every visit to clinic.

4.93 Management of Seizures

 Management consists of clozapine dose reduction or discontinuation, or cautious use of sodium valproate or lamotrigine. Sodium valproate is contraindicated if pregnancy is a possibility; female patients of child-bearing age must be counselled on the teratogenic properties of the drug and a consent form must be completed. Please see the [ELFT protocol](http://elftintranet/download/9e21d9ab-9622-4a8a-a476-2c25162ab240/f/Valproate_in_female_patients_VALP_Protocol_v7_May_2018_Changes_in_red.pdf) for further details. Sodium valproate and lamotrigine are also associated with an increased risk of neutropenia/ agranulocytosis. Use of carbamazepine is contraindicated with clozapine 6.

Should a seizure occur, withhold clozapine for one day and restart at a lower dose. Those needing higher doses of clozapine more commonly associated with causing seizures (500-600mg) daily may be prescribed sodium valproate at doses between 1000-2000mg /day concurrently, use of modified release preparations (Epilim® Chrono) may aid concordance as it can be given once daily and may be better tolerated.

**4.10 Thromboembolism**

Since clozapine may be associated with thromboembolism, immobilisation of patients should be avoided. Cases of venous thromboembolism (VTE) have been reported with antipsychotic drugs. Since patients treated with clozapine often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with clozapine and preventive measures undertaken 2.

All Patients are to have a screening risk for Venous Thrombosis Embolism within 14 hours of admission and VTE assessment carried out as required and recorded on RIO Patient electronic template under Physical Health.

If the service user has significantly reduced mobility at any time during their admission the following assessment from the Nice Guidance 2021 must be carried out: [NICE guidance](https://www.nice.org.uk/guidance/qs201)

[VTE screening and assessment](https://technology-trust-news.org/1TXQ-8174H-32/sv.aspx)

**4.11 Summary Matrix of Mandatory Monitoring Parameters for Clozapine Treatment in in ELFT.**

|  |  |
| --- | --- |
| Monitoring Parameter | Week of Clozapine Treatment |
| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 20 | 22 | 24 | 26 | 28 | 30 | 32 | 34 | 36 | 38 | 40 | 42 | 44 | 46 | 48 | 50 | 52 |
| FBC+ differential | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 |
| Troponin level+ CRP | 🗸 | 🗸 | 🗸 | 🗸 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| BP and pulse | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 |
| Weight/Height(BMI) | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 |
| Temperature | Monitored daily whist on titration and remains as inpatient. In community measured at clinical discretion if service user appears unwell or there is cause for concern. |
| Random Blood Glucose (Non-DM) | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 |
| Constipation | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 |
| Seizures | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 | 🗸 |

\* Beyond first year of treatment, all tests with exception of Troponin, CRP and temperature should be undertaken on a monthly basis.

\*\*In the case of a treatment break, the blood test frequency will be altered. See section 11.0 for further detail

1. **Other Side Effects associated with clozapine**
	1. **Hypersalivation**
	2. Hypersalivation is a common side effect experienced by service users and is often given as a reason for wanting to stop clozapine. It usually occurs at night but can also occur during the day. It can be mild or excessive. It may be experienced frequently or intermittently. It usually occurs during the first few months of therapy, but can persist beyond this. Hypersalivation has a negative impact on a patient’s quality of life and can potentially contribute to the development of aspiration pneumonia. It should be treated as a matter of urgency 1.
	3. Hypersalivation is usually treated with Hyoscine Hydrobromide (Kwells®) which can be either chewed or left to dissolve in the mouth. Other treatments such as pirenzepine can also be used. Like clozapine these drugs also have an anti-cholinergic effect, which may increase the risk of constipation and anticholinergics can negatively impact cognition. There is a lack of a robust evidence base for any treatment for clozapine induced hypersalivation 2.
	4. Other means of dealing with hypersalivation might include using two pillows to sleep with and wrapping pillows in towels. It may also be beneficial to raise the height of the pillows to sleep with. If hypersalivation is experienced during the day then chewing gum (sugar free) may be beneficial.
	5. Clozapine-induced hypersalivation may be dose related and it may be worth the RC considering a dose reduction if possible although this needs to be considered with caution.
	6. If the service user is not maintaining an adequate daily fluid balance of around 2-3 litres and they are also hypersalivating, then they may become dehydrated. Dehydration should be avoided as it can increase the risk of or worsen any constipation that might be experienced. The patient should be assessed for dehydration and fluid intake queried at each clinic appointment.
	7. **Dizziness**
	8. Dizziness is a common side effect experienced by service users and it can be very distressing. It can be postural in nature but it can also occur without any change in posture.
	9. There are a number of reasons why service users taking clozapine may experience dizziness.

 • Time of clozapine dose

 • Dose of clozapine

 • Dehydration

 • Low blood pressure

* 1. Clozapine is always initially prescribed in twice daily doses after the first day. It may be that the morning dose is causing dizziness during the day and the RC should consider moving the majority of or the entire Clozapine dose to night time. As dizziness is a dose related side effect it may even be necessary to consider a dose reduction.
	2. Dehydration can cause dizziness, see 5.15.
	3. Low blood pressure can also cause dizziness. This may be pre-existing low blood pressure or it may be a dose related side effect of clozapine. If low blood pressure is apparent through observation then this should be made known to the RC and GP.
	4. Sudden dizziness can cause falls and the service user should consider sitting and resting should dizziness occur.
	5. Dizziness can occur if clozapine is also taken with other medications, especially anxiolytics or other anti-psychotic or antihypertensive medications.

* 1. **Sedation**
	2. Generally experienced when first starting clozapine. However this can be ongoing. Clozapine is always initially prescribed in twice daily doses. It may be that the morning dose is causing sedation during the day and the RC should consider moving the majority of or the entire clozapine dose to night time. As sedation is a dose related side effect it may even be necessary to consider a dose reduction.
	3. Sedation can also occur if clozapine is also taken with other medications, especially anxiolytics or other anti-psychotic medications.
	4. **Nausea/ Vomiting**
	5. Nausea is identified as being experienced by around 11% of service users and it can be very distressing 7. It is also reported that this most frequently occurs in the later stages of treatment; however service users do commonly report this within the first few months after starting Clozapine.
	6. There are a number of reasons why service users taking Clozapine may experience nausea.

 • Dose of clozapine

 • Increase in food intake

 • Delayed gastric emptying

 • Hypersalivation/dehydration

* 1. As nausea is a dose related side effect it may even be necessary to consider a reduction in the dose of clozapine. This may reduce or stop the experience of nausea.
	2. Clozapine is well known to cause increased appetite. It is important to discuss this side effect with service users prior to commencing and during treatment with clozapine in order to assist them with any lifestyle changes that they may need to make. A referral to a Dietician may also be of use.
	3. Delayed gastric emptying can be as a result of a number of things, for instance; an increase in food intake, a high fat content in the diet, cigarette smoking and consumption of alcohol amongst others.
	4. The service user should be encouraged to maintain a healthy diet; eating more slowly and changing portion size and meal frequency if required. They should also be encouraged to meet with their GP as they may require prescribing of anti-emetics or antacids.
	5. Hypersalivation is a very common side effect of clozapine and can cause dehydration if an adequate daily fluid balance of around 2-3 litres is not maintained. If the service user is vomiting frequently this can contribute to any dehydration. Dehydration should be avoided as it can increase the risk of or worsen any constipation that might be experienced 2.
	6. **Dry mouth**
	7. This is often experienced in the morning when waking having hypersalivated throughout the night. However this can occur at other times of the day also and not in relation to hypersalivation. The Service User should be advised to maintain an adequate daily fluid balance of around 2-3 litres.
	8. **Urinary problems**
	9. Urinary frequency and urgency are often experienced; this can occur or abate at any time during Clozapine therapy. It can be increased in severity to the point of experiencing enuresis particularly at night-time. A decrease in clozapine dose maybe required. Nocturia may be alleviated through avoiding fluids at night and moving the dosage to avoid periods of deep sedation. The Service User should be advised to attend their GP. Clinic staff should notify RC and GP if this occurs 1.
	10. **Pneumonia**
		1. There is anecdotal evidence that clozapine may be associated with increased risk of chest infections, which may prove fatal. The proposed mechanism is unknown, but hypersalivation leading to pulmonary aspiration, impaired oesophageal peristalsis, use of antacids (reflecting upper GI problems), gastro-oesophageal reflux and smoking cessation (leading to increased clozapine levels) have all been implicated1. The presence of asthma may exacerbate the risk of developing pneumonia.
		2. Service users taking clozapine should be closely monitored for symptoms of chest infection and pneumonia (fever, aches and pains, breathlessness, wheeze, sputum production etc). Any purported risk factor, such as a history of asthma, change in smoking habit, hypersalivation or upper GI symptoms, should be carefully noted and treatment commenced if indicated. Assessment should include measurement of temperature, pulse and blood pressure.
		3. The development of a chest infection in patients taking clozapine should result in immediate treatment, including specialist referral if necessary If pneumonia develops, consideration should be given to discontinuing clozapine sooner rather than later, particularly if it is suspected as being the causative agent. Alternative antipsychotics should be commenced. Amisulpride is associated with a low risk of pneumonia and a suitable alternative if clinically appropriate.
	11. This is not an exhaustive list of side effects associated with clozapine.Staff should refer to either the [BNF](https://bnf.nice.org.uk/), SPC of the clozapine brand, or Maudsley Prescribing Guidelines for information on other side effects associated with clozapine and their management.
	12. **Clozapine and Covid**

|  |
| --- |
|  |

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| --- |
| * + 1. Mild and transient neutropenia can occur in patients taking Clozapine who have COVID-19. Clozapine-related neutropenia is more likely to be ruled out in patients with coinciding COVID-19 infection, if they have been taking Clozapine for more than 6 months (and especially if over a year) and have never had neutropenia (RED or AMBER results) before.
		2. Clinicians should always rule out COVID-19 infection in patients presenting with a neutrophil drop and/or symptoms of COVID (such as fever, cough, sore throat, shortness of breath, and sudden loss of taste and/or smell). If there is suspicion of neutropenia and agranulocytosis with Clozapine, an urgent FBC is required to rule out blood dyscrasias. Blood dyscrasias with the criteria below are likely to be related to Clozapine, and therefore continued Clozapine treatment is likely to result in a more rapid and severe neutropenia or agranulocytosis. Please seek advice for such patients from your ELFT pharmacy team and the clozapine monitoring service.
* Inconsistent with previous WCC
* Occurred in the first 18 weeks of treatment
* Severe (neutrophils < 1 x 109/L)
* Prolonged
	+ 1. For further details on WBC and neutrophils ranges please refer to the ‘Clozapine use in context of COVID-19’ guidance
		2. Systemic infections inhibit clozapine metabolism through cytokine production and can quickly lead to high clozapine plasma levels. In addition, smoking cessation can cause a further rise in plasma levels (factor 2 to 10) e.g. hospitalised patients forced to stop smoking.
		3. For patients with confirmed COVID-19 or signs of infection the clozapine dose may need to be temporarily reduced until the infection resolves.  The Zaponex Treatment Access Service (ZTAS) strongly recommend an immediate 50% Clozapine dose reduction to prevent clozapine toxicity in mentally stable patients (not awaiting current plasma level assay results, which can take several days). For patients with high risk of psychotic relapse, an initial 25% dose reduction could be considered and further reductions depending on actual assay levels or overdose symptoms.
		4. ELFT recommends using clinical judgement to determine the dose reduction on an individual basis and monitoring for signs of Clozapine toxicity.
		5. In patients who develop clozapine overdose symptoms such as drowsiness, sedation, lethargy, confusion, agitation, tachycardia, hypotension, respiratory depression and seizures, high plasma levels should be suspected and a plasma level assay should be done to confirm or exclude this. In such patients, clinician may need to temporarily reduce the Clozapine dose using their clinical judgement. ·
		6. Further information can be found within the Trust guidance:  [Clozapine use in context of COVID-19](https://www.elft.nhs.uk/Professionals/Information-for-ELFT-Staff/Clinical-Guidance/ELFT-Guidance)
 |

1. **Preparing for Initiating Clozapine**
	1. **Referring the service user to Clozapine Clinic**

6.11 Service users cannot be initiated on clozapine until their referral to the clozapine clinic has been accepted. There is one [clozapine clinic referral form](http://elftintranet/download/c9e23199-43dd-4430-93a3-61a6870f6661/f/Clozapine_Referral_Form.doc) used throughout the Trust for both inpatients and outpatients and this should be sent to the relevant Clozapine Clinic.

6.12 There are four clozapine clinics in operation in ELFT and their contact details are as follows:

|  |  |
| --- | --- |
| **City and Hackney Clozapine Clinics** | **Newham Clozapine Clinic** |
| Tel: 0208 525 111523 Primrose SquareLondon E9 7TSelft.CityandHackneyClozapine@nhs.net | Matthew OppongClozapine & Primary Care Liaison Lead 115 Balaam StreetLondon E13 8AFelft.ClozapineTeam@nhs.netTel: 020 8548 5181  Fax: 020 8548 5165 |
| **Forensics Clozapine Clinics** | **Tower Hamlets Clozapine Clinic** |
| John Howard CentreCurtis ReeceBen GrantBroadgate wardTel; 0208 5102060Fax: 0208 5102315elft.ForensicClozapineClinic@nhs.netWolfson HouseChouna SmithJulie MitchellSandra May Alexander0203 222 7150/7108[elft.wolfsonhouseclozapineclinic@nhs.net](file:///C%3A%5CUsers%5Clinesm%5CDesktop%5CMatt%20desktop%5Celft.wolfsonhouseclozapineclinic%40nhs.net) | Makeda Douglas/ Laura PisaneschiClozapine Clinic Manager/Clozapine Clinic service Manager 54-86, Old Montague Street,London, E1 5NN.elft.TH-Clozapine@nhs.netTel: 0207 426 2350 Mob: 07572 140 863Fax: 0207 426 2497 |
| **n Clozapine Clinic** | **Bedford Clozapine Clinic** |
| 1st Floor Calnwood CourtCalnwood RoadLutonLU4 0LXemail: elft.LutonClozapine@nhs.net**Contact number:** 01582510084 | Leigh RobinsonFlorence Ball HouseBedford Health Village 3 Kimbolton Road Bedfordshire MK40 2NTEmail: elft.BedfordshireClozapine@nhs.net**Contact number: 01234 310043** |

6.13 The following baseline tests must be carried out before a referral:

* Full blood count
* HbA1C and fasting blood glucose
* LFTs and U+Es
* Fasting lipids
* Weight
* Sitting and standing Blood Pressure
* Pulse
* Temperature
* ECG
* CRP
* Troponin
* Assess for current existing constipation and treat prior to initiating Clozapine.

6.14 All CPA/CRAM documents should be up to date on RiO and the Clozapine Clinic staff should be made aware of any active risk factors.

* 1. **Registration with Clozapine monitoring systems**

6.21 ELFT currently uses Zaponex and Denzapine**™** brands of clozapine. Denzapine is used in the Luton locality; Newham, City & Hackney and Tower Hamlets services use Zaponex. Clozaril is provided in some NHS trusts, so patients may be prescribed this prior to treatment from ELFT services. Denzapine is the only brand with a liquid formulation; however this is not used routinely. Pharmacy should be contacted for advice regarding switching clozapine brands.

6.22 The clozapine monitoring systems of each brand of clozapine provides centralised monitoring of leukocyte and neutrophil counts, which are mandatory for all service users in the UK that are treated with clozapine.

6.23 Therefore, before any service user can be initiated on clozapine, they must be registered with the respective clozapine monitoring system.

6.24 The clozapine [patient registration form](http://ztas.co.uk/pdf/01-A-PatientDataForm.pdf) should only be completed following the successful referral of the service user to the Clozapine Clinic. The completed form will only be sent after the clozapine pharmacist has clinically screened the service user’s existing medication and has approved treatment with clozapine.

6.25 The prescribing RC and clozapine pharmacist must be registered with the respective clozapine monitoring system to enable them to prescribe and dispense clozapine to the patient.

6.26 The Zaponex monitoring system is ZTAS, their contact number is (0207) 365 58 42. Denzapine uses the Denzapine Monitoring system, they can be contacted on (0)118 920 9500. The Clozaril monitoring service is known as CPMS, the contact number is 0845 7698269.

**7.0 Initiating Clozapine**

**7.1 General Information**

7.11 In ELFT, three initiation pathways are available depending on whether the service user is starting clozapine as an inpatient, day patient or outpatient.

7.12 The decision as to which initiation pathway is used is at the discretion of the ward or community based clinical teams within the borough, it is dependent on the service user’s clinical circumstances and also the clinical resources available. All trusts offer an inpatient titration pathway. Bedford can initiate patients as outpatients. Tower Hamlets patients can receive day case titration at Crisis House facilitated by the HTT. The Newham HTT can also provide day case titration services. City & Hackney currently only facilitate inpatient titrations

7.13 Clozapine titrations should generally be started at the beginning of the week. This is because the risk of serious adverse reactions is higher in the first few days of treatment. Staffing levels are generally higher during weekdays, providing the infrastructure to carry out enhanced monitoring and to also deal with any emergent serious adverse reactions. It is for this reason that the initiation of clozapine titrations at the end of the week or weekends is not recommended.

**7.2** **Providing Information to the service user and carer**

 7.21 Before treatment with clozapine, the service user should be given the following:

* An ELFT [Clozapine information leaflet](https://www.elft.nhs.uk/About-Us/Publications/Florid-Medications/drugs_detail.aspx?ID=141&ResultList=1).
* A clear explanation of the requirement for blood tests, the duration and frequency of these.
* A clear explanation of potential adverse effects, especially constipation and what they should do if they experience these.
* An explanation of why adherence is important. What the service user must do if they have not taken clozapine for more than 48 hours.
* Contact numbers for the clozapine clinic. If the service user is titrating on the day patient or community pathways, they should also have emergency contact numbers for the ward/community team undertaking the titration.

**7.3** **Inpatient Titration**

7.31 Summary of titration

 Service user is initiated on clozapine on the ward as part of a normal inpatient admission.

* 1. Who is this titration suitable for?

 This is the preferred method of clozapine titration and is suitable for all service users who meet the general inclusion criteria for treatment with clozapine.

* 1. Prescribing clozapine during titration

An inpatient clozapine titration should be prescribed using the pre-built protocols in EPMA. Select ‘Add drug’ on the ‘Inpatient Rx’ page, locate the ‘Protocol’ tab and select the appropriate clozapine inpatient titration protocol. Please note there are separate protocols available for Clozaril, Denzapine tablets, Denzapine liquid, Zaponex and Zaponex orodispersible tablets. These protocols include reminders for pre and post-dose blood pressure and pulse monitoring, and weekly troponin monitoring for the first 4 weeks. These protocols will titrate the service user to a daily dose of 300mg (100mg MANE and 200mg NOCTE) in 17 days, although it should be noted that there is no standard dose of this drug, with some service users requiring smaller doses whilst others larger doses. If a slower or faster titration is necessary, the prescriber will need to prescribe each dose manually using the STAT dose function.

Once the titration has reached a target dose of 100mg MANE and 200mg NOCTE, the protocol will persist with these doses prescribed indefinitely. The protocol will need to be discontinued before a maintenance dose is prescribed.

**It is important to note that paper clozapine titration sheets should no longer be used for inpatient titrations.** Inpatient clozapine titrations should be prescribed using EPMA only. The EPMA ‘dummy drug’ titled ‘CLOZAPINE ORAL / IM TITRATION CHART – refer to paper chart’ should only be used in titrations involving intramuscular clozapine. Please refer to the ‘IM Clozapine Policy’ for more information regarding intramuscular administration of clozapine.

The ward doctor will review, at a minimum, once every week. The doctor will assess the service user's progress, enquire into any adverse reactions to clozapine and manage any other anti-psychotic medication; cross- tapering etc. In some cases it may be necessary to slow or alter the titration regime (for example if the standard titration is too rapid, or if service user has developed complications during the titration). In such cases, the clozapine titration protocol should be discontinued and individual STAT doses should be prescribed manually on EPMA at an appropriate titration speed. To discontinue a clozapine titration, select the next dose due on the ‘Inpatient Rx’ page, locate the ‘order modify’ tab and select ‘discontinue order’. This will discontinue the titration and all remaining doses.

* 1. Monitoring to be carried out during titration period

|  |
| --- |
| **PHYSICAL OBSERVATIONS** |
| All monitoring should be recorded on the physical health form in RiO for the entire titration period. The EPMA titration protocol will prompt pre and post-dose monitoring of blood pressure and pulse.**Before every clozapine dose:** Blood pressure (lying and standing), pulse and temperature. If observations are clinically appropriate, clozapine dose to be administered. **2 hours after every clozapine dose:** Blood pressure (lying and standing), pulse and temperature.Service user should be regularly prompted about constipation. |
| **BLOOD TESTS** |
| Full Blood Count plus differential, CRP and troponin levels will be organised by the Clozapine Clinic and taken on a weekly basis on the ward. CRP and troponin should only be continued weekly for the first 4 weeks of treatment. The EPMA titration protocol will prompt for weekly troponin levels for the first 4 weeks of treatment.Random Blood Glucose will be monitored by ward staff using a Glucometer on a weekly basis. * For non-diabetic service users, any results greater than 7mmols/L should be reported to the ward doctor.
* With known diabetics any result outside of the range 5-8mmols/L should be reported to the ward doctor.
 |

* 1. Supply and administration of clozapine during titration period

Clozapine will be ordered and dispensed weekly in accordance with the service user’s inpatient medication chart on EPMA and following the receipt of a valid blood result as indicated by ZTAS – that is a ‘green’ or ‘amber’ result.

Nursing staff may only administer clozapine to a service user if the service user has their own labelled supply that has been issued by pharmacy. If the service user does not have their own labelled clozapine supply, the nurse must contact pharmacy and not administer another service user’s supply.

* 1. Leave from the ward during titration period

Days 1-6

It is recommended that the service user remains on the ward for the first week of titration. This is because many of the emergent adverse drug reactions are more likely to occur during the early stages of treatment.

Day 7-onwards

Leave from the ward is at the clinical discretion of the medical team. Service users must not be sent on leave until at least 2 hours after their clozapine dose. Physical observations should be within normal limits (or agreed limits) and they should be considered medically fit for leave.

The service user should ideally be accompanied by a carer or responsible adult when on leave. If overnight leave is required, there must be an adult at the service user’s home whilst they stay overnight

**7.4 Day patient Titration**

7.41 Summary of titration

 Service user technically remains an outpatient, but attends the ward during the day to take clozapine and for associated monitoring required during the course of the titration.

7.42 Who is this titration suitable for?

This titration is suitable for those service users who would normally be considered suitable for outpatient or community team care. It is expected that the clinician has given due consideration and discussed the pros and cons of initiating clozapine on a day patient basis taking into account medical co-morbidities that may present a risk during clozapine titration (for example epilepsy or problems with hypotension). There must be an adult at the service user’s home (or the address where he or she would be residing) whilst they are on titration. There must also be access to an in-patient bed in the event that their mental or physical state deteriorates during the titration.

This titration is useful when it is not possible for the community team (Home Treatment Team) to facilitate clozapine initiation for those service users who do not need to be inpatients.

* 1. Prescribing Clozapine During Titration

A day patient titration should be prescribed using the [blank clozapine community titration sheet](http://elftintranet/download/63ecb0b0-831e-4845-bcbf-12237c8609bb/f/Clozapine_Community_Titration_Blank_2017.doc). This must be attached to the front of the service user’s drug chart and in the regular section of the drug chart ‘Clozapine-see titration sheet’ should be written. This will titrate the service user to a daily dose of 300mg in 17 days, although it should be noted that there is no standard dose of this drug, with some service users requiring smaller doses whilst others larger doses.

The titration is almost identical to the inpatient titration, with the exception of the PM dose being administered at 18.00 rather than 22.00. This enables the service user to leave the ward in the evening.

The ward doctor will review, at a minimum, once every week. The doctor will assess the service user's progress, enquire into any adverse reactions to Clozapine and manage any other anti-psychotic medication; cross- tapering etc. In some cases it may be necessary to slow or alter the titration regime (for example if the standard titration is too rapid, or if service user has developed complications during the titration).

* 1. Monitoring to be carried out during titration period

|  |
| --- |
| **PHYSICAL OBSERVATIONS** |
| All monitoring should be recorded on the clozapine titration sheet for the entire titration period.**Before every clozapine dose:** Blood pressure (lying and standing), pulse and temperature. If observations are clinically appropriate, clozapine dose to be administered. **2 hours after every clozapine dose:** Blood pressure (lying and standing), pulse and temperature.Service user should be regularly prompted about constipation. |
| **BLOOD TESTS** |
| Full Blood Count plus differential, CRP and troponin levels will be organised by the Clozapine Clinic and taken on a weekly basis on the ward. CRP and troponin should only be continued weekly for the first 4 weeks of treatment.Random Blood Glucose will be monitored by ward staff using a Glucometer on a weekly basis. * For non-diabetic service users, any results greater than 7mmols/L should be reported to the ward doctor.
* With known diabetics any result outside of the range 5-8mmols/L should be reported to the ward doctor.
 |

* 1. Supply and administration of clozapine during titration period

Clozapine will be ordered and dispensed weekly in accordance with the service user’s inpatient medication chart and following the receipt of a valid blood result as indicated by the clozapine monitoring system – that is a ‘green’ or ‘amber’ result.

Nursing staff may only administer clozapine to a service user if the service user has their own labelled supply that has been issued by pharmacy. If the service user does not have their own labelled clozapine supply, the nurse must contact pharmacy and not administer another service user’s supply.

* 1. Leave from the ward

Day 1

The service user should arrive on the ward for 09.00, in order to receive their first dose of clozapine. They should remain on the ward until their physical observations are re-checked at 18.00. These should be within normal limits (or agreed limits) and they should be considered medically fit for leave. The service user should ideally be accompanied by a carer or responsible adult when on leave.

Days 2-6

The service user should arrive on the ward for 09.00, in order to receive their morning dose of clozapine. They should remain on the ward the entire day. They should not be sent on leave until at least 2 hours after their 18.00 clozapine dose. Physical observations should be within normal (or agreed) limits and they should be considered medically fit for leave. The service user should ideally be accompanied by a carer or responsible adult when on leave.

Day 7-onwards

The service user should arrive on the ward for 09.00, in order to receive their morning dose of clozapine. They may be sent on leave 2 hours after their morning dose if their physical observations are within normal (or agreed) limits and they are considered medically fit.

The service user should return to the ward for 18.00 for their evening dose of clozapine. They must not be sent on leave until at least 2 hours after their clozapine dose. Physical observations should be within normal limits (or agreed limits) and they should be considered medically fit for leave.

**7.5 Community Titration**

7.51 Summary of titration

 Service user is initiated on clozapine by the Home Treatment Team.

7.52 Who is this titration suitable for?

This titration is suitable for those service users who are considered suitable for community initiation. It is expected that the clinician has given due consideration and discussed the pros and cons of initiating clozapine in the community taking into account medical co-morbidities that may present a risk during clozapine titration (for example epilepsy or problems with hypotension).

There must also be an adult at the service user’s home (or the address that he or she would be residing) for the entire time that they are on titration and they must consent to daily (and in the first 4 days twice daily) visits from the Home Treatment Team or Assertive Outreach Team coordinating the titration.

There must be access to an in-patient bed in the event that the service user’s mental or physical state deteriorates during the initiation.

* 1. Prescribing Clozapine During Titration

Community clozapine titrations should be prescribed using the [Trust blank](http://elftintranet/download/63ecb0b0-831e-4845-bcbf-12237c8609bb/f/Clozapine_Community_Titration_Blank_2017.doc) clozapine community titration sheet. This must be attached to the front of the service user’s community drug chart and in the regular section of the drug chart ‘Clozapine-see titration sheet’ should be written.

The community team doctor will review, at a minimum, once every week. The doctor will be expected to assess the service user's progress, enquire into and review any adverse reactions to clozapine and manage any other anti-psychotic medication; cross- tapering etc.

* 1. Monitoring to be carried out during titration period

|  |
| --- |
| **PHYSICAL OBSERVATIONS** |
| Visits should be undertaken by at least one mental health practitioner who is competent at taking physical observations.All monitoring should be recorded on the [Trust physical observation sheet.](http://elftintranet/our_library/clinical_forms.asp)**DAYS 1-4****Before every clozapine dose:** Blood pressure (lying and standing), pulse and temperature. If observations are clinically appropriate, clozapine dose to be administered. **2 hours after every clozapine dose:** Blood pressure (lying and standing), pulse and temperature.Service user should be regularly prompted about constipation.**DAYS 5-14**Clinical decision made by team as to frequency of monitoring based on previous physical observations.If no concerns:**Before morning clozapine dose:** Blood pressure (lying and standing), pulse and temperature. If observations are clinically appropriate, clozapine dose to be administered and evening dose of clozapine will be left as a TTA.**At night time:** Member of HTT to phone service user and check how they are.Service user should be regularly prompted about constipation.If higher level of monitoring required:**Before morning clozapine dose:** Blood pressure (lying and standing), pulse and temperature. If observations are clinically appropriate, clozapine dose to be administered.**Before night-time clozapine dose:** Blood pressure (lying and standing), pulse and temperature. If observations are clinically appropriate, clozapine dose to be administered.Service user should be regularly prompted about constipation.**DAY 14 ONWARDS**Alternate day blood pressure (lying and standing), pulse and temperature. If observations are clinically appropriate, clozapine dose to be administered and TTA left for that evening and the following day.Service user should be regularly prompted about constipation. |
| **BLOOD TESTS** |
| Full Blood Count plus differential, CRP and troponin levels will be organised by the Clozapine Clinic and taken on a weekly basis on the ward. CRP and troponin should only be continued weekly for the first four weeks of treatment.Random Blood Glucose will be monitored by ward staff using a Glucometer on a weekly basis (see section 4.72) |

* 1. Supply and administration of clozapine during titration period

Clozapine will be ordered and dispensed weekly in accordance with the service user’s community medication chart and following the receipt of a valid blood result as indicated by ZTAS – that is a ‘green’ or ‘amber’ result.

 Nursing staff may only administer clozapine to a service user if the service user has their own labelled supply that has been issued by pharmacy. If the service user does not have a labelled clozapine supply, the nurse must contact pharmacy and not administer another service user’s supply.

 7.6 **Clozapine brands and formulations**

Clozapine brands used in ELFT are Zaponex (City & Hackney, Tower Hamlets and Newham) and Denzapine (Luton and Bedfordshire). Zaponex and Denzapine are both available in tablets and oral suspension. Zaponex is also available as oro-dispersible tablets.

Intramuscular clozapine is an option for certain patients. See the Intramuscular Clozapine policy for inclusion criteria.

**8.0 Maintenance treatment with clozapine and further dose changes**

8.1For inpatient titrations on EPMA, once the titration has reached a target dose of 100mg MANE and 200mg NOCTE, the protocol will persist with these doses indefinitely. It is therefore essential that the titration protocol and the persisting doses are discontinued prior to prescribing a regular, maintenance clozapine dose. For non-EPMA clozapine titrations, the titration sheet should be filed in the service user’s medical notes and a new prescription of clozapine prescribed in the regular section of their drug chart. Any subsequent dose increases are limited to a maximum of 50mg a day, to reduce the risk of orthostatic hypotension and other complications. Any further dose increases do not require the enhanced monitoring associated with the titration period.

8.2 Clozapine will be ordered and dispensed weekly in accordance with the service user’s community medication chart and following the receipt of a valid blood result as indicated by clozapine monitoring system – that is a ‘green’ or ‘amber’ result.

8.3 Nursing staff may only administer clozapine to a service user if the service user has their own labelled supply that has been issued by pharmacy. If the service user does not have a labelled clozapine supply, the nurse must contact pharmacy and not administer another service user’s supply.

**9.0 Discharge Planning**

9.1 When considering discharging service users from the ward please ensure that:

* You have informed the Clozapine Clinic and the Pharmacy Department of impending discharge.
* That you are certain the service user has a follow up appointment with the Clozapine Clinic **(Please see section 4.1 for clinic contact details).** Preferably their first appointment should be once they have attained one week’s leave from the ward.
* That a discharge care plan and a comprehensive discharge summary is sent to the Clozapine Clinic and Pharmacy Dept.
* An outpatient clozapine prescription is completed and given to pharmacy so that the service user can receive a continued supply of clozapine post discharge. This prescription should only contain medicines that cannot be prescribed by the GP.

9.2If at any time anyone involved in the service users care is concerned about side effects or any other aspect of their presentation, they should contact the Ward, Pharmacy Department and/or the Clozapine Clinic to seek further advice.

**10.0 Outpatient Care and Prescribing**

10.1 Following discharge, the clozapine clinic will coordinate all operational aspects around treatment with clozapine in the community. These will include undertaking and processing the required blood tests, undertaking necessary physical health monitoring, issuing medication and liaising with the relevant Mental Health team and GP where appropriate. For a full list of these aspects please refer to the Clozapine Clinic Standard Operating Procedure. **The clozapine clinic does not take over any care coordinator responsibilities.**

10.2 All outpatient prescribing is via clozapine outpatient prescription forms. These are held centrally at Mile End Pharmacy where prescriptions are dispensed. Medication is then sent to the relevant Clozapine Clinic for issue to the service user. Owing to the centralised location of the clozapine prescriptions, pharmacists may make dose alterations or other changes to these prescriptions following a written request from the prescriber with words to this effect.

**11.0 Treatment Breaks**

11.1 If a service user misses a single dose, the next dose should not be doubled. The service user should continue with their next prescribed dose as normal.

11.2 Clozapine must not be re-started at the original dose if there has been a treatment break of greater than 48 hours. Re-starting at the original dose after a treatment break could prove harmful to the service user, increasing their susceptibility to severe side effects including seizures.

11.2 Following a break in treatment, the appropriate Clozapine monitoring service must be contacted to clarify the necessary monitoring requirements. If the treatment break is **greater than three days**, the service user will **require weekly FBC monitoring for six weeks.** After this time period the service user can revert to their original blood test frequency. If the treatment break was for **four weeks** or greater, the patient will **require weekly monitoring for 18 weeks**, before they can revert to their original blood test frequency.

11.3 Those service users who re-start clozapine will require re-titration to their original dose. The speed of this re-titration will be dependent on the duration of clozapine abstinence, the service user’s mental state, medical co-morbidities as well as team specific operational factors.

11.4 Re-titration is service user specific and the Clozapine Clinic pharmacist and consultant psychiatrist should devise a suitable and appropriate re-titration prescription for each individual service user. In some cases, it may be possible to undertake an accelerated re-titration (that is, faster than the standard titration set out in this policy). Nevertheless, more cautious dosage titration is recommended for the elderly and patients with medical conditions that will lead to increase side effects e.g. cardiac, renal impairment and Parkinson’s disease. Hypotension, tachycardia and seizures are risks when restarting clozapine.

 The pace of titration should be guided by the physical health monitoring done pre and post dose i.e. BP and pulse

11.5 The dose prescribed must be able to be administered from the available tablets doses of clozapine (ie 25mg or 100mg). Splitting tablets must be done by score line or tablet cutter where doses are half or quarter. Consider use of oro-dispersible where doses tablet strengths are more varied. Check BNF and ward pharmacist.

11.6 Troponin and CRP monitoring during re-titration of clozapine for patients previously exposed to the drug should be considered on a case- by- case basis by clinicians. The decision whether to or not to perform the required monitoring should take into consideration factors such as; the patient’s previous medical history, length of time of clozapine discontinuation, and any known cardiac risk factors the patient may have.

**12.0 Ceasing Treatment of Clozapine**

12.1 The Clozapine Clinic should be informed when there are plans to discontinue clozapine. Where possible, clozapine should be gradually reduced over a period of at least two weeks to reduce the risk of psychotic and cholinergic rebound.

12.2 The Clozapine Clinic will contact clozapine monitoring system to notify them of the plan to discontinue clozapine.

12.3 Blood test monitoring will still needs to continue for a further four weeks following ceasing clozapine.

**13.0** **Treating Out of Area Service Users with Clozapine**

13.1ELFT staff should use the following [algorithm](http://elftintranet/our_library/medicines_forms_and_templates.asp) for dealing with out of area patients already established on clozapine.

13.2 Supplies of clozapine should be obtained from the service user’s local clozapine service.

13.3 In exceptional circumstances ELFT pharmacy may be able to supply up to 48 hours supply of clozapine until more can be obtained from the patient’s normal clozapine service. In some circumstances (for example long stay medical admission) it may be more appropriate to transfer the service user’s clozapine service over to ELFT. However this would require transfer of the service user’s psychiatric care over to a local consultant whilst they remain in the medical facility.

**14.0 Service Users Going on Holiday**

14.1 Owing to the mandatory MHRA requirement for blood tests there are limits to how much clozapine may be supplied to the service user. The amount that can be supplied will be dependent on the service user’s current frequency of blood tests:

|  |  |  |  |
| --- | --- | --- | --- |
| **Frequency of Blood Test** | **Standard duration of time clozapine may be supplied for** | **Emergency duration of time clozapine may be supplied for if service user ‘late’** | **Total duration of time that clozapine may be supplied for** |
| 1/52 | 1/52 | 1/52 | 2/52 |
| 2/52 | 2/52 | 1/52 | 3/52 |
| 4/52 | 4/52 | 2/52 | 6/52 |

14*.2* If the service user is planning to go on holiday for a time period greater than the duration of clozapine that can be supplied, they should see their psychiatrist. In this meeting a treatment plan for alternative antipsychotic treatment arrangements will need to be made. ELFT should have no further responsibility for organising supplies of medication beyond holiday durations of 8 weeks.

14.3 It may be advisable for service users to keep a cover letter from their consultant/Care Coordinator if they are carrying a large amount of medication, to avoid any issues with customs.

14.4 The Clozapine Clinic is unable to accept the results of blood tests for service users that have been taken and measured outside of the UK.

14.5 If a treatment break occurs, clozapine monitoring system should be informed as set out in section 11.0 of this policy.

**15.0 Smoking, Smoking Cessation and Clozapine**

15.1 Smoking reduces clozapine plasma levels by up to 50% depending on the number and type of cigarettes smoked.

15.2 This effect is unrelated to nicotine and is caused by polycyclic aromatic hydrocarbons (PAHs) present in tobacco smoke. PAHs increase activity of the cytochrome P450 system that is responsible for the metabolism of a number of commonly used psychotropics.

15.3 Following smoking cessation, the service user is no longer exposed to PAHs and metabolism of these psychotropics decreases, resulting in increased plasma levels. Plasma levels will rise regardless of whether a patient is treated with smoking cessation aids such as NRT, bupropion or varenicline.

15.4 If smoking cessation is planned a clozapine plasma level should be taken whilst still smoking. On stopping smoking the clozapine dose should be reduced gradually (over a week) until around 75% dose reached. A clozapine plasma level should be repeated one week after stopping. Further dose reductions should be considered if necessary.

15.5 If the service user is re-starting smoking, the clozapine dose should be increased to the previous ‘normal’ smoking dose over one week. A clozapine plasma level should then be taken and dose adjustments made if necessary.

15.6 For further information, staff should refer to the [ELFT guidelines for smoking cessation pharmacotherapy](http://elftintranet/download/15bb262d-9249-4579-8d84-587f350c3ea0/f/Nicotine_Replacement_Guidelines_Jan_2016.docx).

16.0 Nursing Staff Responsibilities (Inpatient Units and Community Teams)

16.1 To ensure that all baseline and subsequent monitoring is carried out as set out in this policy.

16.2 To report any adverse effects or abnormal results to the medical team as appropriate.

16.3 To provide counselling and information to service users and carers as required.

16.4 To only administer clozapine to a service user if the service user has a labelled supply that has been issued by pharmacy. If the service user does not have a labelled clozapine supply, the nurse must contact pharmacy and not administer another service user’s supply.

16.5 To ensure that clozapine is not administered to service users who have not had clozapine for greater than 48 hours. The nurse should contact the doctor/clozapine clinic/pharmacy for further information.

**17.0 Medical Responsibilities**

17.1 To refer patients to the clozapine clinic by completing the [ELFT clozapine clinic referral form](http://elftintranet/download/c9e23199-43dd-4430-93a3-61a6870f6661/f/Clozapine_Referral_Form.doc) together with the full baseline tests performed as set out in this policy.

17.2 To register the patient with ZTAS and where necessary take required baseline blood samples and send to the local haematology departments for analysis.

* + 1. Once the patient has been discharged from the inpatient setting, a copy of the discharge summary, completed CPA documentation and risk assessment should be sent to the clinic.
	1. Responsible consultant to inform the clinic staff, pharmacy and G.P. of any changes in the dose of clozapine and other medications.
	2. To review all patients as requested by the clinic staff.
	3. Each patient attending the clinic should be reviewed by his or her responsible consultant /junior doctor every six months.
	4. To inform clinic, pharmacy and G.P. when clozapine is to be discontinued.
	5. To inform clinic if patient's care is transferred to/from another consultant.

**18.0 Pharmacy Responsibilities**

18.1 To be clinically responsible and oversee the safe and efficient dispensing and monitoring of clozapine for both in and out- patients.

18.2 To monitor the blood results for clozapine issued to wards using the clozapine monitoring system.

* 1. To provide counselling and information to patients and carers as required.
	2. To provide training to clinic and other relevant staff as required.
	3. To hold clozapine outpatient prescriptions. To make changes to these prescriptions if necessary under the written instructions of the Responsible Consultant. To ensure that all prescriptions are current and obtain new ones as necessary.

**19.0 Clozapine clinic responsibilities**

19.1 Liaise and co-ordinate care with the patients, their carers and care coordinator, consultants, psychiatric registrars, GPs and in-patient nursing staff.

* 1. To check that the referral form is completed and accurate and baseline observations are complete and within range and act on these as appropriate.
	2. To ensure that appropriate baseline and subsequent blood and physical health monitoring is carried out as set out in this policy.
	3. To inform the respective GP of any new service user to the clinic and of the clinic contact details.
	4. To liaise with the care coordinator, responsible consultant and/or SHO when concerned about the patient’s mental health. Concerns about physical health should be addressed to the G.P and responsible consultant and care coordinator.
1. **Training**

20.1 The Clozapine Clinic Managers throughout the Trust are to provide training for the Trusts medicines management training days. This is to be carried out on a rotational basis.

20.2 The Clozapine Clinic Manager is to provide training to all Care Co-ordination teams, inpatient services and to all of the relevant supported housing projects throughout their borough on a yearly basis.

20.3 The Clinic will provide a training environment for student nurses and students of other disciplines, e.g. OT and pre-registration Pharmacy students.

1. **Clozapine Plasma Levels**

21.1 A clozapine plasma level should be taken annually and when requested by the prescriber (clozapine assay or serum clozapine level).

21.2 Monitoring blood clozapine levels for toxicity is advised in certain clinical situations:

• change of smoking status or switching to an e-cigarette

• concomitant medicines may interact to increase blood clozapine levels

• a patient has pneumonia or other serious infection

• poor (reduced) clozapine metabolism is suspected

• toxicity is suspected

• adverse reaction to clozapine

• poor/non-concordance is suspected.

21.3 If blood clozapine level monitoring is carried out, this should be in addition to the required blood tests to manage the risk of agranulocytosis. Refer to the full Summaries of Product Characteristics for other important warnings, interactions, and recommendations for clozapine.

21.4 Clozapine plasma levels may be useful as a guide to dosing in conjunction with clinical presentation, most reference sources recommend aiming for a level between 0.35 – 0.6mg/L 1 8.

21.5 This should be a ‘Trough level’. For accuracy, it should be carried out 12 hours after last dose of clozapine. Usually clozapine is taken at 10pm the night before the test. The blood test to take place at around 10am. Any morning dose of clozapine must be omitted until after the blood test. The Service User does not need to be ‘Nil by mouth’ and they can take all other medications.

21.6 Levels should be taken using the sample packs in clinic and should be sent directly to Toxicology Unit. Packs include a lavender topped EDTA (FBC) bottle, labelled with a haematology label and packaged in a rigid transporter. This should then be placed in the sealable plastic bag along with the completed [Kings Path request form](file:///%5C%5CSVR-FS01.xelcmht.nhs.uk%5CK_SharedDepts%5CPharmacy%5CClinical%5CClozapine%5CKing%27s%20flyers%20and%20forms%5CClozapine%20Request%20Form%20KCH%20Final.doc) and then placed in the envelope. This package should be posted to the below address with a Trust ‘return address’ label on the reverse. Magna Labs are also used in addition to Kings Path.

**Toxicology Unit,**

**Bessemer Wing,**

**Kings College Hospital,**

**Denmark Hill,**

**London,**

**SE5 9RS**

21.7 Clinic staff/Pharmacy Dept will be notified by email that the result is available on the [Kings College Hospital Pathology website.](https://www.kch.nhs.uk/gps/gp-pathology-guide/pathology-contact-details) All Clinic Nurses should be registered with this site. Once received, the Clinic Manager or other Clinic staff will then email the result directly to the RC and any other involved professionals including care co-ordinator and mental health team. The prescriber then needs to decide on any dose changes or the covering consultant in their absence which must be documented on RiO.

21.8 An aid to interpret and act on plasma level results is provided by the monitoring scheme for each Clozapine brand.

21.9 Typical side effects associated with high plasma levels or clozapine toxicity, are orthostatic hypotension, dizziness, hypersalivation, sedation, tachycardia, nocturnal enuresis, irritability, and confusion / mental status change. The risk of seizures significantly increases with clozapine plasma levels greater than 0.6 mg/L but below 1mg/L, the recommendation would be a clinical decision, based on the patient’s clinical response and side effect profile and would either be a, dose reduction of clozapine and/or addition of an anticonvulsant.

21.10 Clozapine and norclozapine plasma levels are both reported on via lab reports. A clozapine/norclozapine ratio greater than 2, may suggest a non-trough sample. A ratio below 0.5 suggests either poor adherence within the last 24 hours or so, or that alterations in dose schedule would probably be beneficial. A relatively high ratio in combination with a normal clozapine level (e.g. low nor-clozapine level) could indicate non-compliance disguised by recent taking of prescribed doses, but other explanations are possible. For interpretation it is vital that other aspects indicating non-compliance are also taken into account.

* 1. In general, dose reductions should be done gradually. Very high plasma levels may result in a longer elimination time. Therefore, in patients with extremely high plasma levels it may be appropriate to omit a dose and/or to immediately continue on a lower dose, to allow the excess clozapine to clear. This should be discussed with the prescriber and pharmacy and if the prescriber is not available this should be discussed with the covering consultant to consider if the patient should be referred to A and E depending on the clinical presentation and signs of toxicity.
1. **Communication with GP’s**
	1. All patients prescribed Clozapine should have Clozapine listed as a prescribed medication in discharge summary/clinic letters sent to GP’s, this should include who the prescriber is and contact details for supply. Clozapine Clinics can also notify GP’s to request the Clozapine is listed as a prescribed medication onto the GP clinical system.

22.2 Once the GP has transcribed this information onto their clinical system, other services are then able to view this on the summary care records (SCR) for the patient.

22.3 Clozapine Clinic leads for each borough will carry out 6 monthly audits for all new patients, plus a random sample of 20 Clozapine patients, to ensure this information is visible on SCR. Any discrepancies should be brought to the attention of the relevant GP practice.

 [External memo sent 08.09.2022](file:///C%3A%5CUsers%5Cpisaneschil%5CDownloads%5CRecording%20medicines%20prescribed%20elsewhere.%20.pdf)

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