

Key messages for patients taking clozapine in EKHUFT

The appropriate use of clozapine in acute care is important as missed doses may result in relapse of psychotic illness and if more than 48 hours has elapsed since the last dose, necessitate re-titration of the treatment because of the risk of serious, potentially fatal side effects if treatment is restarted at full dose after this time.

Clozapine may not always appear on the regular medications list from a patient's general practitioner as clozapine is managed by Mental Health Trusts.

Therefore, if a patient is admitted/presents with a past medical history of either

1. Schizophrenia (especially if documented as treatment resistant) or
2. Psychosis during the course of Parkinson's disease

And there is no documented antipsychotic medication listed on their GP record then the possibility of the use/prescription of clozapine must be considered and investigated.

Following advice from the [MHRA in August 2020](#) monitoring blood clozapine levels for toxicity is now advised in certain clinical situations such as when:

1. A patient stops smoking or switches to an e-cigarette – for example this may be associated with hospital admission because the patient is unable to smoke or switched to nicotine patches
2. Medicines are prescribed may interact to increase blood clozapine levels (see below)
3. The patient has pneumonia or other serious infection
4. Poor (reduced) clozapine metabolism is suspected
5. Poor patient compliance is suspected
6. Toxicity is suspected
7. Any patient presenting with a daily dose of >600mg/day
8. Any patient displaying excessive side effects, for example excessive drooling being quite a common side effect when patients are poorly compliant with dosing/taking ad-hoc doses.

if blood clozapine level monitoring is carried out, this should be in addition to the required blood tests to manage the risk of agranulocytosis

Please note EKHUFT pathology does not have the facility to analyse samples for clozapine levels, however the adult mental health liaison psychiatry team has the kits to do this.

In all cases the patient must be referred to the Adult Mental Health liaison psychiatry team.

Commonly interacting drugs - Clozapine

1. **Bone marrow suppressants** (e.g. carbamazepine, sulphonamides (e.g. co-trimoxazole), and cytotoxic agents)
2. **Medication with Anticholinergic actions** (e.g. many antidepressants, drugs used in the treatment of movement disorders, anti-emetic drugs) as constipation in patients who are taking clozapine can be **fatal**
3. **Erythromycin and ciprofloxacin** can significantly raise clozapine plasma levels and prolong QTc intervals
4. **CNS depressants** e.g. benzodiazepines that can increase sedative and respiratory depressant effects

BACKGROUND

Clozapine is used for indications related to psychosis, resistant to other treatments. Therefore patients prescribed clozapine have a more severe illness. Clozapine is a critical medication as omission can cause withdrawal problems. Patients prescribed clozapine are subject to mandatory regular FBC monitoring, because of a relatively high risk of neutropenia/ agranulocytosis during

treatment. Thus the drug is used in the UK via a clozapine monitoring service which authorizes on going supply of clozapine and the drug may only be initiated by a psychiatrist. GPs do not provide prescriptions in East Kent. The [MHRA now requires monitoring of blood concentrations of clozapine](#) (Clozaril ® (only brand used in Kent), Denzapine ®, Zaponex ®) in certain clinical

situations which were not compulsory previously. In the Trust clozapine levels have to be arranged through the liaison psychiatric service who have access to the special kits required.

The Trust is aware of historic poor knowledge amongst clinicians of the potential significance of clozapine concomitant use in presentations with severe constipation, paralytic ileus, cardiomyopathy or diabetes.

Clinicians can use MIG2 (GP record option in Patient Timeline) or the Kent and Medway clinical record portal from May 2021 to access the Mental Health electronic record to allow confirmation of attendance at a local Clozapine clinic

ACTION POINTS for prescribers, and pharmacists

- Recognize that patients on clozapine are likely to require specific actions on presentation and refer to guidelines in pharmacy microguide>Prescribing Guides>Medicines used in Psychiatry or accessible via [formulary](#)
- Omission of clozapine for more than 48 hours necessitates re titration of the dose, during which frequent monitoring of physical parameters is mandatory.
- Contact Liaison Psychiatry urgently if a patient needs re titration
- Contact Liaison Psychiatry routinely to arrange blood levels if any of following apply to your patient
 - Stops smoking or switches to an e cigarette (note we are a non smoking Trust so this will apply to many admissions)
 - Are started on concomitant medicines that may interact to increase blood clozapine levels. These include: hormonal contraceptives, fluvoxamine, ciprofloxacin, fluconazole, miconazole, valproate, modafinil and caffeine. As other strong CYP1A2 inhibitors or inhibitors of cytochrome P450 isozymes could have this interaction it would be advisable to err on side of caution with for example clarithromycin, levofloxacin and any azole antifungal or HIV drugs
 - Has pneumonia or other serious infection
 - Poor (reduced) clozapine metabolism is suspected
 - Toxicity is suspected
- Do not give concomitant clozapine with any drug with myelosuppression risk. This includes: carbamazepine, chloramphenicol, sulphonamides (e.g. cotrimoxazole), penicillamine, carbimazole, immunosuppressants, DMARDs, and cytotoxic agents.
- Emergency physicians must check a FBC if a patient on clozapine presents with symptoms like sore throat that can be associated with myelosuppression.
- All doctors but in particular surgeons, cardiologists, emergency physicians and haematologists need to be aware of significant known side effects of clozapine

- Severe constipation, leading to impaction and obstruction
- Paralytic ileus
- Myocarditis/cardiomyopathy
- Disturbed glucose control and diabetes
- Myelosuppression

Fuller guidelines for pharmacy staff and others within the Trust are at this [link](#) or [downloadable from formulary](#). The Kent and Medway Partnership Trust Clozapine policy V4.0 from which this is extracted is accessible at <https://www.kmptformulary.nhs.uk/therapeutic-sections/psychosis-related-disorders/treatment-resistant-schizophrenia/> and should be referred to for full detail. The following link is for the local guidance on frequency of [FBC monitoring patients on Clozapine](#).

Contact details:

Advice out of hours on clozapine via the KMPT pharmacy service who can be contacted on 01322622222

Contact details:

TRUST	USUAL PHARMACY THAT SUPPLIES	CLINICAL ADVICE CONTACTS
EAST KENT: Clozaril CPMS 08457698269 www.clozaril.co.uk	Lloyds Pharmacy Singleton 01233635385	Pharmacy team St Martin's Hospital Canterbury 01227812193
WEST KENT Clozaril CPMS 08457698269 www.clozaril.co.uk	Lloyds Pharmacy Rainham 01634375103	Pharmacy team Priority House Maidstone 01622 723219 Pharmacy team Elizabeth Raybould Centre Dartford

Kent and Medway **NHS**
NHS and Social Care Partnership Trust

KMPT Guidance to Acute Trusts

All patients prescribed clozapine in the Acute Trust should remain open to the liaison psychiatry team for ongoing monitoring. Key messages have been highlighted below for acute staff managing patients admitted on clozapine:

- Check patient's compliance with clozapine. Omission of clozapine for more than 48 hours necessitates re-titration of the dose, during which frequent monitoring of physical parameters is mandatory. Ensure the Liaison Psychiatry Consultant is informed urgently if a patient has missed their dose for more than 48 hours and do not prescribe clozapine until directed by the liaison team.
- Confirm the clozapine brand and dose the patient takes e.g. from patients own drugs, community clozapine prescription or by contacting the Community Mental Health Team and the pharmacy that dispenses the clozapine. In Kent & Medway Partnership Trust, Lloyds Pharmacy supply the Clozaril brand of clozapine to our patients. Note: GP summary care

records may not include current information as clozapine is generally not prescribed by the GP.

- It is important to establish what the patients Full Blood Count monitoring frequency is i.e. weekly, fortnightly or monthly. This can be confirmed with your local KMPT pharmacy team.
- The liaison psychiatry team will inform the patients Community consultant and Care-coordinator of the patient's admission to the Acute Hospital.
- Ensure staff are aware of the side-effects of clozapine which may include:
 - Severe constipation, leading to impaction and obstruction– **this can be fatal if left untreated, if necessary clozapine should be withheld until such time as the constipation has been rectified**
 - Myocarditis/cardiomyopathy
 - Disturbed glucose control and diabetes
- In some medical scenarios e.g. acute infection such as pneumonia or certain cardiac symptoms, patients may need a lower dose of clozapine than usual. This should be discussed with the liaison psychiatry Consultant.
- Raised clozapine plasma levels may cause drowsiness, ataxia, confusion, seizures. Clozapine plasma levels may be markedly raised by:
 - Cessation/reduction of cigarette smoking – be aware of this if smoking is stopped or prevented during admission. Nicotine replacement therapy DOES NOT prevent this rise in plasma levels. As a rule of thumb clozapine plasma levels can rise by up to 70% after stopping smoking and the effects can be seen within 3 – 7 days
 - Interaction with other medicines including antibiotics such as erythromycin and ciprofloxacin which patients may be prescribed in the Acute Trust to treat infections.
- If you suspect clozapine toxicity or patient has stopped smoking then a clozapine plasma level should be done and packs have been supplied to all the liaison psychiatry teams. Note the pathology labs in Kent do not check clozapine plasma levels. For further advice contact your local KMPT pharmacy team.

When patients are discharged from the Acute Hospital the liaison psychiatry team will notify the patient's Community Consultant and care-coordinator to ensure the patient is followed up.

GUIDELINES FOR PHARMACY STAFF MANAGING CLOZAPINE FOR PATIENTS ADMITTED TO ACUTE HOSPITALS

1 INTRODUCTION

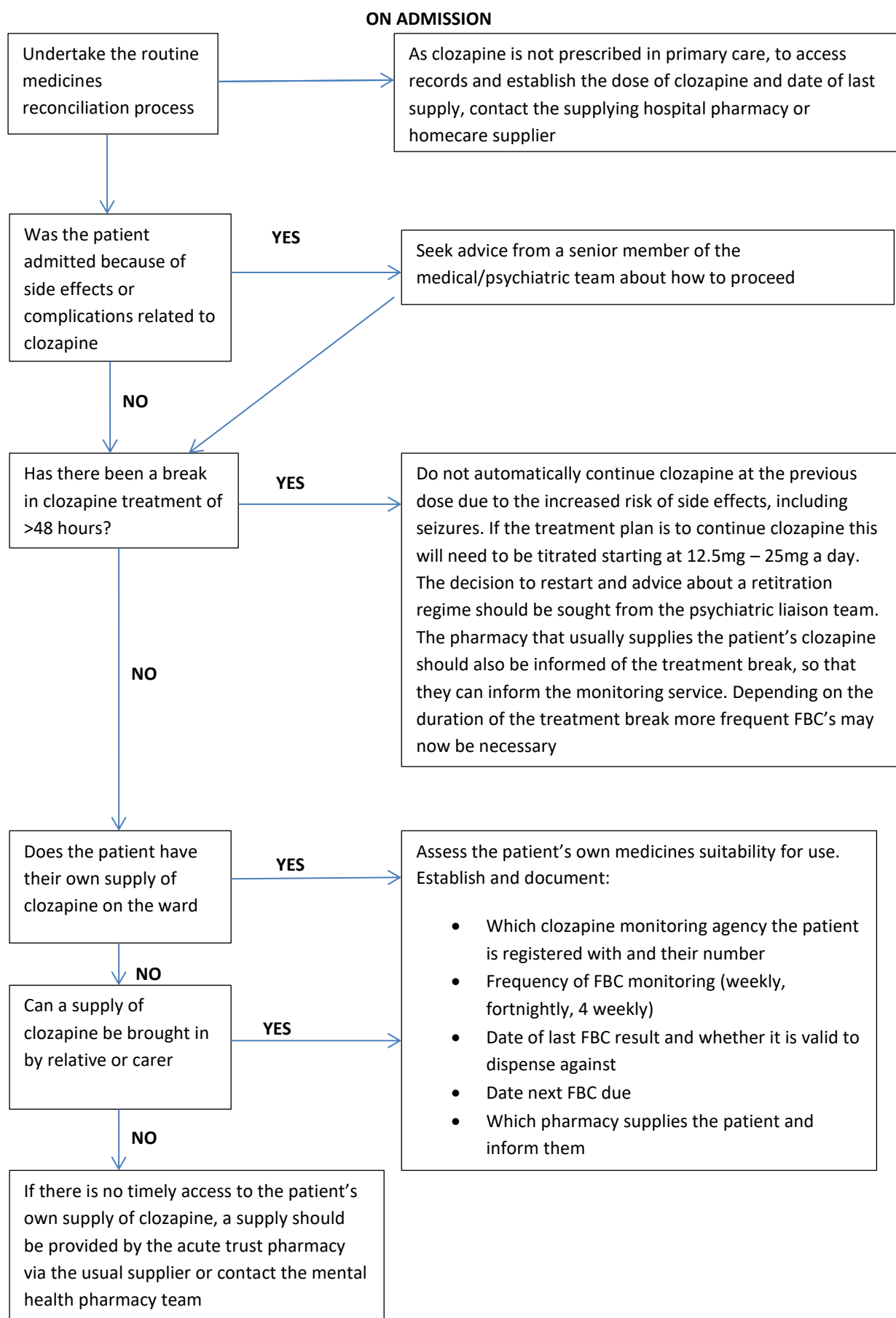
- 1.1 Clozapine is an antipsychotic used most commonly in the treatment of schizophrenia resistant to other treatments. Therefore patients prescribed clozapine have a more severe illness.
- 1.2 Patients prescribed clozapine are subject to mandatory regular FBC monitoring, because of a relatively high (approx. 1%) risk of neutropenia/agranulocytosis during treatment. These FBC's are recorded by a clozapine monitoring service which authorises on-going supply of clozapine.
- 1.3 Clozapine prescribing cannot be transferred to primary care without an agreed shared-care protocol.
- 1.4 It is a requirement that all patients prescribed clozapine; their consultant psychiatrist and the supplying pharmacy are registered with a clozapine monitoring service. There are 3 agencies nationally – ZTAS, CPMS and DMS. Only pharmacies registered with one of these can dispense clozapine.
- 1.5 Co-prescription of other medicines with clozapine that may cause blood dyscrasias increases the risk of neutropenia or agranulocytosis.
- 1.6 Omission of clozapine for more than 48 hours necessitates re-titration of the dose starting at 12.5mg or 25mg a day, and during which frequent monitoring of physical parameters is mandatory. Whenever possible, such a treatment break should be avoided. Sudden discontinuation of clozapine may result in an abrupt and severe relapse of psychotic symptoms.
- 1.7 Side effects of clozapine may include:
 - Severe constipation, leading to impaction and obstruction
 - Myocarditis/cardiomyopathy
 - Disturbed glucose control and diabetes
- 1.8 In some medical scenarios e.g. acute infection such as pneumonia, certain cardiac symptoms or following a sudden cessation or decrease in smoking, patients may need a lower dose of clozapine than usual. The management of individual cases is best discussed with the liaison psychiatric team.
- 1.9 Raised clozapine plasma levels may cause drowsiness, ataxia, confusion, seizures. Clozapine plasma levels may be markedly raised by:
 - Cessation/reduction of cigarette smoking – be aware of this if smoking is stopped or prevented during admission. Nicotine replacement therapy DOES NOT prevent this rise in plasma levels.
 - Interaction with other medicines including erythromycin and ciprofloxacin

2 WHAT TO DO

- 2.1 Consider the role of clozapine and its side effects in the context of:

- The current presentation, including cardiomyopathy/myocarditis, constipation and problems related to raised plasma levels
 - Recent, current and intended co-prescribed medicines
 - Changes in smoking status
- 2.2 Check FBC to exclude clozapine-induced agranulocytosis/neutropenia. Clozapine must be stopped if WBC $<3 \times 10^9$ /L or neutrophils $<1.5 \times 10^9$ /L
- 2.3 Confirm dose of clozapine e.g. from patients own drugs, relevant pharmacy or mental health trust. GP Summary Care Records may not include current information as clozapine is generally not prescribed by GP.
- 2.4 Confirm that the patient has been compliant with treatment, notably over the previous 48 hours. If so, and otherwise clinically appropriate, prescribe.

3 HOW TO MAINTAIN SUPPLIES OF CLOZAPINE FOR PATIENTS



Clozapine should be considered a critical medicine, and supplies should be made in a timely manner. Delays in doses mean the patient is liable to acute psychotic relapse, which may complicate their physical care. Re-titrating to the previous maintenance dose may take 2-3 weeks.

potential impact of enforced smoking cessation on their clozapine plasma levels to avoid toxicity, check plasma levels and amend dose as necessary. Contact mental health pharmacy team for advice

- Continue to monitor FBC results at the intervals recommended by the clozapine monitoring service that the patient is registered with
- Report FBC values to the relevant clozapine monitoring service
- Continue to supply clozapine for the duration of the admission
- Inform the usual supplying pharmacy of the patient's admission, and that therefore there is no need for them to supply

ON DISCHARGE

- Provide the same duration of supply of clozapine to the patient as per usual discharge medicines, but reduce if needed be in line with the duration allowed by the FBC monitoring regulations
- Inform the usual supplying pharmacy of the patient's discharge , and the details of the amount of clozapine supplied

CONTACT DETAILS

TRUST	USUAL PHARMACY THAT SUPPLIES	CLINICAL ADVICE CONTACTS	OUT OF HOURS CONTACTS
EAST KENT: Clozaril CPMS 08457698269 www.clozaril.co.uk	Lloyds Pharmacy Singleton 01233635385	Pharmacy team St Martin's Hospital Canterbury 01227812193	On call Pharmacist 01322622222
WEST KENT Clozaril CPMS 08457698269 www.clozaril.co.uk	Lloyds Pharmacy Rainham 01634375103	Pharmacy team Priority House Maidstone 01622 723219 Pharmacy team Elizabeth Raybould Centre Dartford 01322622070	On call Pharmacist 01322622222