Health and Social Care in Northern Ireland

Clozapine Care Pathway

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Use addressograph or write in CAPITAL LETTERS

Surname: ……

First names: ……

HCN: ……

DOB: …….. Check Identity

STAFF INFORMATION

This Pathway should be used as a guideline towards the safe and effective delivery of care necessary for the initiation and titration of patients prescribed Clozapine. Throughout the document the clozapine patients monitoring service will refer to the incumbent supplier of clozapine in Northern Ireland, currently ZTAS.

It replaces all previous documentation.

CLOZAPINE PATHWAY SIGNATURE SHEET

If you use initials only at any-time throughout the care pathway, this page serves as a record of your full signature, and thus satisfies Medico-legal requirements. Accordingly, all staff using initials only throughout the Pathway must complete the details below

DATE	**FULL NAME** *(block capitals)*	**DESIGNATION** *(block capitals)*	**PROFESSIONAL REGISTRATION NUMBER**	**SIGNATURE**	**INITIALS**

Name		H&C No	

REFERRAL FOR CLOZAPINE

Key staff details	Patient details
G.P – Name, Phone Number	**Write in CAPITAL LETTERS or use addressograph** **Surname: ……..** **First name: ……** **HCN: ……..** **DOB: ……..**

Clozapine status on assessment	Date		Signature &Date
Is this a re-titration?	No ☐ *(Proceed to PRE-INITIATION CHECKLIST)*	Yes ☐ *(Complete the duration of treatment break below)*	
Record duration of treatment break	*Please state duration* _____*hours/days* *(Proceed to RE-TITRATION CHECKLIST)*	**NB if this is more than 28 days, this is classed as a new registration proceed as below** *(Proceed to PRE-INITIATION CHECKLIST)*	
Is this a re-challenge?	No ☐	Yes ☐ *(SEE NOTE BELOW)*	

PLEASE NOTE
If this is a clozapine re-challenge due to serious adverse event, i.e. a previous confirmed RED alert due to Neutropenia or Myocarditis, a multidisciplinary case discussion must be held before proceeding any further. Advice should also be sought from ZTAS.

PRE-INITIATION CHECKLIST		Signature & Date
Indication *Please tick that which applies* • Treatment resistant schizophrenia • Severe, untreatable neurological adverse reactions to other antipsychotic agents, including atypical antipsychotics • Other (please indicate) _____ (Off-Licence Agreement will need to be completed) • Psychosis during the course of Parkinson's disease Refer to specific dosing guidance for this group	☐ ☐ ☐ ☐	
Consideration of the various contra-indications (see **SPC** for full list)	☐	
Any significant physical health concerns • NO PHYSICAL HEALTH CONCERNS **or** • Diabetes: Type 1 Type 2 • Neurological including epilepsy • Severe respiratory disease • Cardiovascular (refer to cardiac assessment section) • Other _____	☐ **or** ☐ ☐ ☐ ☐ ☐	
Clozapine counselling and written information provided	☐	

CLOZAPINE INITIATION MEDICATION CHECKLIST

Previous antipsychotic medication: List previous antipsychotics and doses taken for at least six weeks (Must include at least one atypical antipsychotic)

Name of medicine (Print)	Dose	Approximate duration

Details of significant adverse medication reactions include if no history of problems

Please provide a complete list of currently prescribed medication.
NOTE: This must include all medication not just psychiatric medication.

• **Outpatients**-Provide a current NIECR Medication Printout	☐
• **Inpatients**-Provide a copy of the Prescription Kardex and if inpatient for <1 month provide a copy of NIECR	☐
• **List of medications that interact with clozapine checked (Appendix 1)**	☐

PHARMACY CLOZAPINE INITIATION MEDICATION REVIEW OUTCOME

FOR PHARMACY USE
Record Below any current medicine related issues

Name of medicine	Route, Dose and Frequency	Issue with Clozapine identified	Is combination contraindicated? (yes/no)

Comments and Actions: (See Appendix 1 or Appendix 5 for further information)
Pharmacist should record actions taken to address issues identified. Attach copies of correspondence with Consultant

Initiation of Clozapine has been: Agreed ☐ Deferred and referred ☐	**Signed:**		**Date**	

Name		H&C No	

CLOZAPINE WORK UP – BASELINE BLOODS

Date of test with a tick in the appropriate box when taken, those in bold MUST be within the last 10 days to be valid , those marked with (*) as per local agreement (if results from within the last month are available do not need repeated)

Date	Investigation	Tick	Results	Comments	Signature
	FBC	☐			
	WCC				
	Neutrophils				
	Eosinophils				
	Platelets				
	LFTs	☐			
	eGFR	☐			
	Troponin I or T	☐			
	BNP	☐			
	CRP	☐			
	Prolactin	☐			
	(*)Lipids	☐			
	(*)Glucose *(random or fasting)*	☐			
	(*)HbA1c	☐			
	Other – specify e.g. pregnancy test	☐			

CLOZAPINE WORK UP –BASELINE PHYSICAL EXAMINATION

Date	Observations	Results	Comments	Signature
	BP			
	Pulse			
	Temp			
	PO_2			
	Respiratory rate			
	Weight			
	Height			
	BMI			
	Waist circumference			
	ECG			
	Physical examination (details of same in notes)			
	Other – specify			

If any of the "work up" results shown are not within the normal range – Medical staff MUST be informed and action documented, as per relevant NICE guidance or Lester guidelines, by Medical Staff and /or Nurse

Cardiac Assessment

The assessments/tests below must be carried out for all patients.

- Physical examination including asking about cardiac symptoms.
- Family and personal history with regards cardiac disorders.
- ECG performed
- Troponin level (High sensitivity) >14ng/L, please consult a cardiologist before commencing Clozapine.
- Brain Natriuretic Protein (N Tpro BNP)

If there are no concerns a routine echocardiograph is not required before commencing clozapine. However, if in doubt, consult with a cardiologist.

CLOZAPINE WORK UP – BASELINE PATIENT PREPARATION				
Date	**Checklist**	**Yes**	**No**	**If No reason**
	Has the patient/family/carer been given information on benefits and possible side effects?	☐	☐	
	I have discussed the possibility of increased risk of raised temperature and infection, pneumonia, severe cardiac disease including myocarditis and or cardiomyopathy, seizures, embolism and severe constipation and actions to be taken to reduce these events occurring**.**	☐	☐	
	Does the patient understand the need for regular blood tests and physical monitoring?	☐	☐	
	Does the patient have a history of constipation?	☐	☐	
	Does the patient have any risk factor for constipation? e.g. concurrent opioids	☐	☐	
	If patient answered yes to either of the last two questions, has an action plan been developed?	☐	☐	
	The patient has been advised not to go out travelling alone in the first two weeks due to possible drowsiness and small risk of collapse.	☐	☐	
	The patient has been informed about the importance of not driving during the initiation of clozapine	☐	☐	
	Is the patient a current smoker? (if no omit next two questions)	☐	☐	
	Number of cigarettes smoked per day	☐ **per day**		
	Has smoking cessation advice been offered?	☐	☐	
	A baseline GASS (overleaf) has been completed.	☐	☐	
	Has the patient ben given the ZTAS "Information about registration with ZTAS" in accordance with GDPR regulations on processing of personal information (where appropriate this can be done at a later stage)	☐	☐	
Signed		Date		

CLOZAPINE WORK UP –CLOZAPINE TO PROCEED				
Date				**Consultant Signature**
	YES	☐	**Proceed to FINAL CLOZAPINE INITIATION PATHWAY CHECKLIST FOR INITIATION**	
	NO	☐	**Proceed to CLOZAPINE INITIATION NOT TO PROCEED**	

GLASGOW ANTIPSYCHOTIC SIDE-EFFECT SCALE (GASS)- CLOZAPINE

Name:		**Age:**		**Sex: M / F**
Date				

Caffeine intake Cups of tea or coffee per day……

Has there been a recent change in your smoking habit No ☐ Yes ☐ Details below

Increase/Decrease by ……. Cigarettes per day

This questionnaire is about how you have been recently. It is being used to determine if you are suffering from excessive side effects from your antipsychotic medication.
Please place a tick in the column which best indicates the degree to which you have experienced the following side effects. Tick the **end** box if you found that the side effect distressed you.

*Over the **past week**:*	*Never*	*Once*	*A few times*	*Everyday*	*Tick this box if distressing*
1. I felt sleepy during the day					
2. I felt drugged or like a zombie					
3. I felt dizzy when I stood up and/or have fainted					
4. I have felt my heart beating irregularly or unusually fast					
5. I have experienced jerking limbs or muscles					
6. I have been drooling					
7. My vision has been blurry					
8. My mouth has been dry					
9. I have felt like I am going to be sick or have vomited					
10. I have felt gastric reflux or heartburn					
11 I have had problems opening my bowels (constipation/diarrhoea)					
12. I have wet the bed					
13. I have been passing urine more often					
14 I have been thirsty					
15 I have felt more hungry than usual or have gained weight					
16. I have been having sexual problems					

I have also experienced
(Please write down any other side effects of physical problems or complaints that you may have had over the last week)

17
18
19
20

Staff Information

1. Allow the service user to fill in the questionnaire themselves, in some circumstances staff may have to support the patient to complete the assessment. Questions 1-20 relate to the previous week.

2. Scoring

For questions 1-16 award

0 points for an answer of "never".
1 point for the answer "once",
2 points for the answer "a few times"
3 points for the answer "everyday".

Total for all questions

3. For all patients a *total score* of:

0-16 = absent/mild side effects
17-32 = moderate side effects
over 32 = severe side effects

4. Side effects covered by questions

1-2 *S*edation and CNS side effects
3 *Postural hypotension*
4 *Tachycardia*
5 *Myoclonus*
6 *Hypersalivation* extra-pyramidal side effects
7-8 *A*nticholinergic side effects
9-10 *G*astro-intestinal side effects
11 *Constipation/overflow*
12 *Nocturnal enuresis*
13-14 *Screening for diabetes mellitus*
15 *W*eight gain
16 *Sexual dysfunction*

The column relating to the distress experienced with a particular side effect is not scored, but is intended to inform the clinician of the service user's views and condition.

Question 17-20 invite the service user to report any other side effects or problems not already mentioned. These questions are not scored but may instigate a discussion with the service user if clinically appropriate.

FINAL CLOZAPINE INITIATION PATHWAY CHECKLIST FOR INITIATION

Consultant declaration

I understand and have read the ZTAS Guidelines and the assessment and monitoring recommendations:

- The patient has had a physical examination and the results of his/her tests have been reviewed by me and I feel that the patient is suitable for commencing clozapine. ☐
- The medication checklist from pharmacy has been reviewed and actioned ☐
- I agree that a senior doctor will review the patient at least weekly during the titration process. ☐
- A member of the medical staff will be readily available by telephone during the first two weeks of initiation. ☐
- I recommend and have arranged that this patient will have the titration carried out via Community (slow titration) ☐ In patient unit/HTT (standard titration) ☐

Register patient with ZTAS using 'Patient Data Form' (as per local arrangements)	☐
Anticipated target clozapine dose documented, consider gender and smoking status (see below)	☐
Enter ZTAS PIN number in appropriate 'Clozapine Initiation Prescription, Administration and Monitoring Chart' prior to initiation	☐
Relevant 'Clozapine Prescription, Administration and Monitoring Chart' signed in the appropriate prescriber's signature box and copy sent to pharmacy, along with any local prescription/requisition requirements.	☐
Clozapine also prescribed on the in-patient chart/HTT record (as relevant) and annotated as an "additional chart"	☐
Where clozapine intramuscular is considered necessary the Regional Protocol for Intramuscular Clozapine MUST be used (to be ticked only when relevant)	☐

Signed **CONSULTANT PSYCHIATRIST**	Date

For information only

Clozapine issued to ward/area as per local arrangement(s).

FBC to be done weekly during initiation for 18 weeks then fortnightly for the first year.

Patient monitored as per appropriate Clozapine Initiation Prescription, Administration and Monitoring Chart Where additional monitoring is required, use appropriate trust forms

Target dose for a level of approximately 0.35 mg/L in a 40-year-old would be on average:

	Male	*Female*
Smoker	*525mg*	*325mg*
Non-smoker	*435mg*	*265mg*

Dosing considerations for Parkinson's disease this requires individual patient assessment:

The starting dose is usually 6.25mg-12.5mg/day, taken in the evening. Subsequent dose increases must be no more than 12.5mg increments, with a maximum of two 12.5mg increments a week, up to a maximum of 50mg, a dose that cannot be reached until the end of the second week. The mean effective daily dose is usually between 25mg and 37.5mg.

The total daily amount should preferably be given as a single dose in the evening. Dose increases should be limited or deferred if orthostatic hypotension, excessive sedation or confusion occurs.

The dose of 50mg/day should only be exceeded in exceptional cases, and the maximum dose of 100mg/day must never be exceeded. In the event that treatment for at least one week with a dose of 50mg fails to provide a satisfactory therapeutic response, dosage may be cautiously increased by increments of 12.5mg/week.

Name		H&C No	

RE-TITRATION CHECKLIST	
The patient has had a physical examination and the results of his/her tests have been reviewed and the patient is suitable for re-commencing clozapine.	☐
Confirm duration of treatment break. If the treatment break is < 48 hours prescribe normal dose as soon as possible and provided this is administered within 48 hours of last confirmed dose then there is no need for any further documentation.	☐
If the treatment break is > 48 hours then inform ZTAS of break in treatment	☐
Confirm ZTAS PIN number, previous maintenance dose, date of last FBC and arrange urgent blood as necessary. If treatment break >1 week then re-titrate as if a new patient. *(Stop and return to **CLOZAPINE WORK UP – BASELINE BLOODS**)*	☐
Complete 'Clozapine Standard Initiation Prescription, Administration and Monitoring Chart' and send a signed copy to pharmacy along with any local prescription requirements. Rate of re-titration will depend on duration of break in treatment and medical co-morbidities, seek advice from mental health pharmacist if necessary.	☐
Clozapine prescribed also on in-patient chart/HTT record and annotated as an "additional chart"	☐
Signed **CONSULTANT PSYCHIATRIST**	Date
For information only	
Patient monitored as per appropriate relevant 'Clozapine Prescription, Administration and Monitoring Chart' until stabilised on maintenance dose. *Where additional monitoring is required, use appropriate trust forms.* *FBC to be carried out weekly if treatment break > 72 hours in accordance with ZTAS recommendations.*	

CLOZAPINE INITIATION NOT TO PROCEED			
Reason for clozapine not proceeding			
	YES	**NO**	**If No reason**
Can patient be considered for clozapine in future	☐	☐	
Patient informed of reason	☐	☐	
Carer informed of reason	☐	☐	
Signed **CONSULTANT PSYCHIATRIST**	Date		

CLOZAPINE STOPPED			
Reason		**Details**	
Declined or consent withdrawn	☐		
Adverse effects	☐		
Other	☐		
	YES	**NO**	**If No reason**
Can patient be considered for clozapine in future	☐	☐	
Patient involved with decision	☐	☐	
Carer informed of reason	☐	☐	
GP advised of same	☐	☐	
ZTAS informed of same	☐		
Yellow card submitted	☐	☐	
Is there a need for an SAI	☐	☐	
Signed **CONSULTANT PSYCHIATRIST**	Date		

DISCHARGE / TRANSFER CHECKLIST For use when a patient is being discharged transferred from a ward/service to a new service/team/Trust.		**Signature & Date**
Link/MDT meeting: Relevant Teams/Keyworker/Pharmacist (when possible) to attend. To confirm: • Date of previous green result_____ • Date of next blood test(s) _____ • Frequency of dispensing _____ • Blood sample location _____ • Physical health check _____		
Ensure that where instalment clozapine supply is required e.g. on-going weekly dispensing or in a blister pack the appropriate adherence documentation has been completed for assessment of same if required.	☐	
OUT OF TRUST DISCHARGE ONLY Ensure the appropriate hospital pharmacy department has been notified of discharge/transfer	☐	
Ensure that sufficient clozapine is supplied consistent with blood validity and as per local arrangements with the receiving hospital pharmacy.	☐	
Ensure the appropriate hospital pharmacy has an up to date clozapine script (Appendix 2)	☐	
Clozapine Information sheet sent to GP/Practice based pharmacist (see Appendix 3) and community pharmacy where appropriate	☐	
Ensure the patient is registered to the appropriate consultant when necessary.	☐	
Ensure clozapine pathway is sent to appropriate team if necessary.	☐	

Appendix 1 Common Drug Interactions with Clozapine

Please note this list is not exhaustive. Prescribers should consult the current BNF for a full list of drug interactions. Full prescribing information for all Clozapine products can be found on the Electronic Medicines Compendium available at www.medicines.org.uk

Common Pharmacodynamic interactions with clozapine **Drugs in CAPITALS are particularly hazardous and are CONTRAINDICATED.**		
Drug or Drug Class	Potential additive side effects	Comments
CARBAMAZEPINE, **CARBIMAZOLE,** **CHLORAMPHENICOL,** **CYTOTOXICS,** **LONG-ACTING DEPOT-ANTIPSYCHOTICS,** **PENICILLAMINE,** **PHENYLBUTAZONE,** **SULPHONAMIDES** **(E.G. CO-TRIMOXAZOLE)** Rarely Other Antibiotics	Increased risk of Neutropenia	Titration can't proceed until contraindicated medicines have been withdrawn N.B. In exceptional circumstances an off-license agreement MAY be suitable contact pharmacy for further advice.
Alcohol, Antihistamines, *Benzodiazepines*, Mirtazapine, Opioid Analgesics, Other antipsychotics, Trazodone, Tricyclic antidepressants	Increased Sedation/CNS Depressant Effects	Tolerance builds over time. Slow dose titration helps avoid excessive sedation Possible increased risk of respiratory depression and circulatory collapse when clozapine added to established benzodiazepine regimen
Amiodarone, Antipsychotics, Antidepressants, Domperidone, Other QT prolonging drugs	QT Prolongation	Baseline ECG required before starting clozapine. Keep under regular review, particularly when new medicines are prescribed
LOPERAMIDE Anticholinergic drugs (e.g. procyclidine, hyoscine etc.) Some antipsychotics Opioid analgesics Tricyclic antidepressants	Increased risk of anticholinergic side-effects	Clozapine can cause clinically significant gastric hypo-motility and fatalities have occurred as a result of bowel obstruction, perforation or paralytic ileus. Prescriber to review ongoing need to these medicines and to remind patient to report constipation promptly. Monitor for urinary retention, blurred vision, confusion
ACE Inhibitors, Alcohol, Antihypertensives, Some other antipsychotics, Tricyclic antidepressants	Decreased blood pressure or falls	Tolerance to this effect usually occurs. Slow down titration if there are blood pressure problems.
Other antipsychotics, Sudden benzodiazepine withdrawal, Tricyclic antidepressants	Risk of seizures	Not normally in issue during titration, may be significant at higher dose of clozapine
Lithium	Risk of Neuroleptic malignant syndrome (NMS)	Often presents with non-classical symptoms (muscle rigidity, raised temperature, autonomic instability) Raised Creatinine Kinase (CK) levels are a more reliable marker.

Potential Pharmacokinetic Interactions with Clozapine **Drugs in CAPITALS are particularly hazardous and are CONTRAINDICATED**		
Drug Name	Interaction with Clozapine	Action
FLUVOXAMINE	Increases clozapine levels significantly Significance-high	**Contraindicated.** Do not use during clozapine initiation. Might be appropriate when patient stabilised in order to raise clozapine levels
Paroxetine, Fluoxetine, Sertraline, Citalopram	Increases clozapine levels Significance-low/moderate	Advise prescriber to consider monitoring clozapine plasma levels when dose stable or if the antidepressant is stopped
Omeprazole	Reduces clozapine levels Significance-moderate (levels can be reduced by up to 45%)	Advise of interaction and the possibility of an increase in clozapine levels if omeprazole stopped. Consider switching to lansoprazole
Ciprofloxacin	Clozapine levels increased Significance-high	**Not contraindicated but avoid if possible.** If combination cannot be avoided care is required. Monitor for adverse effects-dose reduction may be required
RITONAVIR	Increases clozapine levels Significance-low	**Contraindicated by UK manufacturer** due to increased plasma concentrations of clozapine which increases risk of serious haematological abnormalities, and adverse effects.

Health and Social Care in Northern Ireland

Clozapine Prescription

Use addressograph or write in CAPITAL LETTERS		ZTAS PIN	
Name		**Blood Sampling Frequency**	
Address		Weekly ☐ Fortnightly ☐ 4 weekly ☐	
H&C number		**Dispensing Frequency**	
DOB		Weekly ☐ Fortnightly ☐ 4 weekly ☐	
Check Identity		**Clozapine collection/delivery arrangements**	
Consultant			
Keyworker		**Blister pack required** if yes reason for same (see Regional adherence documentation)	
Contact details		No ☐	
Pharmacy		Yes ☐	
Annual full Clinical Check		**Additional information** e.g. off-license, smoking status	

Allergies / Drug Sensitivities	
Allergen/Drug (generic name	Type of reaction (e.g. rash)
Or NKDA ☐	

Clozapine will be dispensed from this prescription according to the frequency above or as per clozapine patient monitoring service for a period not exceeding the validity stated below, which unless stated otherwise, will be for a MAXIMUM of 12 months. A new prescription MUST be sent to the dispensing pharmacy as soon as possible after any changes in dose are required in addition please indicate if

The change is to implemented immediately please tick ☐

Alternatively if the change can wait until the next scheduled supply please tick ☐

Drug Name & Form	Enter dose due at each time			
	Morning	Lunch	Tea	Night

Signature of Prescriber		**Date**	
Print Name		***Registration number***	
Address			
Designation	**Consultant ☐ Staff Grade ☐ Other (specify)**		

Supply Valid for (Max 12 months)	**Expiry date:**

For Pharmacy Use Only (CC= clinical check, L Labelled, D, Dispensed, FC= Final Check)

Cost Centre	
Dispensing group *(where applicable)*	

							If required by pharmacy and if appropriate sign and date box(es)		
Date	**Quantity issued**		**CC**	**L**	**D**	**FC**	**Blood Status (G, A or R)**	**Bloods Checked**	**Comments**
	25mg	**100mg**							

Photocopy and attach additional copies as need for recording dispensing

Appendix 3

Recipient's Name
Recipient's Address 1
Recipient's Address 2
Recipient's Address 3
Recipient's Postcode

Type the name of your Department here

Insert Date

Our Ref: Patient name DoB
Patient's address
H&C no.

Dear Doctor

I am writing to inform you that the above named person has been commenced on clozapine (Zaponex®) for the management of treatment resistant schizophrenia. Clozapine is a red list drug so the Consultant psychiatrist will arrange routine monitoring and the supply of clozapine through one of the hospital pharmacy departments.

I would greatly appreciate if you would ensure that the below recommendations are **prominent and obvious** at each consultation.

- That the patient has a record of clozapine on your computer (as a hospital supplied RED list drug) in order to check for interactions with other prescribed medication.
- Clozapine is a critical medication and should not normally be stopped for more than 48 hours, unless clinically indicated; please IMMEDIATELY inform consultant/mental health team if clozapine is held.
- That if the patient presents with signs of infection including sore throat & flu symptoms a full blood count should be urgently performed and secondary care team notified see later.
- That the patient receives an annual physical health check including cardiovascular risk assessment; this will normally be facilitated through local arrangements.
- That the patient is on the practice Serious Mental Illness register.

Clozapine can cause a wide range of side effects and has numerous interactions the following material is not exhaustive and further information is available from the Zaponex SPC I have also included a flowchart which outlines the main acute clinical issues.

- **Constipation:** due to very significant slowing of intestinal peristalsis. Any patient on clozapine should be routinely asked about their bowel movements and any signs of constipation acted on; this will include regular laxatives for many patients including stool softener and stimulant.
  Constipation should not be ignored as deaths from paralytic ileus have been reported.
- **Persistent Tachycardia**: Tachycardia is common and occurs in up to 25% of patients during initiation. However persistent tachycardia when associated with chest pain or shortness of breath could be a sign of cardiomyopathy or myocarditis and merit URGENT review and discussion with consultant psychiatrist and consideration for cardiology referral.
- **Seizures:** The risk is dose dependent and can occur especially with doses in excess of 600mg. Prophylactic anticonvulsants may be prescribed. However if a seizure occurs stop clozapine and contact the consultant psychiatrist immediately for advice on ongoing management.
- **Pyrexia:** temperature above 38°C is often normal in the first three weeks of treatment. However, a full blood count should be taken to exclude agranulocytosis.
- **Drowsiness**: this is usually within the first four weeks. Can be managed by giving more of the dose at bedtime and increasing the dose more slowly.

- **Hypersalivation:** appears early in treatment. If troublesome anticholinergics can be helpful although these increase the risk of constipation and care is needed.
- **Hypotension:** can occur during the initiation process but may persist and merit review of concurrent prescribed medication.
- **Weight gain:** can be more than 5kg. Give advice about exercise and diet. It is easier to minimise weight gain over the first few months than to try to lose it afterwards.
- **Risk of suicide:** improvements in mental state and insight can also lead to an increased risk of suicide. Use risk assessment and direct questioning at two weekly intervals for the first 2 months.
- **Urinary incontinence:** May respond to an adjusted dose schedule
- **Diabetes and impaired glucose tolerance:** Ongoing review of blood glucose or HbA_{1c}

Infection Advice

Neutropenia or agranulocytosis is an important and potentially life threatening side effect from treatment with clozapine. Routine monitoring of full blood counts are mandatory and will be undertaken by secondary care service and sent to the clozapine provider; benign hyperthermia with leucocytosis and/or raised ESR can occur with clozapine treatment in the first few weeks of treatment.

However patients presenting with raised temperature should have an additional full blood count undertaken as a precautionary measure. This MUST be shared with secondary care so that the clozapine provider can be notified, however, provided WCC> 3 and/or neutrophils > 1.5, clozapine treatment may continue. Clozapine treatment **MUST** stop if the blood results are in the Red range (WCC < 3 and/or neutrophils <1.5.

Continuing treatment with clozapine during an infection is not a contraindication provided the infection has not occurred as a result of clozapine-induced neutropenia. Whenever possible, additional full blood tests should be taken to confirm that white cell and neutrophil counts remain in the normal range. Antipyretics can be used to help lower the temperature. For patients with severe infections and when clozapine is continued, the client's condition must be kept under continuous review and if necessary, should they continue to deteriorate or if their recovery is unusually prolonged, then the possibility that the client has a clozapine induced neutropenia should be considered.

In the event that you consider clozapine treatment should or MUST be discontinued please seek urgent advice from the patients Consultant psychiatrist bearing in mind the risk of relapse.

Treatment Breaks

If clozapine treatment is stopped for more than 48 hours then it MUST be re-titrate slowly from 12.5mg once or twice daily. This MUST be done under the direct supervision of the patients' mental health team; the dose will gradually be increased back to the original dose provided any bloods and the on-going and physical health monitoring are satisfactory.

Smoking

Please be aware that stopping cigarette smoking, this includes switching to vaping or nicotine replacement therapy, can significantly increase clozapine levels (up to 70% increase), this significantly increases the risk of dose related adverse effects, including but not limited to seizures and constipation. While we would encourage patients to stop smoking we would appreciate if their keyworker be advised as there may be an increased likelihood of side-effects.

We will endeavor to keep you informed of any changes to the treatment process. There are a number of medications that can interact with clozapine (see table overleaf), therefore during clozapine treatment we will contact you to discuss any changes or additions to the other prescribed medicines, and ask that you do likewise

If you require any further information, please do not hesitate to contact the team or alternatively the patient's Community Mental Health Keyworker (insert name) on telephone (insert full number).

Yours Sincerely

Signatory
Designation

Clozapine Information Sheet for General Practitioners.

Drug Interactions

There are a number of medications that can interact with clozapine, this includes any medicine known to depress the white blood cell count, lower the seizure threshold, or be sedating or cause hypotension. For further details regarding specific interactions and side effects, please refer to the BNF or the Summary of Product Characteristics (http://emc.medicines.org.uk/). The following are a list of examples however this list is not exhaustive

Class of common drug interaction	Interaction	Comment
Antimotility drugs e.g. loperamide codeine	Particular consideration given to the risk of constipation	**Clozapine can cause clinically significant gastric hypomotility and deaths have occurred as a result of bowel obstruction, perforation or paralytic ileus.**
Anticholinergic agents	Potentiates of the anticholinergic effect.	Particular consideration given to the risk of constipation, especially if anticholinergics are prescribed to control hypersalivation.
Antipsychotic drugs	Antipsychotics may increase the risk of QTc prolongation increasing the risk of sudden death	All multiple antipsychotic regimes should be kept under regular review
Antihypertensive agents	Increased risk of hypotension	Use with caution with clozapine especially during initiation.
Bone marrow suppressants e.g. Carbamazepine, sulphonamides, penicillamine, cytotoxic agents, depot antipsychotics	Increases the risk and/or severity of bone marrow suppression	Drugs known to have a substantial potential to depress bone marrow function MUST not be used concurrently with clozapine In exceptional cases an individual patient plan will be drawn up with the clozapine provider, consultant psychiatrist and hospital pharmacy. You will be notified of same.
CNS depressants e.g. alcohol, narcotics benzodiazepines	May enhance sedative effect of clozapine and interference with cognitive and motor functions	Patients should be monitored and consideration given to changing the medication. Patients should be advised to avoid alcohol. Benzodiazepines may increase the risk of respiratory depression and circulatory collapse
Enzyme Inducers e.g. phenytoin, rifampicin omeprazole	Can decrease clozapine levels	Contact the mental health team to ensure serum clozapine levels are maintained with the therapeutic range Monitor for recurrence or worsening of psychotic symptoms
Enzyme inhibitors e.g. **Erythromycin, cimetidine, fluvoxamine**, fluoxetine & paroxetine	Can increase clozapine levels	Avoid combination is possible. Fluvoxamine inhibits CYP1A2 and can result is very significant increases and is best avoided. Fluoxetine and paroxetine may be co-prescribed
Highly protein bound drugs e.g. warfarin	Other drugs may be displaced by clozapine	Patients should be monitored for the occurrence of side effects associated with these substances, and doses of the protein bound substance adjusted, if necessary.

Health and Social Care

CLOZAPINE - MANAGING SERIOUS ADVERSE EFFECTS

PRESENTATION

Signs of infection including fever or sore throat.

CONSIDER CLOZAPINE INDUCED NEUTROPENIC SEPSIS

WBC 10^9/l	NEUTROPHIL 10^9/l	ACTION
≥3.5	≥2.0	Continue clozapine
≥3.0 & <3.5 and/or	1.5 - 2.0	Continue clozapine FBC within 24 hrs Notify ZTAS*
<3.0 and/or	<1.5	Stop clozapine Urgent FBC Notify ZTAS*

MANAGEMENT

- For a result in the RED range, **STOP CLOZAPINE** and manage according to ZTAS Red Alert Guidelines available from ZTAS or Trust Intranet
- For results in green or amber ranges continue clozapine. Manage any infection according to clinical guidelines. Repeat FBC within 24hrs
- If Red Alert with Pyrexia manage according to Neutropenic Sepsis Guideline (NICAN).

PRESENTATION

Persistent tachycardia at rest, palpitations, arrhythmias, chest discomfort, heart failure, fatigue, dyspnoea, tachypnoea or symptoms that mimic myocardial infarction.

CONSIDER MYOCARDITIS OR CARDIOMYOPATHY

DIAGNOSTIC AIDS FOR MYOCARDITIS

- Remember myocarditis may be asymptomatic
- Tachycardia and elevated temperature can be benign transient side effects of clozapine
- Eosinophilia may be present but is a poor prognostic marker for myocarditis
- Elevated troponin, CRP or NTProBNP may be reported with myocarditis
- ECG changes and abnormal ECHO may occur.

MANAGEMENT

- **STOP CLOZAPINE**
- Consult urgently with cardiology
- See ZTAS Myocarditis and Tachycardia Fact Sheets available from ZTAS* or Trust Intranet.

PRESENTATION

Constipation, diarrhoea (overflow), abdominal pain, fever, nausea, or distended abdomen.

CONSIDER CLOZAPINE INDUCED CONSTIPATION

RISKS

- Onset of severe symptoms may be sudden
- Risk increased with high clozapine dose and other drugs/conditions linked to constipation
- Intestinal obstruction and paralytic ileus can occur
- Deaths have occurred.

MANAGEMENT

- Manage according to severity of symptoms
- In very severe cases consider withholding clozapine until symptoms have resolved
- See ZTAS Constipation Fact Sheet available from ZTAS* or Trust Intranet

Other Clinical Issues

- Stopping smoking, having pneumonia or other serious infection, may significantly increase clozapine levels leading to possible toxicity, clozapine dose may need to be reduced
- Seizures can occur with clozapine, these are dose related
- Neuroleptic malignant syndrome can occur rarely. The presentation can be atypical with absence of raised temperature and muscle rigidity. Creatinine Kinase levels may be raised.

Caution: Avoid unnecessary breaks in clozapine treatment. Consider a lower dose instead of stopping clozapine. If clozapine has been not been taken for over 48hrs, DO NOT RESTART without consultation with Psychiatry Liaison or other appropriate mental health team.

For all inpatients, advice and management is available from Psychiatry Liaison or other appropriate mental health team. For advice on outpatient management, contact the relevant community mental health team. Out of hours advice may be sought from Psychiatrist On-Call or pharmacy.

*ZTAS FACT Sheets and other management advice can be obtained by calling 0207 3655842 at any time

Appendix 4

Health and Social Care in Northern Ireland

Recipient's Name
Recipient's Address 1
Recipient's Address 2
Recipient's Address 3
Recipient's Postcode

Type the name of your Department here

Insert Date

Our Ref: Patient name DoB
Patient's address
H&C no.

Dear Doctor

I am writing to inform you that the above named person has discontinued clozapine (Zaponex®). Clozapine is a red list drug and I had previously asked to ensure that the below recommendations were **prominent and obvious**. *Can you please remove the following warnings from your system*:

- That the patient has a record of clozapine on your computer (as a hospital supplied RED list drug) in order to check for interactions with other prescribed medication.
- Clozapine is a critical medication and should not normally be stopped for more than 48 hours, unless clinically indicated, please inform consultant/mental health team if clozapine is held.
- That if the patient presents with signs of infection including sore throat & flu symptoms a full blood count should be urgently performed and secondary care team notified see later.

The other recommendations from this time remain in place

- That the patient receives an annual physical health check including cardiovascular risk assessment; this will normally be facilitated through local arrangements.
- That the patient is on the practice Serious Mental Illness register.

We will endeavor to keep you informed of any further changes in the patient's process though the normal arrangements via our outpatient support and recovery service. If you require any further information, please do not hesitate to contact the team or alternatively the patient's Community Mental Health Keyworker (insert name) on telephone (insert full number).

Yours Sincerely

Signatory
Designation

APPENDIX 5: CLOZAPINE AND ADVICE ON MANAGEMENT OF ADVERSE EFFECTS

Below is a list of the most COMMON AND SERIOUS SIDE EFFECTS (not a comprehensive list). See the relevant clozapine SPC at www.medicines.org.uk for more information.

Most side-effects are dose-dependent and associated with the speed of titration. They also tend to be more common at the beginning of therapy. It is therefore best to start therapy at a low dose and increase the dose gradually in order to minimise these problems. If the patient is not tolerating a particular dose, consider decreasing it to one that was tolerated and then increase the dose again but at a slower rate.

Table adapted from common adverse effects in Maudsley 13th edition (refer to same for further information). In addition further information is available in a series of fact sheets from ZTAS.

Adverse effect	Time Course	Action
Constipation	First 4 months are the highest risk. Usually persists	Advise patients of the risks before starting, screen regularly, ensure adequate fibre, fluid and exercise. Prophylactic laxatives, docusate and senna should be considered in any patient starting clozapine. Actively and systematically screen and monitor for symptoms of constipation. Stop other medicines that may be contributing and reduce clozapine dose if possible. ***Effective treatment or prevention of constipation is essential as death may result.***
Hypersalivation	First few months. May persist, but sometimes wears off. Often very troublesome at night.	Give hyoscine 300microgram sucked and swallowed up to three times a day. Other options are available. Note anti-cholinergics worsen constipation and cognition
Sedation	First few months. May persist, but usually wears off to some extent.	Give smaller dose in the morning. Reduce dose if necessary. The patient must be advised not to drive if affected and not at all during titration
Weight gain	Usually during the first year of treatment	Dietary counselling is essential. Advice may be more effective if given before weight occurs. Weight gain is common and often profound (>10lb). Other treatment options are available. Monitor weight
Hypotension	First 4 weeks	Advise patient to take time when standing up. Reduce dose or slow down rate of increase. Increase fluid intake to 2L daily. If severe consider or fludrocortisone. Over longer term, weight gain may lead to hypertension.
Hypertension	First 4 weeks, sometimes longer	Monitor closely and increase dose as slowly as is necessary. Hypertensive therapy is sometimes required
Tachycardia	First 4 weeks, but sometimes persists	Monitor pulse, Seek medical advice if pulse >120bpm. Very common in early stages of treatment but usually benign. Tachycardia, if persistent at rest and associated with fever, hypotension or chest pain, may indicate myocarditis. Urgent referral to a cardiologist is advised. Clozapine should be stopped if tachycardia occurs in context of chest pain or heart failure. Benign sinus tachycardia can be treated with bisoprolol. Ivabradine may be used if hypotension or contraindications limit the use of beta-blockers. Note that prolonged tachycardia can itself precipitate cardiomyopathy

Adverse effect	Time Course	Action
Nausea	First 6 weeks	May give anti-emetic. Avoid prochlorperazine and metoclopramide if previous EPS. Avoid domperidone if underlying cardiac risk or QTc prolongation. Ondansetron is a good choice
Nocturnal enuresis	May occur at any time	Try reducing the dose or manipulating dose schedule to avoid periods of deep sedation. Avoid fluids before bedtime. May resolve spontaneously, but may persist for months or years. May affect one in five people on clozapine. In severe cases, desmopressin nasal spray (10µg-20µg nocte) is usually effective but is not without risk: hyponatraemia may result. Anticholinergic agents may be effective but support for this approach is weak and constipation and sedation may worsen
Fever, sore throat or other signs of infection.	First 4 weeks but can occur at any time.	Clozapine induces inflammatory response (increased CRP and interleukin-6). Seek medical advice. Give paracetamol but check FBC for neutropenia. Reduce rate of dose titration. This fever is usually related to blood dyscrasias but beware myocarditis and NMS
Myocarditis	Greatest risk in the first 2 months of treatment but can occur at any time.	Myocarditis or cardiomyopathy should be suspected in patients who experience persistent tachycardia at rest, and/or palpitations, arrhythmias, chest pain and other signs and symptoms of heart failure (e.g. unexplained fatigue, dyspnoea, tachypnoea) or symptoms that mimic myocardial infarction. If myocarditis or cardiomyopathy are suspected, clozapine treatment should be promptly stopped, an ECG performed and the patient immediately referred to a cardiologist. Patients who develop clozapine-induced myocarditis or cardiomyopathy should not be re-exposed to clozapine.
Neutropenia/ agranulocytosis	First 18 weeks (but may occur at any time)	Stop clozapine immediately if they have a "**RED**" blood result; refer to hospital if agranulocytosis confirmed.
Myoclonus	During dose titration or plasma level increases	May precede full tonic-clonic seizure. Reduce dose. Anticonvulsants may help, and will reduce the likelihood of progression to seizures. Valproate is first choice; lamotrigine may worsen some types of myoclonus
Seizures	May occur at any time	Related to dose, plasma level and rapid dose escalation. Consider prophylactic lamotrigine or valproate* if on high dose (≥500mg/day) or with high plasma level (≥500 µg/L). Note that some suggest risk of seizure below 1300 µg/L (about 1 in 20 people) is not enough to support primary prophylaxis. After a seizure, consider advice from neurology; withhold clozapine for one day; restart at half previous dose, give anticonvulsant as suggested+. EEG abnormalities are common those on clozapine

*Usual dose is 1000-2000mg/day. Plasma levels may be useful as a rough guide to dosing- aim for 50-100mg/L. Use of modified release preparation (Epilim Chrono®) may aid compliance: can be given once daily and may be better tolerated. Valproate is contraindicated in women of reproductive age

+ Use valproate if schizoaffective; lamotrigine if poor response to clozapine or continued negative symptoms.

CRP. C-reactive protein; EEG, electroencephalogram; EPS, extrapyramidal side effects; FBC, full blood count; NMS, neuroleptic malignant syndrome.