Government of **Western Australia**
Department of **Health**

WA Clozapine Initiation and Titration Chart

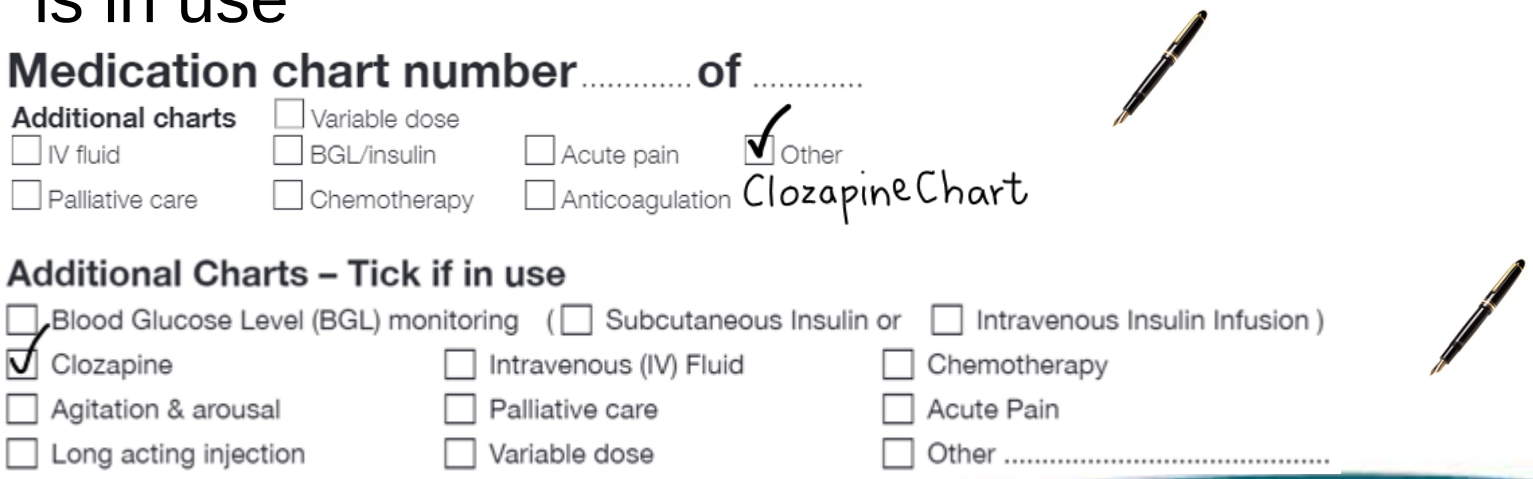
Version 5, 2024

Introduction

- Clozapine is a high risk medication
- It was released in early 1970s and withdrawn from market due to incidents of neutropenia, myocarditis and sudden death.
- Re-introduced for use in Australia with stringent monitoring and guidance for use in conjunction with the Clozapine Monitoring System (ClopineCENTRAL™)
- Specialised chart developed for WA Health to co-ordinate management of clozapine.
- This presentation will provide education on features. prompts and alerts in the chart.

General Requirements

- Chart to be completed for **all in-patients** initiated and re-titrated on clozapine
- The National Inpatient Medication Chart **MUST** be annotated clearly to identify when a clozapine chart is in use



Medication chart number ..... **of** .....

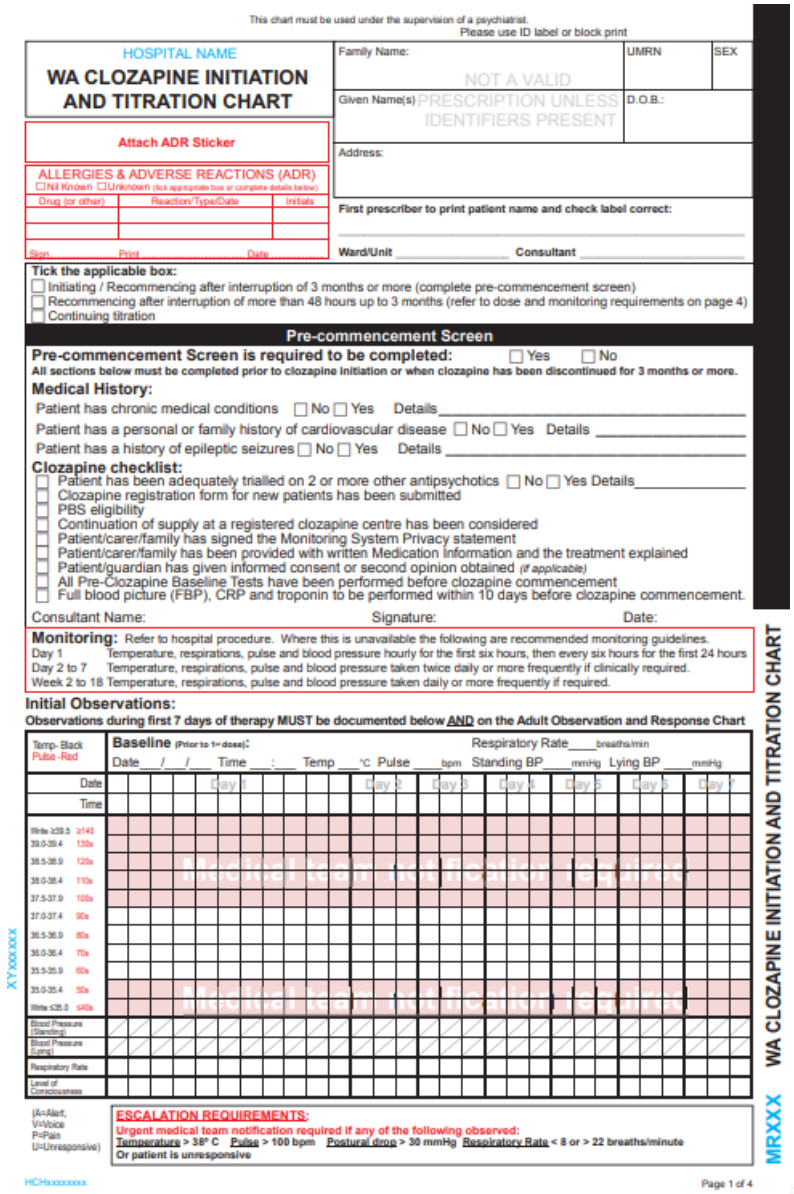
Additional charts

- ☐ Variable dose
- ☐ IV fluid
- ☐ BGL/insulin
- ☐ Acute pain
- ☑ Other — ClozapineChart
- ☐ Palliative care
- ☐ Chemotherapy
- ☐ Anticoagulation

Additional Charts – Tick if in use

- ☐ Blood Glucose Level (BGL) monitoring (☐ Subcutaneous Insulin or ☐ Intravenous Insulin Infusion)
- ☑ Clozapine
- ☐ Intravenous (IV) Fluid
- ☐ Chemotherapy
- ☐ Agitation & arousal
- ☐ Palliative care
- ☐ Acute Pain
- ☐ Long acting injection
- ☐ Variable dose
- ☐ Other .....

Chart Layout



This chart must be used under the supervision of a psychiatrist.
Please use ID label or block print

HOSPITAL NAME

WA CLOZAPINE INITIATION AND TITRATION CHART

Family Name: NOT A VALID PRESCRIPTION UNLESS IDENTIFIERS PRESENT | UMRN | SEX

Given Name(s) | D.O.B.:

Address:

Attach ADR Sticker

ALLERGIES & ADVERSE REACTIONS (ADR)
☐Nil Known ☐Unknown (tick appropriate box or complete details below)

Drug (or other)	Reaction/Type/Date	Initials

Sign Print Date

First prescriber to print patient name and check label correct:

Ward/Unit Consultant

Tick the applicable box:
☐ Initiating / Recommencing after interruption of 3 months or more (complete pre-commencement screen)
☐ Recommencing after interruption of more than 48 hours up to 3 months (refer to dose and monitoring requirements on page 4)
☐ Continuing titration

Pre-commencement Screen

Pre-commencement Screen is required to be completed: ☐ Yes ☐ No
All sections below must be completed prior to clozapine initiation or when clozapine has been discontinued for 3 months or more.

Medical History:
Patient has chronic medical conditions ☐ No ☐ Yes Details
Patient has a personal or family history of cardiovascular disease ☐ No ☐ Yes Details
Patient has a history of epileptic seizures ☐ No ☐ Yes Details

Clozapine checklist:
☐ Patient has been adequately trialled on 2 or more other antipsychotics ☐ No ☐ Yes Details
☐ Clozapine registration form for new patients has been submitted
☐ PBS eligibility
☐ Continuation of supply at a registered clozapine centre has been considered
☐ Patient/carer/family has signed the Monitoring System Privacy statement
☐ Patient/carer/family has been provided with written Medication Information and the treatment explained
☐ Patient/guardian has given informed consent or second opinion obtained *(if applicable)*
☐ All Pre-Clozapine Baseline Tests have been performed before clozapine commencement
☐ Full blood picture (FBP), CRP and troponin to be performed within 10 days before clozapine commencement.

Consultant Name: Signature: Date:

Monitoring: Refer to hospital procedure. Where this is unavailable the following are recommended monitoring guidelines.
Day 1 Temperature, respirations, pulse and blood pressure hourly for the first six hours, then every six hours for the first 24 hours
Day 2 to 7 Temperature, respirations, pulse and blood pressure taken twice daily or more frequently if clinically required.
Week 2 to 18 Temperature, respirations, pulse and blood pressure taken daily or more frequently if required.

Initial Observations:
Observations during first 7 days of therapy MUST be documented below AND on the Adult Observation and Response Chart

Temp- Black
Pulse -Red

Baseline (Prior to 1st dose):
Date ___/___/___ Time ___:___ Temp ___°C Pulse ___bpm Respiratory Rate ___breaths/min Standing BP ___mmHg Lying BP ___mmHg

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Date							
Time							
Write ≥39.5 ≥140							
39.0-39.4 130s							
38.5-38.9 120s							
38.0-38.4 110s							
37.5-37.9 100s							
37.0-37.4 90s							
36.5-36.9 80s							
36.0-36.4 70s							
35.5-35.9 60s							
35.0-35.4 50s							
Write ≤35.0 ≤40s							
Blood Pressure (Standing)							
Blood Pressure (Lying)							
Respiratory Rate							
Level of Consciousness							

Medical label identification required

Medical label identification required

(A=Alert, V=Voice P=Pain U=Unresponsive)

ESCALATION REQUIREMENTS:
Urgent medical team notification required if any of the following observed:
Temperature > 38° C Pulse > 100 bpm Postural drop > 30 mmHg Respiratory Rate < 8 or > 22 breaths/minute
Or patient is unresponsive

HCHxxxxxxxx

Page 1 of 4

XYxxxxxx

WA CLOZAPINE INITIATION AND TITRATION CHART

MRXXX

Front Page:

- Patient Identification
- Allergies and Adverse Drug Reactions
- Pre-commencement documentation and checklist
- Observations
  - •Temperature
  - •Pulse
  - •Blood pressure
  - •Respiratory rate
  - •Level of consciousness

Chart Layout

HOSPITAL NAME

WA CLOZAPINE INITIATION AND TITRATION CHART

Year 20 ___ ___

Please use ID label or block print

Family Name: NOT A VALID PRESCRIPTION UNLESS IDENTIFIERS PRESENT	UMRN	SEX
Given Name(s)	D.O.B.:	
Address:		

Clozapine Dose Orders

⚠ ***DO NOT prescribe clozapine until approved by Clozapine Monitoring Centre and Clozapine Patient Number allocated. Commence clozapine preferably in the morning to allow hourly monitoring for the first six hours.***

Medication **Clozapine** Formulation: **Clozapine Patient Number:**

Route: **oral** Indication:

Pharmacy use: Weekly monitoring until: / /

Date	Day	Blood test due (✓)	Prescriber Signature	Prescriber Name (PRINT)	Morning dose 08:00hr	Nurse initials Nurse 1/ Nurse 2	Night dose 20:00hr	Nurse initials Nurse 1 / Nurse 2	Drug level	Pharmacy
	1									
	2									
	3									
	4									
	5									
	6									
	7									
	8									
	9									
	10									
	11									
	12									
	13									
	14									
	15									

DO NOT WRITE IN BINDING MARGIN

DO NOT WRITE IN BINDING MARGIN

Clozapine Dose Titration Schedule

This table serves as a guide only and dose titration should be individualised – refer to treating psychiatrist.
Patients > 65 years of age may require a slower dose increase titration regimen.
Titration beyond 200 mg/day: If well tolerated, the daily dose may be increased slowly in increments of 25-50 mg (maximum 100 mg/week).

Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Morning	12.5 mg	25 mg	25 mg	25 mg	25 mg	25 mg	25 mg	25 mg	50 mg	50 mg	50 mg	50 mg	50 mg	50 mg
Evening	X	X	X	25 mg	25 mg	50 mg	75 mg	100 mg	100 mg	100 mg	125 mg	125 mg	125 mg	150 mg

Monitoring Checklist – Baseline Measurements When Commencing Clozapine

Blood group _____ Height _____m Smoking status: ☐ Smoker ☐ Non Smoker

	Intervals	Pre-clozapine baseline Date	Pre-clozapine baseline Results	Day 7 Date:	Day 14 Date:	Day 21 Date:	Day 28 Date:	Minimum ongoing monitoring
To be completed by doctor / nurse / dietician	Dietician review		☐ Performed					Annually
	Weight		kg					Weekly first 18 weeks – then every 28 days
	Waist circumference		cm					
	BMI weight (kg) / height (m²)							
	Constipation monitoring	Daily checks for 4 weeks: Use bowel chart						Inpatients: minimum weekly Outpatients: check bowel habits at each review
To be completed by doctor	Full physical exam		☐ Performed					Annually
	Full Blood Count		☐ Performed	☐ Performed	☐ Performed	☐ Performed	☐ Performed	Weekly first 18 weeks - then every 28 days
	White Blood Count		x10⁹/L	x10⁹/L	x10⁹/L	x10⁹/L	x10⁹/L	
	Neutrophils Absolute		x10⁹/L	x10⁹/L	x10⁹/L	x10⁹/L	x10⁹/L	
	Eosinophils Absolute		x10⁹/L	x10⁹/L	x10⁹/L	x10⁹/L	x10⁹/L	
	Liver function test		☐ Performed					6 monthly
	Urea & Electrolytes		☐ Performed					6 monthly
	Fasting plasma glucose		mmol/L					At 3 months, 6 months, then 6 monthly
	Total cholesterol (fasting)		mmol/L					
	LDL (fasting)		mmol/L					
	HDL (fasting)		mmol/L					
	Triglycerides (fasting)		mmol/L					
	Troponin		nanograms/L	nanograms/L	nanograms/L	nanograms/L	nanograms/L	As clinically indicated thereafter
	C-Reactive Protein (CRP)		mg/L	mg/L	mg/L	mg/L	mg/L	
	ECG (QT interval)							Weekly for first 4 weeks, then as clinically indicated
	Cardiac echocardiogram							At 3 months, then 1, 2, 5 yrs
	Beta HCG (female)							When needed

These are suggested guidelines only and do not replace the need for clinical discretion. Refer to the treating psychiatrist for individual monitoring requirements

Reason For Not Administering (codes must be circled)

Absent	(A)	**On Leave**	(L)	**Refused – notify doctor**	(R)	**Vomiting – notify doctor**	(V)
Fasting	(F)	**Not Available – obtain supply and/or notify doctor, consider incident report**	(N)	**Withheld – enter reason in clinical record**	(W)	**Self-Administering – observed or claimed**	(S)

Inside Page: (Opens into A3)

- Dose Orders
- Suggested Dosing Regimen
- Monitoring

Chart Layout

Clozapine Blood Results Monitoring System		Recommended Action
Green Range	WBC greater than 3.5 x 10^9/L AND Neutrophils greater than 2.0 x 10^9/L	Continue clozapine therapy
Amber Range	WBC 3.0 - 3.5 x 10^9/L AND/OR Neutrophils 1.5 - 2.0 x 10^9/L	Continue clozapine therapy with twice-weekly blood tests until return to "green" range
Red Range	WBC less than 3.0 x 10^9/L AND/OR Neutrophils less than 1.5 x 10^9/L	Stop clozapine therapy immediately. Contact haematologist and Clozapine Monitoring Centre

Recommencing Therapy after Interruption

Dosing recommendations if clozapine dose is missed for more than 48 hours

- Obtain psychiatric review prior to recommencing clozapine
- Recommence at 12.5 mg once or twice daily on the first day. Refer to what side effects the patient had previously when starting clozapine. The rate of re-titration can be adjusted to take into account emergent side effects and period of interruption
- This is a guide only – for further dosing options refer to treating psychiatrist.

Blood Test Monitoring after Interruption of Therapy

Monitoring frequency	Clozapine missed for 72 hours or less	Clozapine missed for more than 72 hours up to 28 days	Clozapine missed for more than 28 days
Weekly	No change in monitoring	Monitor weekly for at least 6 weeks or for as long as necessary to achieve a total of 18 weeks of weekly monitoring	Recommence as for a new patient
Monthly		Monitor weekly for 6 weeks then continue with monthly monitoring if no problems detected	

Side effects Associated with Clozapine Therapy Modified from the Maudsley Prescribing Guidelines 14th ed 2021

Side effect	Signs and symptoms / Onset	Recommended Action
Neutropenia / agranulocytosis	WBC < 3.0 x 10^9/L or Neutrophils < 1.5 x 10^9/L. Flu-like symptoms such as sore throat & fever. (First 18 weeks – but may occur at any time)	Contact doctor. Withhold clozapine. Contact haematologist at Clozapine Monitoring Centre.
Myocarditis / cardiomyopathy	Fast or irregular heartbeat at rest with rapid breathing, dyspnoea, hypotension, raised jugular venous pressure, fatigue, infective symptoms (including gastrointestinal, urinary, and/or respiratory), chest pain or fever. Cardiomyopathy may occur at any time. Myocarditis – within 4 weeks of starting)	Withhold Clozapine. Repeat ECG and echocardiogram. Check C-Reactive Protein (CRP) and troponin. Refer to cardiologist.
Fever	> 38° C (First 4 weeks)	Contact doctor. Reduce rate of dose titration of clozapine. Check WBC, neutrophils, troponin and CRP. Physical examination for signs of infection. Consider ECG, Echocardiogram. Give paracetamol and notify doctor to exclude agranulocytosis / myocarditis.
Seizures	Increases with high doses, rapid dose titration, concurrent use of drugs that lower seizure threshold and preexisting seizure disorders and concurrent illness. (May occur at any time)	Medical emergency, manage seizure. Withhold clozapine for one day and restart at half the dose. Consider prophylactic antiepileptic. Risk of seizures increases with higher serum clozapine levels; check serum clozapine levels.
Hypersalivation	Excessive drooling – Very troublesome at night. (First few months)	Contact doctor. Check with pharmacist for pharmacological options.
Constipation	Less frequent bowel motions, hard stools, abdominal bloating, cramping or pain, decreased appetite or fatigue. (Usually persists) Severe Clozapine Induced Gastrointestinal Hypomotility (CIGH) can be fatal.	Contact doctor. Recommend increased fluid intake and exercise. Consider pre-emptive laxatives for all patients. Review contributing medicines and consider dose reduction. Treat CIGH aggressively with laxatives and consider cessation of clozapine if treatment fails. Avoid bulk forming laxatives.
Nocturnal enuresis	Loss of bladder control, especially at night. (May occur at any time)	Contact doctor. Avoid fluids after 7pm. Check males for other causes. Continence referral. Check with pharmacist for pharmacological options.
Weight gain	This may occur early in treatment and can be significant	Dietary and lifestyle counselling before weight gain occurs. Ongoing monitoring and support.

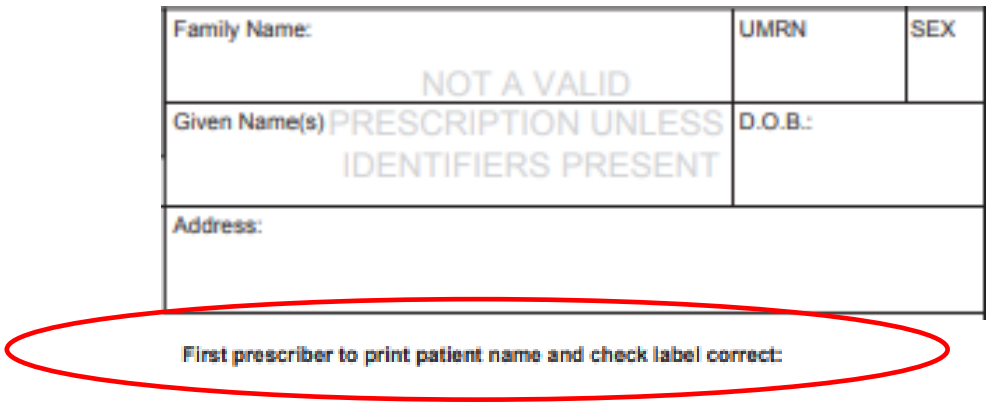
This is not an exhaustive list of side effects. Please see product information for further advice. It is recommended that concurrent use of antipsychotic therapy be avoided where possible as this increases the patient's risk of side effects.

WA Health acknowledges contributions from Queensland Health Medication Management Services in the development of this chart.

Back Page:

- Clozapine blood results monitoring system
- Guidelines for recommencing therapy after interruption
- Guidelines for blood test monitoring after interruption of therapy
- Side-effects associated with Clozapine therapy and recommended action

Patient Identification

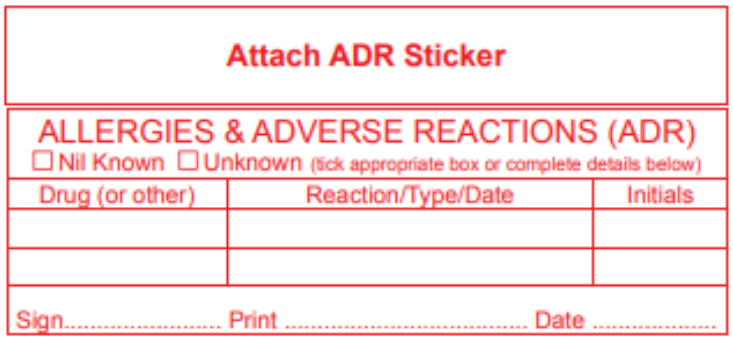


- ✓ Affix patient ID label or write information on pages 1 and 2 of chart
- ✓ If using labels: First prescriber **MUST HANDWRITE (PRINT)** patient name and **CHECK LABELS** are correct

Allergies & Adverse Reactions (ADR)

Accurate information prevents harm from known ADRs

Adverse Drug Reaction



Attach ADR Sticker

ALLERGIES & ADVERSE REACTIONS (ADR)

☐ Nil Known ☐ Unknown (tick appropriate box or complete details below)

Drug (or other)	Reaction/Type/Date	Initials

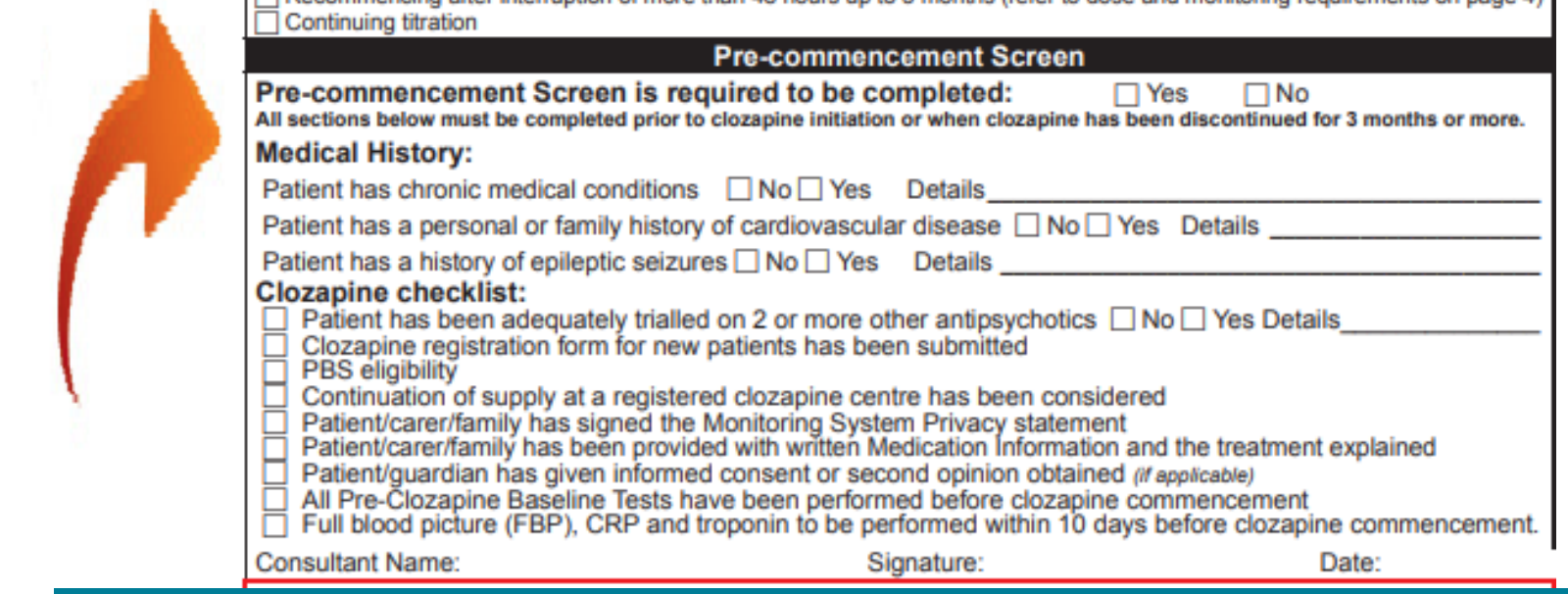
Sign..... Print ..... Date .....

TICK BOX if patient has 'Nil Known' or 'Unknown' allergies or ADRs

✓ **If ADR exists,** then **affix ADR sticker** to page 1 and document:

- Drug name
- Reaction details
- Date of reaction
- Sign entry

Pre-commencement Screen



Tick the applicable box:

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☐ Recommencing after interruption of more than 48 hours up to 3 months (refer to dose and monitoring requirements on page 4)
☐ Continuing titration

Pre-commencement Screen

Pre-commencement Screen is required to be completed: ☐ Yes ☐ No

All sections below must be completed prior to clozapine initiation or when clozapine has been discontinued for 3 months or more.

Medical History:

Patient has chronic medical conditions ☐ No ☐ Yes Details_____

Patient has a personal or family history of cardiovascular disease ☐ No ☐ Yes Details _____

Patient has a history of epileptic seizures ☐ No ☐ Yes Details _____

Clozapine checklist:

☐ Patient has been adequately trialled on 2 or more other antipsychotics ☐ No ☐ Yes Details_____
☐ Clozapine registration form for new patients has been submitted
☐ PBS eligibility
☐ Continuation of supply at a registered clozapine centre has been considered
☐ Patient/carer/family has signed the Monitoring System Privacy statement
☐ Patient/carer/family has been provided with written Medication Information and the treatment explained
☐ Patient/guardian has given informed consent or second opinion obtained *(if applicable)*
☐ All Pre-Clozapine Baseline Tests have been performed before clozapine commencement
☐ Full blood picture (FBP), CRP and troponin to be performed within 10 days before clozapine commencement.

Consultant Name: Signature: Date:

Pre-commencement Screen

- A tick box to indicate if pre-commencement screen is required to be completed
- A section to ensure a medical history is obtained from the patient
- A checklist to ensure all pre-commencement clozapine requirements have been completed

Pre-commencement Screen

Tick the applicable box:

☐ Initiating / Recommencing after interruption of 3 months or more (complete pre-commencement screen)
☐ Recommencing after interruption of more than 48 hours up to 3 months (refer to dose and monitoring requirements on page 4)
☐ Continuing titration

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☐ Patient/guardian has given informed consent or second opinion obtained *(if applicable)*
☐ All Pre-Clozapine Baseline Tests have been performed before clozapine commencement
☐ Full blood picture (FBP), CRP and troponin to be performed within 10 days before clozapine commencement.

Consultant Name: Signature: Date:

✓ Complete “Clozapine checklist”.

Prompts to:

- return completed ‘Clozapine Referral Form’ to a pharmacist
- check PBS eligibility
- consider continuation of supply
- provide ‘Clozapine Notification Form’; CMI and explain treatment
- obtain consent/second opinion
- perform all Pre-Clozapine Baseline Tests, prior to starting Clozapine
- perform FBP, CRP and troponin within 10 days prior to starting Clozapine

Preparation Prior to Initiation

Tick the applicable box:

- ☐ Initiating / Recommencing after interruption of 3 months or more (complete pre-commencement screen)
- ☐ Recommencing after interruption of more than 48 hours up to 3 months (refer to dose and monitoring requirements on page 4)
- ☐ Continuing titration

Pre-commencement Screen

Pre-commencement Screen is required to be completed: ☐ Yes ☐ No

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Patient has a personal or family history of cardiovascular disease ☐ No ☐ Yes Details _____

Patient has a history of epileptic seizures ☐ No ☐ Yes Details _____

Clozapine checklist:

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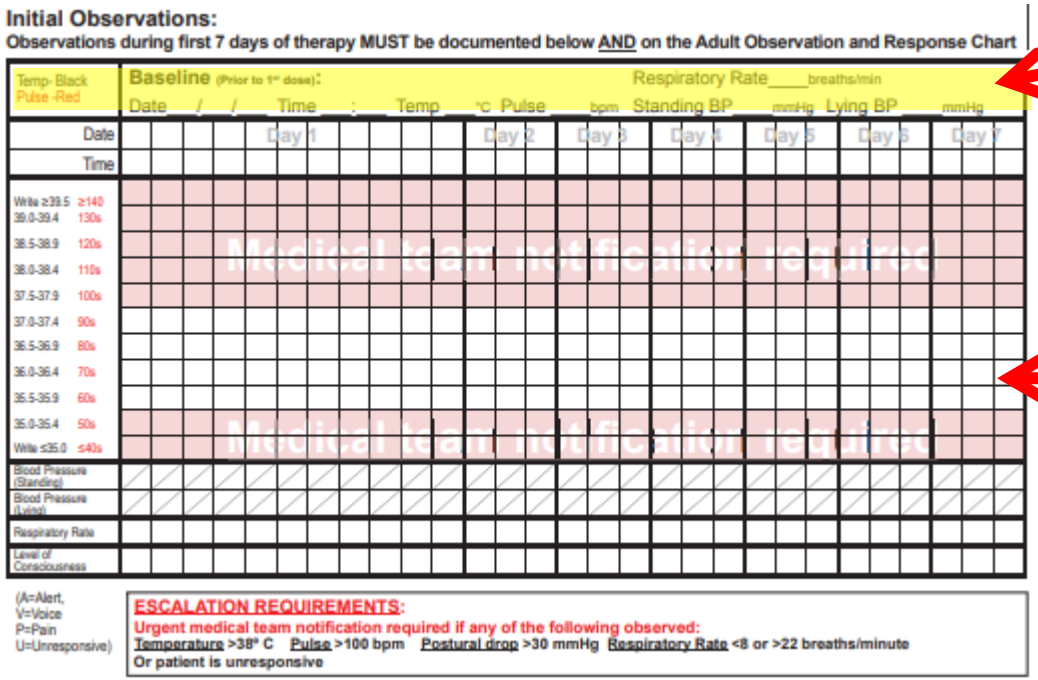
- ☐ Full blood picture (FBP), CRP and troponin to be performed within 10 days before clozapine commencement.

Consultant Name: Signature: Date:

✓ All sections **MUST BE** completed and consultant to print name, sign and date

Initial Observations

Careful observations to identify adverse events and respond appropriately



Initial Observations:

Observations during first 7 days of therapy MUST be documented below AND on the Adult Observation and Response Chart

Temp- Black
Pulse -Red

Baseline (Prior to 1st dose): Respiratory Rate____breaths/min

Date __/__/__ Time __:__ Temp __°C Pulse __bpm Standing BP __mmHg Lying BP __mmHg

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Date							
Time							
Write ≥39.5 ≥140 39.0-39.4 130s							
38.5-38.9 120s							
38.0-38.4 110s							
37.5-37.9 100s							
37.0-37.4 90s							
36.5-36.9 80s							
36.0-36.4 70s							
35.5-35.9 60s							
35.0-35.4 50s							
Write ≤35.0 ≤40s							
Blood Pressure (Standing)							
Blood Pressure (Lying)							
Respiratory Rate							
Level of Consciousness							

Medical team notification required

Medical team notification required

(A=Alert, V=Voice P=Pain U=Unresponsive)

ESCALATION REQUIREMENTS:
Urgent medical team notification required if any of the following observed:
Temperature >38° C Pulse >100 bpm Postural drop >30 mmHg Respiratory Rate <8 or >22 breaths/minute
Or patient is unresponsive

Record Baseline (Prior to 1st dose)

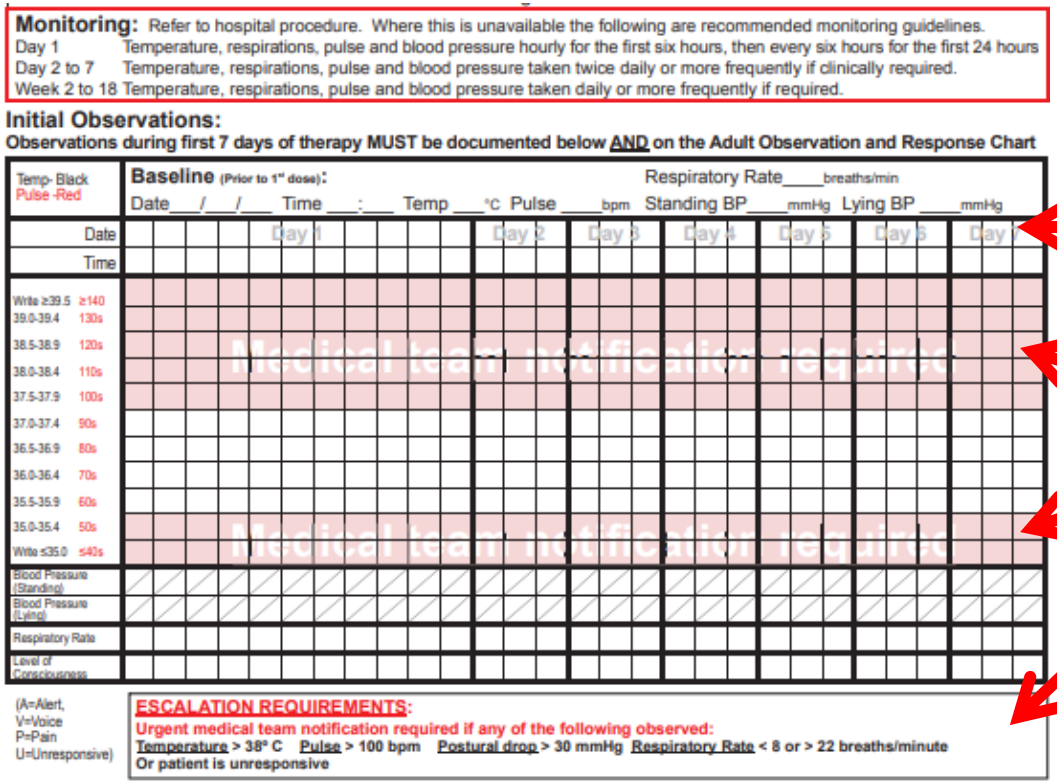
- Date
- Time
- Temp
- Blood pressure
- Respiratory Rate
- Pulse

Record the first 7 days of observations here

- Temperature – Black
- Pulse- Red
- Blood Pressure (standing and lying)
- Respiratory Rate
- Level of Consciousness

After 7 days, continue documentation of observations on the Adult Observation and Response Chart.

Initial Observations



Monitoring: Refer to hospital procedure. Where this is unavailable the following are recommended monitoring guidelines.

Day 1 Temperature, respirations, pulse and blood pressure hourly for the first six hours, then every six hours for the first 24 hours

Day 2 to 7 Temperature, respirations, pulse and blood pressure taken twice daily or more frequently if clinically required.

Week 2 to 18 Temperature, respirations, pulse and blood pressure taken daily or more frequently if required.

Initial Observations:

Observations during first 7 days of therapy MUST be documented below AND on the Adult Observation and Response Chart

Temp- Black
Pulse -Red

Baseline (Prior to 1st dose):

Respiratory Rate____breaths/min

Date___/___/___ Time ___:___ Temp ___°C Pulse ____bpm Standing BP____mmHg Lying BP ____mmHg

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Date							
Time							
Write ≥39.5 ≥140							
39.0-39.4 130s							
38.5-38.9 120s							
38.0-38.4 110s							
37.5-37.9 100s							
37.0-37.4 90s							
36.5-36.9 80s							
36.0-36.4 70s							
35.5-35.9 60s							
35.0-35.4 50s							
Write ≤35.0 ≤40s							
Blood Pressure (Standing)							
Blood Pressure (Lying)							
Respiratory Rate							
Level of Consciousness							

Medical team notification required

Medical team notification required

(A=Alert, V=Voice P=Pain U=Unresponsive)

ESCALATION REQUIREMENTS:

Urgent medical team notification required if any of the following observed:

Temperature > 38° C Pulse > 100 bpm Postural drop > 30 mmHg Respiratory Rate < 8 or > 22 breaths/minute

Or patient is unresponsive

Prompts for frequency of monitoring

Prompts to identify when to notify a doctor who will be able to advise on whether to continue treatment

Dose orders

Clozapine Dose Orders

⚠ ***DO NOT** prescribe clozapine until approved by Clozapine Monitoring Centre and Clozapine Patient Number allocated.*
Commence clozapine preferably in the morning to allow hourly monitoring for the first six hours.

Medication **Clozapine** Formulation: **Clozapine Patient Number:**

Route: **oral** Indication:

Pharmacy use: Weekly monitoring until : / /

Date	Day	Blood test due (✓)	Prescriber		Morning dose 08:00hr	Nurse initials	Night dose 20:00hr	Nurse initials	Drug level	Pharmacy
			Signature	Name (PRINT)		Nurse 1/ Nurse 2		Nurse 1 / Nurse 2		
	1									
	2									
	3									
	4									
	5									
	6									

Document:

- ✓ Formulation (suspension / tablets)
- ✓ Clozapine Patient Number
- ✓ Indication
- ✓ Weekly monitoring until : / /

Dose orders

Clozapine Dose Orders

⚠ ***DO NOT** prescribe clozapine until approved by Clozapine Monitoring Centre and Clozapine Patient Number allocated. Commence clozapine preferably in the morning to allow hourly monitoring for the first six hours*

Medication **Clozapine**			Formulation:				Clozapine Patient Number:			
Route: **oral**			Indication:							
Pharmacy use:							Weekly monitoring until : / /			
Date	Day	Blood test due (✓)	Prescriber		**Morning dose 08:00hr**	Nurse initials Nurse 1/ Nurse 2	**Night dose 20:00hr**	Nurse initials Nurse 1 / Nurse 2	Drug level	Pharmacy
			Signature	Name (PRINT)						
	1									
	2									
	3									
	4									
	5									
	6									

Doses **ONLY** to be prescribed when **<u>approved by clozapine monitoring centre</u>** and **<u>clozapine patient number allocated</u>**

Clearly document:

- ✓ Date when medication started (Chart can accommodate 28 days)
- ✓ Prescriber name (to be printed) and signature
- ✓ Dose - morning (8:00) and/or night (20:00). Commence clozapine in the morning and avoid weekends
- ✓ Each nurse to double-sign each individual dose indicating dose checked and administered
- ✓ Drug level
- ✓ Pharmacy - To identify medication chart has been reviewed by pharmacist

Clozapine – Dosing Regimen

Cautious titration and divided dosage are necessary to minimise adverse events (e.g. hypotension, seizures, sedation…)

Quick reference for the suggested starting regimen for clozapine based on the (Maudsley Prescribing Guidelines)

This is **ONLY** a guide and dose titration should be individualised

Clozapine Dose Titration Schedule

This table serves as a guide only and dose titration should be individualised – refer to treating psychiatrist.
Patients > 65 years of age may require a slower dose increase titration regimen.
Titration beyond 200mg/day: If well tolerated, the daily dose may be increased slowly in increments of 25-50mg (maximum 100mg/week).

Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Morning	12.5mg	25mg	25mg	25mg	25mg	25mg	25mg	25mg	50mg	50mg	50mg	50mg	50mg	50mg
Evening				25mg	25mg	50mg	75mg	100mg	100mg	100mg	125mg	125mg	125mg	150mg

Monitoring Checklist

Complete all baseline measurements not more than 10 days of commencing clozapine. Date and document or ☑ tick the corresponding boxes

Monitoring Checklist – Baseline Measurements When Commencing Clozapine

Blood group _____ Height _____m Smoking status: ☐ Smoker ☐ Non Smoker

	Intervals	Pre-clozapine baseline Date	Pre-clozapine baseline Results	Day 7 Date:	Day 14 Date:	Day 21 Date:	Day 28 Date:	Minimum ongoing monitoring
To be completed by doctor / nurse / dietician	Dietician review		☐ Performed					Annually
	Weight		kg					Weekly first 18 weeks – then every 28 days
	Waist circumference		cm					
	BMI weight (kg) / height (m²)							
	Constipation monitoring	Daily checks for 4 weeks: Use bowel chart						Inpatients: minimum weekly Outpatients: check bowel habits at each review
To be completed by doctor	Full physical exam		☐ Performed					Annually
	Full Blood Count		☐ Performed	☐ Performed	☐ Performed	☐ Performed	☐ Performed	Weekly first 18 weeks - then every 28 days
	White Blood Count		x10⁹/L	x10⁹/L	x10⁹/L	x10⁹/L	x10⁹/L	
	Neutrophils Absolute		x10⁹/L	x10⁹/L	x10⁹/L	x10⁹/L	x10⁹/L	
	Eosinophils Absolute		x10⁹/L	x10⁹/L	x10⁹/L	x10⁹/L	x10⁹/L	
	Liver function test		☐ Performed					6 monthly
	Urea & Electrolytes		☐ Performed					6 monthly
	Fasting plasma glucose		mmol/L					At 3 months, 6 months, then 6 monthly
	Total cholesterol (fasting)		mmol/L					
	LDL (fasting)		mmol/L					
	HDL (fasting)		mmol/L					
	Triglycerides (fasting)		mmol/L					
	Troponin		nanograms/L	nanograms/L	nanograms/L	nanograms/L	nanograms/L	As clinically indicated thereafter
	C-Reactive Protein (CRP)		mg/L	mg/L	mg/L	mg/L	mg/L	
	ECG (QT interval)							Weekly for first 4 weeks, then as clinically indicated
	Cardiac echocardiogram							At 3 months, then 1, 2, 5 yrs
	Beta HCG (female)							When needed

These are suggested guidelines only and do not replace the need for clinical discretion. Refer to the treating psychiatrist for individual monitoring requirements

The following pre-clozapine baseline measurements **must** be completed **within 10 days** prior to commencing clozapine therapy:

- ☐ Blood group
- ☐ Full physical examination
- ☐ Pregnancy test (if applicable)
- ☐ Troponin/ CK-MB
- ☐ Echocardiogram (ECG)
- ☐ Full blood Count

The following pre-clozapine baseline measurements are also recommended:

- ☐ Smoking status
- ☐ Weight
- ☐ Waist
- ☐ BMI
- ☐ Dietician review
- ☐ Liver Function Test
- ☐ Urea & Electrolyte
- ☐ Fasting plasma glucose
- ☐ Blood lipid

Monitoring Checklist

Monitoring Checklist – Baseline Measurements When Commencing Clozapine

Blood group _____ Height _____m Smoking status: ☐ Smoker ☐ Non Smoker

	Intervals	Pre-clozapine baseline		Day 7	Day 14	Day 21	Day 28	Minimum ongoing monitoring
		Date	Results	Date:	Date:	Date:	Date:	
To be completed by doctor / nurse / dietician	Dietician review		☐ Performed					Annually
	Weight		kg					Weekly first 18 weeks – then every 28 days
	Waist circumference		cm					
	BMI weight (kg) / height (m²)							
	Constipation monitoring	Daily checks for 4 weeks: Use bowel chart						Inpatients: minimum weekly Outpatients: check bowel habits at each review
To be completed by doctor	Full physical exam		☐ Performed					Annually
	Full Blood Count		☐ Performed	☐ Performed	☐ Performed	☐ Performed	☐ Performed	Weekly first 18 weeks - then every 28 days
	White Blood Count		x10⁹/L	x10⁹/L	x10⁹/L	x10⁹/L	x10⁹/L	
	Neutrophils Absolute		x10⁹/L	x10⁹/L	x10⁹/L	x10⁹/L	x10⁹/L	
	Eosinophils Absolute		x10⁹/L	x10⁹/L	x10⁹/L	x10⁹/L	x10⁹/L	
	Liver function test		☐ Performed					6 monthly
	Urea & Electrolytes		☐ Performed					6 monthly
	Fasting plasma glucose		mmol/L					At 3 months, 6 months, then 6 monthly
	Total cholesterol (fasting)		mmol/L					
	LDL (fasting)		mmol/L					
	HDL (fasting)		mmol/L					
	Triglycerides (fasting)		mmol/L					
	Troponin		nanograms/L	nanograms/L	nanograms/L	nanograms/L	nanograms/L	As clinically indicated thereafter
	C-Reactive Protein (CRP)		mg/L	mg/L	mg/L	mg/L	mg/L	
	ECG (QT interval)							Weekly for first 4 weeks, then as clinically indicated
	Cardiac echocardiogram							At 3 months, then 1, 2, 5 yrs
	Beta HCG (female)							When needed

These are suggested guidelines only and do not replace the need for clinical discretion. Refer to the treating psychiatrist for individual monitoring requirements

Space to document measurements for 28 days if required

Prompts for frequency of monitoring beyond first month of therapy.

Haematological Monitoring

- Regular full blood counts are required as clozapine can cause agranulocytosis
- WBC and Neutrophil counts must be performed :
  - -At least weekly for the first 18 weeks of therapy
  - -At least every four weeks (28 days) after the first 18 weeks of therapy
- Blood results are classified as **green**, **amber** or **red**

Clozapine Blood Results Monitoring System		Recommended Action
Green Range	WBC greater than 3.5 x 10^9/L AND Neutrophils greater than 2.0 x 10^9/L	Continue clozapine therapy
Amber Range	WBC 3.0 - 3.5 x 10^9/L AND/OR Neutrophils 1.5 - 2.0 x 10^9/L	Continue clozapine therapy with twice-weekly blood tests until return to "green" range
Red Range	WBC less than 3.0 x 10^9/L AND/OR Neutrophils less than 1.5 x 10^9/L	Stop clozapine therapy immediately. Contact haematologist and Clozapine Monitoring Centre

Classification of each colour and the recommended action

Haematological Monitoring

POST-THERAPY BLOOD TESTING:

WEEKLY monitoring

Patients on weekly monitoring at the time of discontinuation MUST continue to have 4 weeks of weekly monitoring

MONTHLY monitoring

Patients on monthly monitoring at the time of discontinuation MUST have one further test one month after discontinuation

Recommendations for recommencing therapy after interruption

Recommencing Therapy after Interruption
Dosing recommendations if clozapine dose is missed for > 48 hours • Obtain psychiatric review prior to recommencing clozapine • Recommence at 12.5mg once or twice daily on the first day. Refer to what side effects the patient had previously when starting clozapine.The rate of re-titration can be adjusted to take into account emergent side effects and period of interruption • This is a guide only – for further dosing options refer to treating psychiatrist.

Suggested Action:

If clozapine is missed for > 48 hours, recommence at 12.5mg once or twice daily on the first day.

Refer to what side effects the patient had previously when starting clozapine. The rate of re-titration can be adjusted to take into account emergent side effects and period of interruption. For further dose options refer to the patient's treating psychiatrist.

Recommendations for Missed Doses

Blood Test Monitoring after Interruption of Therapy			
Monitoring frequency	**Clozapine missed for < 72 hours**	**Clozapine missed > 72 hours but less than 4 weeks**	**Clozapine missed > 4 weeks**
Weekly	No change in monitoring	Monitor weekly for at least 6 weeks or for as long as necessary to achieve a total of 18 weeks of weekly monitoring	Recommence as for a new patient
Monthly		Monitor weekly for 6 weeks then continue with monthly monitoring if no problems detected	

Different monitoring frequency is required when clozapine is missed for:

- < 72 hours
- > 72 hours but less than 4 weeks
- > 4 weeks

Side-effects

Side effects Associated with Clozapine Therapy		Modified from the Maudsley Prescribing Guidelines 14th ed 2021
Side effect	**Signs and symptoms / Onset**	**Recommended Action**
Neutropenia / agranulocytosis	WBC < 3.0 x 10^9/L or Neutrophils < 1.5 x 10^9/L. Flu-like symptoms such as sore throat & fever. (First 18 weeks – but may occur at any time)	Contact doctor. Withhold clozapine. Contact haematologist at Clozapine Monitoring Centre.
Myocarditis / cardiomyopathy	Fast or irregular heartbeat at rest with rapid breathing, dyspnoea, hypotension, raised jugular venous pressure, fatigue, infective symptoms (including gastrointestinal, urinary, and/or respiratory), chest pain or fever. Cardiomyopathy may occur at any time. Myocarditis – within 4 weeks of starting)	Withhold Clozapine. Repeat ECG and echocardiogram. Check C-Reactive Protein (CRP) and troponin. Refer to cardiologist.
Fever	> 38° C (First 4 weeks)	Contact doctor. Reduce rate of dose titration of clozapine. Check WBC, neutrophils, troponin and CRP. Physical examination for signs of infection. Consider ECG, Echocardiogram. Give paracetamol and notify doctor to exclude agranulocytosis / myocarditis.
Seizures	Increases with high doses, rapid dose titration, concurrent use of drugs that lower seizure threshold and preexisting seizure disorders and concurrent illness. (May occur at any time)	Medical emergency, manage seizure. Withhold clozapine for one day and restart at half the dose. Consider prophylactic antiepileptic. Risk of seizures increases with higher serum clozapine levels; check serum clozapine levels.
Hypersalivation	Excessive drooling – Very troublesome at night. (First few months)	Contact doctor. Check with pharmacist for pharmacological options.
Constipation	Less frequent bowel motions, hard stools, abdominal bloating, cramping or pain, decreased appetite or fatigue. (Usually persists) Severe Clozapine Induced Gastrointestinal Hypomotility (CIGH) can be fatal.	Contact doctor. Recommend increased fluid intake and exercise. Consider pre-emptive laxatives for all patients. Review contributing medicines and consider dose reduction. Treat CIGH aggressively with laxatives and consider cessation of clozapine if treatment fails. Avoid bulk forming laxatives.
Nocturnal enuresis	Loss of bladder control, especially at night. (May occur at any time)	Contact doctor. Avoid fluids after 7pm. Check males for other causes. Continence referral. Check with pharmacist for pharmacological options.
Weight gain	This may occur early in treatment and can be significant	Dietary and lifestyle counselling before weight gain occurs. Ongoing monitoring and support.
This is not an exhaustive list of side effects. Please see product information for further advice. It is recommended that concurrent use of antipsychotic therapy be avoided where possible as this increases the patient's risk of side effects.		

- This is **NOT** a complete list of clozapine related side effects
- Signs and symptoms of side effects
- To increase awareness of possible side effects
- Prompts for nurses to contact doctor if any of the side effects are present

Forms required for patient registration before initiation

- Before initiating clozapine, contact clinical pharmacist
- Forms that are still required to be completed:

»**Clozapine Registration for New Patients Referral Form**

(For registration of patient: Contact clinical pharmacist)

»**Clozapine Notification Form /Consent Form**

(Patient information)

Summary

- Baseline monitoring **MUST** be performed no more than 10 days before commencing treatment
- Clozapine **MUST** only be prescribed when patient is allocated a clozapine number
- Current Clozapine Initiation Chart to be kept with other medication charts
- Commence clozapine in the morning – avoid weekends (preferable to start early in the week)

Summary

- Printed resources available from pharmacy:

  » Clozapine Registration for New Patients Referral Form
  » Clozapine Counselling Points
  » Clozapine Consumer Medication Information

- Please forward any comments on the Clozapine Chart to your clinical pharmacist or DoH.MedicinesandTechnologyUnit@health.wa.gov.au