"Clozaril (Clozapine) is an antipsychotic agent belonging to Di-Benzodiazepine class of drugs, indicated for the use in Treatment Resistant Schizophrenia as well as Recurrent Suicidal behavior. Clozaril may reduce the number of WBCs in our body .A small fall in the number of WBCs may result in vulnerability to infections ,a condition called **Neutropenia**, while a more dramatic reduction may result in **Agranulocytosis**. If caught early, this fall in WBCs can be reversed. Mandatory blood monitoring & drug dispensing guidelines according to the requirements provide an efficient means of determining developing **Agranulocytosis** (also specified in the Clozaril package insert) includes:

1. Every patient must be screened for blood monitoring at baseline to prevent inappropriate re-treatment.

2. Before starting Clozaril management, there needs to have a baseline Complete Blood Count (CBC); if that comes normal then begin Clozaril treatment & perform necessary blood test every week for **First 18 weeks**; again, if baseline CBC comes within normal limits, then shift to monthly monitoring for **at least 6 months** for as long as you continue treatment.

The risk of **Agranulocytosis** becomes less after 18 weeks of treatment, the longer you are on Clozaril treatment; the need for blood test becomes less frequent.

3. Pharmacist will dispense Clozaril for **7 days only** if WBC test is performed weekly and results show it to be within normal limits.

The blood test range will be categorized using already defined **"Traffic light system" i.e. "*Green", "Amber" & "Red".*** Clozaril will be provided according to the **Blue form eligibility criteria.** Clozaril will not be provided unless you have an up to date blood result. Smooth Clozaril delivery must be ensured and there must not be even a single day gap. If the gap is identified, treatment must be reinitiated from the starting dose.

4. **CPMS protocol** is to provide a ***100% fail-safe system*** for monitoring white blood cell counts (WBCs). Provide comprehensive data collection on the incidence and development of **Agranulocytosis**. CPMS protocol is to support **Novartis Pharma globally**, by facilitating the determination of WBC's & dispensing Clozaril to the patient within specified protocol. Other specific tasks includes follow up missed appointments, ensuring that WBCs are obtained and analyzed weekly, following up the results of these tests, providing liaison with the pharmacy/dispenser, maintaining blood reports for all patients receiving clozapine, sharing any adverse events and conveying all these data to Novartis Pharma.

5. A doctor desires to start a patient on Clozaril treatment, he needs to register himself (Fill out ***Doctor registration form "Yellow form"***), the pharmacist who dispenses the tablets & the person he wishes to treat must fill ***Patient registration form" Yellow form".*** All concerned needs to be registered before Clozaril treatment can begin. ***Only specialist Consultants usually Psychiatrists can start on Clozaril treatment.***

Ensure maintaining & delivery of Clozaril dosage **"Blue forms"** to Novartis Pharma Head office, on monthly basis "

NOVARTIS

Clozaril can cause agranulocytosis. Its use should be limited to patients:
- **with schizophrenia who are non-responsive to or intolerant of classical antipsychotic agents, or with schizophrenia or schizoaffective disorder who are at risk of recurrent suicidal behavior (see section INDICATIONS)**
- **who have initially normal leukocyte findings (white blood cell count (WBC) ≥ 3500/mm³ (≥3.5 x 10⁹/L), and absolute neutrophil counts (ANC) ≥ 2000/mm³ (≥2.0 x 10⁹/L)),**
- **and in whom regular white blood cell counts and absolute neutrophil counts can be performed as follows: weekly during the first 18 weeks of therapy, and at least every 4 weeks thereafter throughout treatment. Monitoring must continue throughout treatment and for 4 weeks after complete discontinuation of Clozaril (see section WARNINGS AND PRECAUTIONS).**

Prescribing physicians should comply fully with the required safety measures. At each consultation, a patient receiving Clozaril should be reminded to contact the treating physician immediately if any kind of infection begins to develop. Particular attention should be paid to flu-like complaints such as fever or sore throat and to other evidence of infection, which may be indicative of neutropenia (see section WARNINGS AND PRECAUTIONS).

Clozaril must be dispensed under strict medical supervision in accordance with official recommendations (see section WARNINGS AND PRECAUTIONS).

Clozaril®

Antipsychotic agent

DESCRIPTION AND COMPOSITION

25 mg Tablet: Each tablet contains 25 mg clozapine.

100 mg Tablet: Each tablet contains 100 mg clozapine.

Pharmaceutical form

Tablets. The scored tablets can be divided into equal halves.

Active substance

Clozapine

Certain dosage strengths may not be available in all countries.

Active moiety

Clozapine

Excipients

Clozaril tablets: magnesium stearate; silica, colloidal anhydrous; povidone; talc; maize starch; lactose monohydrate.

Pharmaceutical formulations may vary between countries.

INDICATIONS

- **Treatment-resistant schizophrenia**
  Clozaril is indicated in patients with treatment-resistant schizophrenia, i.e. patients with schizophrenia who are non-responsive to or intolerant of classic antipsychotics.

  Non-responsiveness is defined as a lack of satisfactory clinical improvement despite the use of adequate doses of at least two marketed antipsychotics prescribed for adequate durations.

  Intolerance is defined as the impossibility of achieving adequate clinical benefit with classic antipsychotics because of severe and untreatable neurological adverse reactions (extrapyramidal side effects or tardive dyskinesia).

- **Risk of recurrent suicidal behavior**
  Clozaril is indicated for reducing the risk of recurrent suicidal behavior in patients with schizophrenia or schizoaffective disorder who are judged to be at chronic risk for re-experiencing suicidal behavior, based on history and recent clinical state. Suicidal behavior refers to actions by a patient that put him/herself at high risk for death.

- **Psychosis during the course of Parkinson's disease**
  Clozaril is indicated in psychotic disorders occurring during the course of Parkinson's disease, in cases where standard treatment has failed.

  The failure of standard treatment is defined as the lack of control of the psychotic symptoms and/or the onset of functionally unacceptable motoric deterioration occurring after the following measures have been taken:
  - Withdrawal of anti-cholinergic medication including tricyclic anti-depressants
  - Attempt to reduce the dose of antiparkinsonian medication with dopaminergic effect

DOSAGE AND ADMINISTRATION

Dosage Information

The dosage must be adjusted individually. For each patient the lowest effective dose should be used. Cautious titration and a divided dosage schedule are necessary to minimize the risks of hypotension, seizure, and sedation.

Initiation of Clozaril treatment must be restricted to those patients with a WBC count ≥3500/mm³ (3.5 x 10^9/L) and an ANC ≥2000/mm³ (2.0 x 10^9/L), and within standardized normal limits.

Dose adjustment is indicated in patients who are also receiving medicinal products that have pharmacokinetic interactions with clozapine, such as benzodiazepines or selective serotonin re-uptake inhibitors (see section INTERACTIONS).

Method of Administration

Clozaril is administered orally.

Switching from a previous antipsychotic therapy to Clozaril

It is generally recommended that Clozaril should not be used in combination with other antipsychotics. When Clozaril therapy is to be initiated in a patient undergoing oral antipsychotic therapy, it is recommended that the dosage of other antipsychotics be reduced or discontinued by gradually tapering it downwards. Based on the clinical circumstances, the prescribing physician should judge whether or not to discontinue the other antipsychotic therapy before initiating treatment with Clozaril.

Treatment resistant schizophrenia

Starting therapy

Clozaril should be started with 12.5 mg (half a 25 mg tablet) once or twice on the first day, followed by one or two 25 mg tablets on the second day. If well tolerated, the daily dose may then be increased slowly in increments of 25 mg to 50 mg in order to achieve a dose level of up to 300 mg/day within 2 to 3 weeks. Thereafter, if required, the daily dose may be further increased in increments of 50 mg to 100 mg at half-weekly or, preferably, weekly intervals.

Therapeutic dose range

In most patients, antipsychotic efficacy can be expected with 300 to 450 mg/day given in divided doses. Some patients may be treated with lower doses, and some patients may require doses up to 600 mg/day. The total daily dose may be divided unevenly, with the larger portion being taken at bedtime.

Maximum dose

To obtain full therapeutic benefit, a few patients may require larger doses, in which case judicious increments (not exceeding 100 mg) are permissible up to 900 mg/day. However the possibility of increased adverse reactions (in particular seizures) occurring at doses over 450 mg/day must be borne in mind.

Maintenance dose

After achieving maximum therapeutic benefit, many patients can be maintained effectively on lower doses. Careful downward titration is therefore recommended. Treatment should be maintained for at least 6 months. If the daily dose does not exceed 200 mg, once daily administration in the evening may be appropriate.

Ending Therapy

In the event of planned termination of Clozaril therapy, a gradual reduction in dose over a 1-to 2-week period is recommended. If abrupt discontinuation is necessary (e.g. because of leucopenia), the patient should be carefully observed for the recurrence of psychotic symptoms and symptoms related to cholinergic rebound (see section WARNINGS AND PRECAUTIONS).

Restarting therapy

In patients in whom the interval since the last dose of Clozaril exceeds 2 days, treatment should be re-initiated with 12.5 mg (half a 25-mg tablet) given once or twice on the first day. If this dose is well tolerated, it may be feasible to titrate the dose to the therapeutic level more quickly than is recommended for initial treatment. However, in any patient who has previously experienced respiratory or cardiac arrest with initial dosing (see section WARNINGS AND PRECAUTIONS), but was then able to be successfully titrated to a therapeutic dose, re-titration should be done with extreme caution.

Reducing the risk of suicidal behavior in schizophrenia and schizoaffective disorder

The dosage and administration recommendations described in the preceding section (DOSAGE AND ADMINISTRATION) regarding the use of Clozaril in patients with treatment-resistant schizophrenia should also be followed when treating patients with schizophrenia or schizoaffective disorder at risk for recurrent suicidal behaviour.

A course of treatment with Clozaril of at least two years is recommended in order to maintain the reduction of risk for suicidal behaviour. It is recommended that the patient's risk of suicidal behaviour be reassessed after two years of treatment and that thereafter the decision to continue treatment with Clozaril be re-visited at regular intervals, based on thorough assessments of patient's risk for suicidal behaviour during treatment.

Psychotic disorders occurring during the course of Parkinson's disease, in cases where standard treatment has failed

Starting therapy

The starting dose must not exceed 12.5 mg/day (half a 25 mg tablet), taken in the evening. Subsequent dose increases must be by 12.5 mg increments, with a maximum of two increments a week up to a maximum of 50 mg, a dose that cannot be reached until the end of the second week. The total daily amount should preferably be given as a single dose in the evening.

Therapeutic dose range

The mean effective dose is usually between 25 and 37.5 mg/day. In the event that treatment for at least one week with a dose of 50 mg fails to provide a satisfactory therapeutic response, dosage may be cautiously increased by increments of 12.5 mg/week.

Maximum dose

The dose of 50 mg/day should only be exceeded in exceptional cases, and the maximum dose of 100 mg/day must never be exceeded.

Dose increases should be limited or deferred if orthostatic hypotension, excessive sedation or confusion occurs. Blood pressure should be monitored during the first weeks of treatment.

Maintenance dose

When there has been complete remission of psychotic symptoms for at least 2 weeks, an increase in anti-parkinsonian medication is possible if indicated on the basis of motor status. If this approach results in the recurrence of psychotic symptoms, Clozaril dosage may be increased by increments of 12.5 mg/week up to a maximum of 100 mg/day, taken in one or two divided doses (see above).

Ending Therapy

When ending therapy, a gradual reduction in dose by steps of 12.5 mg over a period of at least one week (preferably two) is recommended.

Treatment must be discontinued immediately in the event of neutropenia or agranulocytosis as indicated in section (WARNINGS AND PRECAUTIONS). In this situation, careful psychiatric monitoring of the patient is essential since symptoms may recur quickly.

Special populations

Cardiovascular disorders

In patients suffering from cardiovascular disorders (note: severe cardiovascular disorders are contraindications) the initial dose should be 12.5 mg given once on the first day, and dosage increase should be slow and in small increments.

Renal impairment

In patients with mild to moderate renal impairment the initial dose should be 12.5 mg given once on the first day, and dosage increase should be slow and in small increments.

Hepatic impairment

Patients with hepatic impairment should receive Clozaril with caution along with regular monitoring of liver function tests (see section WARNINGS AND PRECAUTIONS).

Pediatrics

No pediatric studies have been performed. The safety and efficacy of Clozaril in children and adolescents have not been established.

Patients 60 years of age and older

It is recommended that treatment in patients 60 years and older is initiated at a particularly low dose (12.5 mg given once on the first day) with subsequent dose increments restricted to 25 mg/day.

CONTRAINDICATIONS

- Known hypersensitivity to clozapine or to any of the excipients of Clozaril.
- Patients unable to undergo regular blood tests.
- History of toxic or idiosyncratic granulocytopenia/agranulocytosis (with the exception of granulocytopenia/agranulocytosis from previous chemotherapy).
- Impaired bone marrow function.
- Uncontrolled epilepsy.
- Alcoholic and other toxic psychoses, drug intoxication, comatose conditions.
- Circulatory collapse and/or CNS depression of any cause.
- Severe renal or cardiac disorders (e.g. myocarditis).
- Active liver disease associated with nausea, anorexia or jaundice; progressive liver disease, hepatic failure.
- Paralytic ileus.

WARNINGS AND PRECAUTIONS

Special precautionary measure

Agranulocytosis

Because of the association of Clozaril with agranulocytosis, the following precautionary measures are mandatory:

- Drugs known to have a substantial potential to depress bone marrow function should not be used concurrently with Clozaril. In addition, the concomitant use of long-acting depot antipsychotics should be avoided because of the impossibility of removing these medications, which may be potentially myelosuppressive, from the body rapidly in situations where this may be required, e.g. granulocytopenia.
- Patients with a history of primary bone marrow disorders may be treated only if the benefit outweighs the risk. They should be carefully reviewed by a haematologist prior to starting Clozaril.
- Patients who have low white blood cell (WBC) counts because of benign ethnic neutropenia should be given special consideration and may be started on Clozaril after agreement of a haematologist.

Clozaril must be dispensed under strict medical supervision in accordance with official recommendations.

White Blood Cell (WBC) counts and Absolute Neutrophil Count (ANC) monitoring
White blood cell count (WBC) and differential blood counts must be performed within 10 days prior to starting Clozaril treatment to ensure that only patients with normal leukocyte (WBC ≥3500/mm^3 (≥3.5 x 10^9/L)) and absolute neutrophil counts (ANC ≥2000/mm^3 (≥2.0 x 10^9/L)) will receive Clozaril. After the start of Clozaril treatment, regular WBC count and ANC must be performed and monitored weekly for 18 weeks and thereafter at least every four weeks throughout treatment and for 4 weeks after complete discontinuation of Clozaril.

Prescribing physicians should comply fully with the required safety measures. At each consultation, the patient should be reminded to contact the treating physician immediately if any kind of infection begins to develop. Particular attention should be paid to flu-like complaints such as, fever or sore throat and to other evidence of infection, which may be indicative of neutropenia. A differential blood count must be performed immediately if any symptoms or signs of an infection occur.

Low WBC count and/or ANC
If during the first 18 weeks of Clozaril therapy, the WBC count falls to between 3500/mm^3 and 3000/mm^3 and/or the ANC falls to between 2000/mm^3 and 1500/mm^3, haematological evaluations must be performed at least twice weekly.

After 18 weeks of Clozaril therapy, haematological evaluations should be performed at least twice weekly if the WBC count falls to between 3000/mm^3 and 2500/mm^3 and/or the ANC falls to between 1500/mm^3 and 1000/mm^3.

In addition, if, during Clozaril therapy, the WBC count is found to have dropped by a substantial amount from baseline, a repeat WBC count and a differential blood count should be performed. A substantial drop is defined as a single drop of 3000 mm^3 or more in the WBC count or a cumulative drop of 3000 mm^3 or more within three weeks.

Immediate discontinuation of Clozaril is mandatory if the WBC count is less than 3000/mm^3 or the ANC is less than 1500/mm^3 during the first 18 weeks of therapy, or if the WBC count is less than 2500/mm^3 or the ANC is less than 1000/mm^3 after the first 18 weeks of therapy. WBC counts and differential blood counts should then be performed daily and patients should be carefully monitored for flu-like symptoms or other symptoms suggestive of infection. Following discontinuation of Clozaril, haematological evaluation is required until haematological recovery has occurred.

If Clozaril has been withdrawn and WBC count falls further to below 2000/mm^3 and/or the ANC falls below 1000/mm^3, the management of this condition must be guided by an experienced haematologist. If possible, the patient should be referred to a specialised haematological unit, where protective isolation and the administration of GM-CSF (granulocyte-macrophage colony stimulating factor) or G-CSF (granulocyte colony stimulating factor) may be indicated. It is recommended that the colony stimulating factor therapy be discontinued when the neutrophil count has returned to a level above 1000/mm^3.

Patients in whom Clozaril has been discontinued as a result of white blood cell deficiencies (see above) must not be re-exposed to Clozaril.

It is recommended that the haematological values be confirmed by performing two blood counts on two consecutive days; however, Clozaril should be discontinued after the first blood count.

Table 1: Blood monitoring during the first 18 weeks of Clozaril therapy

Blood cell count		Action required
WBC/mm^3 (/L)	ANC/mm^3 (/L)	
≥3500 (≥3.5 x 10^9)	≥2000 (≥2.0 x 10^9)	Continue Clozaril treatment.
Between ≥3000 and <3500 (≥3.0 x 10^9 and <3.5 x 10^9)	Between ≥1500 and <2000 (≥1.5 x 10^9 and <2.0 x 10^9)	Continue Clozaril treatment, sample blood twice weekly until counts stabilize or increase.
<3000 (<3.0 x 10^9)	<1500 (<1.5 x 10^9)	Immediately stop Clozaril treatment, sample blood daily until hematological abnormality is resolved, monitor for infection. Do not re-expose the patient.

Table 2: Blood monitoring after 18 weeks of Clozaril therapy

Blood cell count		Action required
WBC/mm^3 (/L)	ANC/mm^3 (/L)	
≥3000 (≥3.0 x 10^9)	≥1500 (≥1.5 x 10^9)	Continue Clozaril treatment.
Between ≥2500 and <3000 (≥2.5 x 10^9 and <3.0 x 10^9)	Between ≥1000 and <1500 (≥1.0 x 10^9 and <1.5 x 10^9)	Continue Clozaril treatment, sample blood twice weekly until counts stabilize or increase.
<2500 (<2.5 x 10^9)	<1000 (<1.0 x 10^9)	Immediately stop Clozaril treatment, sample blood daily until hematological abnormality is resolved, monitor for infection. Do not re-expose the patient.

In the event of interruption of therapy for non-haematological reasons
Patients who have been on Clozaril for more than 18 weeks and have had their treatment interrupted for more than 3 days but less than 4 weeks should have their WBC count and ANC monitored weekly for an additional 6 weeks. If no hematological abnormality occurs, monitoring at intervals not exceeding 4 weeks may be resumed. If Clozaril treatment has been interrupted for 4 weeks or longer, weekly monitoring is required for the next 18 weeks of treatment (see section DOSAGE AND ADMINISTRATION).

Other precautions
Eosinophilia
In the event of **eosinophilia**, discontinuation of Clozaril is recommended if the eosinophil count rises above 3000/mm^3. Therapy should be re-started only after the eosinophil count has fallen below 1000/mm^3.

Thrombocytopenia
In the event of **thrombocytopenia,** discontinuation of Clozaril is recommended if the platelet count falls below 50 000/mm^3.

Cardiovascular disorders
In patients suffering from cardiovascular disorders (note: severe cardiovascular disorders are contraindications) the initial dose should be 12.5 mg given once on the first day, and dosage increase should be slow and in small increments (see section DOSAGE AND ADMINISTRATION).

Orthostatic hypotension, with or without syncope, can occur during Clozaril treatment. Rarely (about one case per 3000 Clozaril-treated patients), collapse can be profound and may be accompanied by cardiac and/or respiratory arrest. Such events are more likely to occur during initial titration in association with rapid dose escalation; on very rare occasions they occurred even after the first dose. Therefore, patients commencing Clozaril treatment require close medical supervision.
Tachycardia that persists at rest, accompanied by arrhythmias, shortness of breath or signs and symptoms of heart failure, may rarely occur during the first month of treatment and very rarely thereafter. The occurrence of these signs and symptoms necessitates an urgent diagnostic evaluation for myocarditis, especially during the titration period. If the diagnosis of myocarditis is confirmed, Clozaril should be discontinued. Later in treatment, the same signs and symptoms may very rarely occur and may be linked to cardiomyopathy. Further investigation should be performed and if the diagnosis is confirmed, the treatment should be stopped unless the benefit clearly outweighs the risk to the patient.

Monitoring of standing and supine blood pressure is necessary during the first weeks of treatment in patients with Parkinson's disease.

Myocardial infarction
In addition, there have been postmarketing reports of myocardial infarction which may be fatal. Causality assessment was difficult in the majority of these cases because of serious pre-existing cardiac disease and plausible alternative causes.

QT interval prolongation
As with other antipsychotics, caution is advised in patients with known cardiovascular disease or family history of QT prolongation.

As with other antipsychotics, caution should be exercised when Clozaril is prescribed with medicines known to increase the QTc interval.

Cerebrovascular adverse events
An increased risk of cerebrovascular adverse events has been seen in the dementia population with some atypical antipsychotics. The mechanism for this increased risk is not known. An increased risk cannot be excluded for other antipsychotics or other patient populations. Clozaril should be used with caution in patients with risk factors for stroke.

Risk of thromboembolism
Since Clozaril may cause sedation and weight gain, thereby increasing the risk of **thromboembolism**, immobilization of patients should be avoided.

Metabolic Changes
Atypical antipsychotic drugs, including Clozaril, have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. These metabolic changes may include hyperglycemia, dyslipidemia, and body weight gain. While atypical antipsychotic drugs may produce some metabolic changes, each drug in the class has its own specific risk profile.

Hyperglycemia
On rare occasions, severe hyperglycemia, sometimes leading to ketoacidosis/hyperosmolar coma, has been reported during Clozaril treatment in patients with no prior history of hyperglycemia. While a causal relationship to Clozaril use has not been definitely established, glucose levels returned to normal in most patients after discontinuation of Clozaril, and re-challenge produced a recurrence of hyperglycemia in a few cases. The effect of Clozaril on glucose metabolism in patients with diabetes mellitus has not been studied. Impaired glucose tolerance, severe hyperglycemia, ketoacidosis and hyperosmolar coma have been reported in patients with no prior history of hyperglycemia. Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Exacerbation should be considered in patients receiving Clozaril who develop symptoms of hyperglycemia, such as polydipsia, polyuria, polyphagia or weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of antidiabetic treatment despite discontinuation of the suspect drug. In patients with significant treatment-emergent hyperglycemia, discontinuation of Clozaril should be considered.

There is a risk of altering the metabolic balance resulting in slight impairment of glucose homeostasis and a possibility of unmasking a pre-diabetic condition or aggravating pre-existing diabetes.

Dyslipidemia
Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics, including Clozaril. Clinical monitoring, including baseline and periodic follow-up lipid evaluations in patients using clozapine, is recommended.

Weight Gain
Weight gain has been observed with atypical antipsychotic use, including Clozaril. Clinical monitoring of weight is recommended.

Seizures
Clozaril may lower seizure threshold. In patients with a history of seizures the initial dose should be 12.5 mg given once on the first day, and dosage increase should be slow and in small increments (see section DOSAGE AND ADMINISTRATION).

Anticholinergic effects
Clozapine exerts anticholinergic activity, which may produce undesirable effects throughout the body. Careful supervision is indicated in the presence of **prostatic enlargement** and **narrow-angle glaucoma**. Probably on account of its anticholinergic properties, Clozaril has been associated with varying degrees **of impairment of intestinal peristalsis**, ranging from **constipation** to **intestinal obstruction, fecal impaction** and **paralytic ileus** (see section ADVERSE DRUG REACTIONS). On rare occasions these cases have proved fatal.

Fever
During Clozaril therapy, patients may experience transient **temperature elevations** above 38°C, with the peak incidence within the first 3 weeks of treatment. This fever is generally benign. Occasionally, it may be associated with an increase or decrease in the WBC count. Patients with fever should be carefully evaluated to rule out the possibility of an underlying infection or the development of agranulocytosis. In the presence of high fever, the possibility of **neuroleptic malignant syndrome** (NMS) must be considered. If the diagnosis of NMS is confirmed, Clozaril should be discontinued immediately and appropriate medical measures should be administered.

Special populations
Hepatic impairment
Patients with stable pre-existing liver disorders may receive Clozaril, but must undergo regular liver function tests. Such tests should be performed immediately in patients who develop symptoms of possible liver dysfunction such as nausea, vomiting and/or anorexia during Clozaril treatment. If the elevation of the values is clinically relevant or if symptoms of jaundice occur, treatment with Clozaril must be discontinued. It may be resumed (see section DOSAGE AND ADMINISTRATION - Re-starting therapy) only when the results of liver function tests are normal. In such cases, liver function should be closely monitored after re-introduction of Clozaril.

Renal impairment
In patients suffering from mild to moderate renal impairment, an initial dose of 12.5 mg/day (half a 25 mg tablet) is recommended (see section DOSAGE AND ADMINISTRATION).

Patients aged 60 years and older
It is recommended that treatment be initiated at a particularly low dose (12.5 mg given once on the first day) and subsequent dose increments be restricted to 25 mg/day.

Clinical studies with Clozaril did not include sufficient numbers of subjects aged 60 years and over to determine whether or not they respond differently from younger subjects.

Orthostatic hypotension can occur with Clozaril treatment and there have been rare reports of tachycardia, which may be sustained, in patients taking Clozaril. Patients aged 60 years and older, particularly those with compromised cardiovascular function, may be more susceptible to these effects.

Patients aged 60 years and older may also be particularly susceptible to the anticholinergic effects of clozapine, such as urinary retention and constipation.

Patients aged 60 years and older with Dementia-related Psychosis
In patients aged 60 years and older with dementia-related psychosis, the efficacy and safety of clozapine has not been studied. Observational studies suggest that patients aged 60 years and older with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. In the published literature, risk factors that may predispose this patient population to increased risk of death when treated with antipsychotics include sedation, the presence of cardiac conditions (e.g. cardiac arrhythmias) or pulmonary conditions (e.g. pneumonia, with or without aspiration). Clozaril should be used with caution in patients aged 60 years and older with dementia.

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(246)

BLUE FORM

HAEMATOLOGY REPORT

Patient's Name: _____ CPMS No. _____

Date of Sample drawn : _____ Lab No. _____

Please Give Results in Absolute Values.

Total Leucocytes (White Blood Count): _____ X 10^9 /L

Neutrophils: _____ X 10^9 /L Basophils: _____ X 10^9 /L

Lymphocytes: _____ X 10^9 /L Monocytes: _____ X 10^9 /L

Eosinophils: _____ X 10^9 /L Platelets: _____ X 10^9 /L

Blood Pressure: _____ Weight: _____

Haematologist's Signature: _____ Date: _____

CLOZARIL RELEASE FORM

Please tick ☐ mark the relevant square

Haematological Status				Patient Clozaril Status
Count	Green ☐	Amber ☐	Red ☐	Pretreatment ☐
Total WBC	> 3.5 x10^9/L	3.0-3.5 x 10^9/L	< 3.5 x10^9/L	Active treatment ☐
Neutrophils	> 2.0 x10^9/L	1.5-2.0 x 10^9/L	< 1.5 x10^9/L	On hold ☐
Platelets	Normal	Normal	< 100 x10^9/L	Discontinue ☐

Blood Count Acceptable : No ☐ Yes ☐ if Yes:-

CLOZARIL PRESCRIPTION

Please issue CLOZARIL _____ mg/day for

☐ ONE week (first 18 wks)

☐ FOUR weeks (For patients who have completed an uninterrupted medication for 18 week

Daily Dosage _____ mg in the morning _____ mg in the evening

Doctor's Signature: _____ Name: _____

Date: _____ Clinic _____

For Novartis Use

Outlet _____

Tablets issued: 100 mg _____ tablets 25mg _____ tablets Signature: _____

Tablets balance: 100 mg _____ tablets 25mg _____ tablets Date _____

1009-CLO