# Clozapine and the Risk Of Agranulocytosis: A Guide for Healthcare Providers

This guide approved by Saudi food and drug Authority

**This Guide discusses:**

- Clozapine and the risk of **agranulocytosis**
- Treatment recommendations and patient absolute neutrophil counts monitoring

**Clozapine and the Risk of agranulocytosis:**

A Guide for Healthcare Providers

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## What is Zapnex and what is it indicated for?

Zapnex is indicated in treatment-resistant schizophrenic patients and in schizophrenia patients who have severe, untreatable neurological adverse reactions to other antipsychotic agents, including atypical antipsychotics. Treatment resistance is defined as a lack of satisfactory clinical improvement despite the use of adequate doses of at least two different antipsychotic agents, including an atypical antipsychotic agent, prescribed for adequate duration. Zapnex is also indicated in psychotic disorders occurring during the course of Parkinson's disease, in cases where standard treatment has failed.

### 1. Absolute Neutrophil Counts, agranulocytosis, and Patient absolute neutrophil counts Monitoring

#### What is Absolute Neutrophil Counts (ANC)?

Absolute neutrophil counts is the laboratory parameter for monitoring patients for clozapine-induced neutropenia. Prescribers must report the absolute neutrophil counts before starting and during clozapine treatment.

ANC is usually available as a component of the complete blood count (CBC), including differential:

- ANC is more relevant to drug-induced neutropenia than white blood cell (WBC) count
- ANC may also be calculated using the following formula:

| | | | |
|---|---|---|---|
| **ANC =** | **Total WBC Count** | **x** | **Total percentage of neutrophils* Obtained from the differential** |

*neutrophil includes “segs” and “bands”

Other granulocytes (basophils and eosinophils) contribute minimally to neutropenia and their measurement is not necessary.

#### What is the risk of agranulocytosis associated with clozapine?

Clozapine can cause agranulocytosis, which can lead to serious infections and death.

Agranulocytosis occurs in a small percentage of patients taking clozapine.

- Agranulocytosis is defined as absolute neutrophil counts less than 500/µL
- The risk appears greatest during the first 18 weeks of clozapine treatment
- The mechanism is not dose-dependent
- If clozapine is used concurrently with a medication(s) known to cause neutropenia:

  - consider monitoring patients more closely than the treatment guidelines recommend, and

  - consult with the treating oncologist in patients receiving concomitant chemotherapy

**What is Benign Ethnic Neutropenia (BEN)?**

BEN is a condition observed in certain ethnic groups whose average absolute neutrophil counts is lower than "standard" laboratory ranges for neutrophils.

A few important things to know about patients diagnosed with BEN:

- It is most commonly observed in individuals of African descent (approximate prevalence of 25-50%), some Middle Eastern ethnic groups, and in other non-Caucasian ethnic groups with darker skin
- BEN is more common in men
- Patients with BEN have normal hematopoietic stem-cell number and myeloid maturation, are healthy, and do not suffer from repeated or severe infections
- Patients with BEN **<u>are not</u>** at increased risk for developing clozapine-induced neutropenia

Additional evaluation may be needed to determine if baseline neutropenia is due to BEN.

Consider a hematology consultation before starting or during clozapine treatment as necessary.

Patients who have low white blood cell (WBC) counts because of BEN should be given special consideration and may be started on Zapnex after agreement of a hematologist.

**What are the treatment recommendations and monitoring requirements for patients taking clozapine?**

**Agranulocytosis**

Zapnex can cause agranulocytosis, therefore requires the following preventive measures: Zapnex treatment must not be started concurrently with substances known to have a substantial potential for causing agranulocytosis; concomitant use of depot antipsychotics is to be discouraged, because these drugs that can be potentially myelotoxic cannot be removed from the body quickly enough in case of need, such as 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 Zapnex, Prescribing physicians should comply fully with the required safety measures. At each consultation, a patient receiving Zapnex 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. Zapnex must be released under strict medical supervision in according to Absolute Neutrophil Counts with official recommendations.

**White Blood Cell (WBC) counts and Absolute Neutrophil Count (ABSOLUTE NEUTROPHIL COUNTS)**

**Monitoring**

WBC and differential blood counts must be performed within 10 days prior to initiating Zapnex treatment to ensure that only patients with normal WBC counts and absolute neutrophil counts (WBC count 3500/$mm^3$ ($3.5x10^9$/l) and ABSOLUTE NEUTROPHIL COUNTS 2000/$mm^3$ ($2.0x10^9$/l)) will receive Zapnex. After the start of Zapnex treatment regular WBC count and ABSOLUTE NEUTROPHIL COUNTS must be performed and monitored weekly for the first 18 weeks and at least at four-week intervals thereafter.

Monitoring must continue throughout treatment and for 4 weeks after complete discontinuation of Zapnex or until haematological recovery has occurred (see "Low WBC count/ABSOLUTE NEUTROPHIL COUNTS" below). At each consultation, the patient must be reminded to contact the treating physician immediately if any kind of infection, fever, sore throat or other flu -like symptoms develop. WBC and differential blood counts must be performed immediately if any symptoms or signs of an infection occur.

**Low WBC count/ABSOLUTE NEUTROPHIL COUNTS**

If-, during the first 18 weeks of Zapnex therapy, either the WBC count falls to between WBC 3,5 x $10^9$/l and 3,0 x $10^9$/l and/or the ABSOLUTE NEUTROPHIL COUNTS falls to between 2,0 x $10^9$/l and 1,5 x $10^9$/l, haematological evaluations must be performed at least twice weekly.

After 18 week of Zapnex therapy, haematological evaluations should be performed at least twice weekly if the WBC count falls to between 3,0 x $10^9$/l and 2,5 x $10^9$/l and/or ABSOLUTE NEUTROPHIL COUNTS falls between 1,5 x $10^9$/l and 1,0 x $10^9$/l.

Furthermore if, during treatment, there is a significant decrease in the number of leukocytes compared with baseline, testing leukocyte count and differential blood count should be repeated. The significant decrease is defined as a single drop in the number of leukocytes 3,0 x $10^9$/l or more or cumulative decline of 3,0 x $10^9$/l or more within three weeks.

Immediate discontinuation of Zapnex treatment is mandatory if either the WBC count is less than 3,0 x $10^9$/l or the ABSOLUTE NEUTROPHIL COUNTS is less than 1,5 x $10^9$/l during the first 18 weeks of treatment, or decrease in leukocyte count below 2,5 x $10^9$/l or ABSOLUTE NEUTROPHIL COUNTS below 1,0 x $10^9$/l after the first 18 weeks of treatment. Determination of leukocyte count and differential

should then be performed daily and patients should be carefully monitored for flu-like symptoms or other signs of infection. After discontinuation of Clozapine, haematological evaluation is required until haematological recovery has occurred.

If Clozapine was discontinued and WBC count falls further under 2,0 x $10^9$/l and/or ABSOLUTE NEUTROPHIL COUNTS fall below 1,0 x $10^9$/l, treatment should be guided by the state experienced hematologist. If possible, the patient should be referred to a specialized hematology department, where protective insulation and 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 over 1,0 x $10^9$/l.

Patients, in whom Zapnex was discontinued due to deficiency of white blood cells (see above), may not be re-exposed to Zapnex.

It is recommended to confirm the blood values of two measurements on two consecutive days; however Zapnex should be discontinued after the first measurement.

Table 1: Monitoring of blood parameters during the first 18 weeks of treatment Zapnex

| **Blood cell count** | | Action required |
|---|---|---|
| WBC/$mm^3$ (/l) | ABSOLUTE NEUTROPHIL COUNTS/mm | |
| ≥ 3500 (≥ 3,5 x $10^9$) | ≥2000 (≥ 2,0 x $10^9$) | Continue Zapnex 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 Zapnex treatment, sample blood twice weekly until counts stabilize or increase |
| < 3000 (<3,0 x $10^9$) | < 1500 (<1,5 x $10^9$) | Immediately stop Zapnex treatment, sample blood daily until haematological abnormality is resolved, monitor for infection. Do not re- expose the patient. |

Table 2: Monitoring of blood parameters after 18 weeks of treatment Zapnex

| **Blood cell count** | | Action required |
|---|---|---|
| WBC/mm3 (/l) | ABSOLUTE NEUTROPHIL COUNTS/mm3 (/l) | |
| ≥ 3000 (≥ 3,0 x $10^9$) | ≥ 1500 (≥ 1,5 x $10^9$) | Continue Zapnex 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 Zapnex treatment, sample blood twice weekly until counts stabilize or increase |
| < 2500 (<2,5 x $10^9$) | < 1000 (<1,0 x $10^9$) | Immediately stop Zapnex treatment, sample blood daily until haematological abnormality is resolved, monitor for infection. Don't re-expose the patient. |

**Discontinuation of therapy for other reasons:**

Patients who have been on Zapnex 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 absolute neutrophil counts monitored weekly for an additional 6 weeks. If no haematological abnormality occurs, monitoring at intervals not exceeding 4 weeks may be resumed. If Zapnex treatment has been interrupted for 4 weeks or longer, weekly monitoring is required for the next 18 weeks of treatment and the dose should be re-titrated.

**Can a patient in whom Zapnex has been discontinued as a result of white blood cell deficiencies continue clozapine treatment?**

**For Patients in the General Population**

Patients, who Zapnex was discontinued due to deficiency of white blood cells, may not be re-exposed to Zapnex. Prescribers should follow the treatment recommendations as **in Table 1 and Table 2.**

For patient with an absolute neutrophil counts less than 1000/µL immediately stop Zapnex treatment, sample blood daily until haematological abnormality is resolved, monitor for infection. Don't re- expose the patient.

**If a patient develops a fever, how is clozapine treatment managed?**

Generally, clozapine treatment should be interrupted as a precautionary measure in any patient who develops a fever of 38.5°C (101.3°F) or greater, and an absolute neutrophil counts should be obtained. Fever is often the first sign of a neutropenic infection.

If fever occurs in any patient with an absolute neutrophil counts less than 1000/ µL, initiate appropriate neutropenia workup and treatment for infection. Refer to **Table 1 and Table 2** for absolute neutrophil counts monitoring recommendations.

If any patient presents with evidence of fever and/or neutropenia, consider a hematology consultation.

**Please refer to the Summary of Product Characteristics (SPC) for more information.**

## 2. Reporting Adverse Events Associated with Clozapine

You can report any problem or adverse events through:

**- The National Pharmacovigilance Center (NPC)**

- Fax: +966-11-205-7662
- Toll free phone: 8002490000
- SFDA Call Center: 19999
- E-mail: npc.drug@sfda.gov.sa
- Website: https://ade.sfda.gov.sa/

You should also report any side effects to Aurobindo Pharma Saudi Arabia Limited, Jeddah, Pharmacovigilance department on +966 (0) 12 6688856 Ext. 107 or pv.apsal@aurobindo.com

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