Direct Healthcare Professional Communication

Feb. 2026

Clozapine: revised recommendations for routine blood count monitoring for the risk of agranulocytosis

Dear Healthcare Professional,

MAH, in agreement with the General Administration for Pharmaceutical Vigilance of the Central Administration for Pharmaceutical Care at The Egyptian Drug Authority, would like to inform you of the following:

Summary

Clozapine increases the risk for neutropenia and agranulocytosis. Regular blood count monitoring is in place to minimise this risk. New evidence has led to revised monitoring recommendations.

Revised ANC thresholds:

• The monitoring requirement for White Blood Cell (WBC) count has been removed since the Absolute Neutrophil Count (ANC) is sufficient
• ANC thresholds for treatment initiation and continuation have been amended in line with the standard definitions of mild (ANC: 1000–1500/mm³), moderate (ANC: 500– 999/mm³), and severe neutropenia (ANC

Revised ANC monitoring requirements:

• The patient's ANC must be monitored as follows:

o weekly during the first 18 weeks of treatment

o then monthly for the following 34 weeks (i.e., until completion of the first year of treatment)

o if there has been no history of neutropenia during the first year of treatment, ANC monitoring can be reduced to once every 12 weeks o if there has been no history of neutropenia during the first two years of treatment, ANC should be collected once a year

• Patients should be reminded at each consultation to contact their physician immediately if signs or symptoms of infection occur. In the event of such symptoms, ANC must be performed immediately

• Additional ANC monitoring may be considered in older patients, or with concomitant treatment with valproic acid, especially during the initiation period.

Actions to be taken depending on ANC values:

• The ANC of patients who experience mild neutropenia (1000-1500/mm3) during treatment that subsequently stabilises and/or resolves, should be monitored monthly throughout treatment. For patients with confirmed BEN the threshold is ANC: 500-1000/mm3 (0.5-1.0 x109/L)

• Patients with an ANC

Recommendations for ANC monitoring upon resuming clozapine after treatment interruption for non-

haematological reasons:

• Stable patients (≥2 years of treatment) without neutropenia can resume their previous schedule, irrespective of the duration of the interruption

• Patients with prior neutropenia or shorter treatment duration (>18 weeks-2 years) need closer monitoring after interruptions ≥3 days but less than 4 weeks

• Patients who interrupted treatment for ≥4 weeks require weekly monitoring and retitration, regardless of previous duration of treatment and prior mild neutropenia.

Background on the safety concern

Clozapine is an atypical antipsychotic indicated in treatment-resistant schizophrenia patients and in schizophrenia patients who have severe, untreatable neurological adverse reactions to other antipsychotic agents. It is also indicated in psychotic disorders occurring during the course of Parkinson's disease, in cases where standard treatment has failed.

Agranulocytosis, a well-known risk associated with the use of clozapine, is minimized through routine hematological monitoring, as outlined in the summary of product characteristics (SmPC).

Following an EU-wide review by the European Medicines Agency (EMA) of the risk of neutropenia and agranulocytosis with clozapine, the recommendations for routine blood count monitoring have been revised.

New evidence from the scientific literature suggests that, although clozapine-induced neutropenia can occur at any time during treatment, it is predominantly observed during the first year, with the incidence peaking in the first 18 weeks of treatment. After this time-point, the incidence decreases, becoming progressively lower after two years of treatment in patients without previous episode of neutropenia. A large metanalysis by Myles et al, which included data from 108 studies encompassing over 450,000 patients exposed to clozapine, reported that the peak incidence of severe neutropenia occurred during the first month of treatment, with 89% of the total events recorded at 24 months and only a minor increase at 36 months and beyond. The incidence of clozapine associated neutropenia was 3.8% (95% CI: 2.7-5.2%) and severe neutropenia 0.9% (95% CI: 0.7- 1.1%). Similarly, a large retrospective cohort study conducted in Australia/New Zealand (Lancet Vol 11 January 2024) analyzed data from over 26,630 clozapine-treated patients in a period of 32 years (1990- 2022). This study found that, in people with no previous exposure to clozapine (n=15 973), the cumulative incidence of serious neutropenia leading to treatment cessation was 0.9% at 18 weeks and 1.4% at 2 years. The weekly incidence rate for serious neutropenia leading to cessation peaked at 9 weeks (0.128%) and fell to a rolling average weekly incidence of 0.001% by 2 years.

These findings are also corroborated by registry-based analyses from the United Kingdom and Ireland which examined over 6,300 patients in a national clozapine monitoring service, showing that the peak incidence of agranulocytosis was in the first 6–18 weeks of treatment, and from a registry in Chile. This study, based on data from a national pharmacovigilance registry among over 5000 people in Chile who began taking clozapine showed that 87.9% of severe neutropenia cases occurred in the first 18 weeks.

Furthermore, monitoring is now recommended to be based solely on the Absolute Neutrophil Count (ANC), aligning with current evidence that ANC is a more specific and clinically relevant marker for assessing the risk of neutropenia. Therefore, the requirement for monitoring of white blood cell (WBC) counts has been removed.

New ANC thresholds should be considered for patients in general, as well as for patients with Benign Ethnic Neutropenia (BEN). Clozapine use should be limited in the general population to patients with initial ANC

≥1500/mm3 (≥1.5x109/L), and in patients with Benign Ethnic Neutropenia (BEN) to those with ANC ≥1000 (≥1.0x109/L). Lowering ANC thresholds for patients with BEN does not compromise patient safety and helps to prevent unnecessary treatment discontinuation.

In Egypt, therefore the product information for all clozapine-containing medicines will be updated to reflect the revised ANC thresholds and monitoring frequency for the risk of clozapine-related agranulocytosis.

Reference

EMA:
https://www.ema.europa.eu/en/documents/dhpc/direct-healthcare-professional-communication-dhpc-clozapine-revised-recommendations-routine-blood-count-monitoring-risk-agranulocytosis_en.pdf

Call for Reporting

Healthcare professionals are asked to report any suspected adverse reactions via the Egyptian reporting system:

Name: General Administration for Pharmaceutical Vigilance

Email: pv.followup@edaegypt.gov.eg

Online reporting: : https://vigiflow-eforms.who-umc.org/eg/med

QR Code:

Hotline: 15301