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IMPORTANT MEDICINE SAFETY INFORMATION

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BY THE

HPRA

An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority



08 Sep 2025

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

Dear Healthcare Professional,

The Marketing Authorisation Holders of medicines containing clozapine in agreement with the European Medicines Agency and the Health Products Regulatory Authority (HPRA) 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 <500/mm³)
- Initiation of clozapine is only recommended in patients with ANC ≥1500/mm³ (≥1.5x10⁹/L) and in patients with confirmed BEN with ANC ≥1000/mm³ (≥1.0x10⁹/L).

Revised ANC monitoring requirements:

- The patient's ANC must be monitored as follows:
 - weekly during the first 18 weeks of treatment
 - then monthly for the following 34 weeks (i.e., until completion of the first year of treatment)
 - if there has been no history of neutropenia during the first year of treatment, ANC monitoring can be reduced to once every 12 weeks
 - 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 <1000/mm³ (<1.0x10⁹/L) must immediately stop treatment and not be re-exposed. For patients with confirmed BEN the threshold is ANC
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<500/mm³ (<0.5×10⁹/L). Patients should be monitored weekly for 4 weeks in case of complete discontinuation.

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 re-titration, 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 minimised through routine haematological 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. (*Acta Psychiatr Scand* 2018; 138: 101–109)¹, 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*)² 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 (*Atkin et al. Br J Psychiatry*)³ 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 (*Mena et al. Int Clin Psychopharmacol* 2019).⁴ 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.

¹ Myles N, Myles H, Xia S, Large M, Kisely S, Galletly C, Bird R, Siskind D. Meta-analysis examining the epidemiology of clozapine-associated neutropenia. *Acta Psychiatr Scand*. 2018 Aug;138(2):101-109. doi: 10.1111/acps.12898. Epub 2018 May 21. PMID: 29786829.

² Northwood K, Myles N, Clark SR, Every-Palmer S, Myles H, Kisely S, Warren N, Siskind D. Evaluating the epidemiology of clozapine-associated neutropenia among people on clozapine across Australia and Aotearoa New Zealand: a retrospective cohort study. *Lancet Psychiatry*. 2024 Jan;11(1):27-35. doi: 10.1016/S2215-0366(23)00343-7. Epub 2023 Nov 28. PMID: 38040009.

³ Atkin K, Kendall F, Gould D, Freeman H, Liberman J, O'Sullivan D. Neutropenia and agranulocytosis in patients receiving clozapine in the UK and Ireland. *Br J Psychiatry*. 1996 Oct;169(4):483-8. doi: 10.1192/bjp.169.4.483. PMID: 8894200.

⁴ Mena CI, Nachar RA, Crossley NA, González-Valderrama AA. Clozapine-associated neutropenia in Latin America: incidence report of 5380 Chilean users. *Int Clin Psychopharmacol*. 2019 Sep;34(5):257-263. doi: 10.1097/YIC.0000000000000270. PMID: 31094900.

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 $\geq 1500/\text{mm}^3$ ($\geq 1.5 \times 10^9/\text{L}$), and in patients with Benign Ethnic Neutropenia (BEN) to those with ANC ≥ 1000 ($\geq 1.0 \times 10^9/\text{L}$). Lowering ANC thresholds for patients with BEN does not compromise patient safety and helps to prevent unnecessary treatment discontinuation.

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.

Call for reporting

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to HPRA pharmacovigilance; website: www.hpra.ie

Company contact points

Suspected adverse drug reactions should also be reported to the relevant Marketing Authorisation Holders (see contact details below). This information is being provided jointly by the following Marketing Authorisation Holders (MAHs):

Marketing Authorisation Holder	Medicinal Product Full Name	Marketing Authorisation Number	Email	Telephone
Viartis Healthcare Limited	Clozaril 25 mg Tablets	PA23355/022/001	<u>Medical Enquiries:</u> info.ie@viartis.com	<u>Medical Enquiries:</u> 01707 853 000 (option 1) <u>Adverse Events:</u> 01707 853 000 (option 5)
	Clozaril 100 mg tablets	PA23355/022/002	<u>Adverse Events:</u> pv.ireland@viartis.com	
Clonmel Healthcare Limited	Denzapine 25 mg Tablets	PA0126/235/001	<u>Medical Enquiries:</u> denzapine@clonmel-health.ie <u>Adverse Events:</u> medicalinformation@clonmel-health.ie	Medical Enquiries: +353 1800 936 081 Adverse Events: +353 52 617 7777 (option 4)
	Denzapine 50 mg Tablets	PA0126/235/003		
	Denzapine 100 mg Tablets	PA0126/235/002		
	Denzapine 200 mg Tablets	PA0126/235/004		
	Denzapine 50 mg / ml Oral Suspension	PA0126/235/005		

Yours faithfully

Marketing Authorisation Holder	Person	Signature	Date
Viatrix Healthcare Limited	Enis Otuk Country Manager - Ireland	<i>Enis Otuk</i>	04-Sep-2025
Clonmel Healthcare Limited	Conor Booth- Medical Affairs manager	<i>Conor Booth</i>	04-Sep-2025