

## Citizen Petition

Date: September 23, 2025

The undersigned submits this petition under 21CFR10.30 of the Federal Food Drug and Cosmetic Act to request the Commissioner of Food and Drugs to take administrative action to issue an additional ‘indication’ for clozapine, an existing prescription medicine.

### A. Specific Action Requested.

Petitioner requests the Commissioner to add a third indication to labeling of all clozapine products, as follows:

**Reduction in the Risk of Recurrent Aggressive Behavior in Individuals with Serious Mental Illness.** Across the spectrum of serious mental illnesses, clozapine is indicated for reducing the risk of recurrent aggressive acts toward others. Potential for aggression is based on history and recent clinical state. Aggressive behavior includes violence, and refers to actions that potentially put others at risk of physical harm or death.

### B. Statement of Grounds

#### Introduction

Reports of unprovoked violence – often with fatal outcomes -- are in the news daily. These tragedies have a devastating impact on communities, the victims, their families, and on law enforcement first-responders who may suffer long-lasting physical and emotional distress. In the aggregate, recent national numbers are staggering: over 20,000 fatal episodes each year<sup>1</sup> and 5 million physical assaults<sup>2</sup>.

While most individuals with a serious mental illness are not prone to violence, a disproportionate rate of violent acts are perpetrated by individuals in the grips of poorly treated mental illness<sup>3</sup>. But there is hope.

Hope begins with ensuring individuals living with a serious mental illness receive proper treatment and care. By adopting a public health perspective and broadening product labeling for clozapine -- a generic medicine with unequalled anti-aggressive properties -- there is every reason to expect that incidents of violence might be reduced significantly.

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<sup>1</sup> Web-based Injury Statistics Query and Reporting System (WISQARS) CDC: National Center for Injury Prevention and Control (2022)

<sup>2</sup> Bureau of Justice Statistics: Criminal Victimization (2023)

<sup>3</sup> Analysis of over 18,000 people in 20 epidemiologic studies that compared violence rates in schizophrenia to the general population, reported that approximately 10% of individuals with schizophrenia, compared to 1.6% of general population, exhibited violent behaviors (Fazel, *et al.* 2009)

## Background

I petition the FDA as both technical expert and concerned citizen. I was responsible for clinical testing and development of clozapine during its investigational stages (1973-1989) and, in collaboration with colleagues at the FDA, played a crucial role in drafting the original product labeling.

After clozapine's initial unique approval in 1989 for use in treatment-resistant psychoses, a second approved indication was developed in the early 2000s, again for a one-of-a-kind therapeutic use: suicide risk reduction in individuals with either schizophrenia or schizo-affective disorders, historical treatment-resistance not required.

However, the anti-suicide indication addressed only one-half of the issue of violence by those with serious mental illnesses: self-harm. The present petition addresses the other half: uncontrolled acts of violence toward others by individuals with untreated mental illness, too often with fatal outcomes.

A growing body of confirmatory evidence indicates that in addition to its proven superior antipsychotic efficacy, clozapine has another feature in its clinical profile: anti-aggressive properties that are unmatched by any other therapeutic agent<sup>4</sup>.

## Analysis

Long-term, maintenance therapy with clozapine has been proven to substantially reduce violent acts among individuals with serious mental illness. Reflecting a consensus, responsible professional entities here and abroad have established clozapine treatment recommendations that reflect its unmatched anti-aggressive properties<sup>5</sup>. These include:

- APA Practice Guidelines (2020): The American Psychiatric Association suggests that “patients with schizophrenia be treated with clozapine if the risk for aggressive behavior remains substantial despite other treatments.”<sup>6</sup>
- Treatment Response and Resistance in Psychosis (TRRIP) Consensus Guidelines (2023) state: “Given clozapine’s beneficial properties in the treatment of suicidality and aggression in schizophrenia and its low risk for tardive dyskinesia and EPS ... clozapine may be more effective than other antipsychotics when used as first- or second-line treatment.”<sup>7</sup>

An additional anti-aggression ‘indication’ in clozapine product labeling would address attention to a major problem of public concern – violence among individuals with serious mental illness receiving sub-standard care -- while helping clinicians and advocates develop a fuller appreciation of this under-utilized medicine’s unique benefits. This in turn would promote application of quality assurance protocols to optimize treatment of individuals with mental illness, and facilitate uncontested access to clozapine through insurance reimbursement authorizations.

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<sup>4</sup> Frogley *et al.* (2012). A systematic review of the evidence of clozapine’s anti-aggressive effects.

<sup>5</sup> Galletly *et al.* (2016). Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines.

<sup>6</sup> Keepers *et al.* (2020). American Psychiatric Association Practice Guidelines for Schizophrenia.

<sup>7</sup> Wagner *et al.* (2023). Clozapine optimization: A Delphi consensus guideline.

From the perspectives of both medical ethics and public health, patients with a history of aggressive acts should, wherever possible, be receiving the ‘gold standard’ of care, clozapine, thus furthering individual welfare while at the same time promoting society’s goals of reducing unacceptable rates of violence and death in our communities. The majority of seriously mentally ill patients need to be on medicines long-term to maintain stabilization and prevent relapse; usually that medicine should be clozapine.

Independent confirmatory evidence of unsurpassed anti-aggressive benefit has accumulated over the 35 years of clozapine’s commercial availability. The most recent comprehensive overview of this extensive clinical research literature was published last year, when Faden and Citrome concluded: “Clozapine is the ‘gold standard’ pharmacologic treatment for the management of persistent agitation and aggression in people with schizophrenia and is consistently recommended by guidelines and reviews for this purpose ... Studies have proposed that clozapine may have specific properties that ameliorate aggression and hostility that are distinct from its antipsychotic effects.” These authors stated further: “The majority of evidence, including from randomized control trials, supports the utilization of clozapine as maintenance treatment for persistent aggressive behavior ... and its anti-aggressive effects may be independent from its antipsychotic properties.”<sup>8</sup>

Additional compelling support for the current proposal to add a new anti-aggression indication to the clozapine package insert comes from a review by Shaheen (2023) who stated: “52 robust studies were retrieved showing consistent evidence to support the use of clozapine as anti-aggressive medication in patients with schizophrenia and schizoaffective disorders.”<sup>9</sup>

### Recommendation

Based on the foregoing information and analysis, I specifically recommend adding one new anti-aggression indication to official labeling for all clozapine products for a total of three, as follows:

**Indication 1. Treatment-Resistant Schizophrenia.** Verbatim – no changes.

**Indication 2. Reduction in the Risk of Recurrent Suicidal Behavior in Schizophrenia or Schizoaffective Disorder.** Verbatim – no changes.

**Indication 3. Reduction in the Risk of Recurrent Aggressive Behavior in Individuals with Serious Mental Illness.** Across the spectrum of serious mental illnesses, clozapine is indicated for reducing the risk of recurrent aggressive acts toward others. Potential for aggression is based on history and recent clinical state. Aggressive behavior includes violence, and refers to actions that potentially put others at risk of physical harm or death.

### Conclusion

FDA approval of an anti-aggression indication in labeling for all clozapine products will help advance the public health goal of reducing unacceptably high rates of violent assaults and deaths. This specific proposal is evidence-based and supported by current practice recommendations established by independent authorities, including the American Psychiatric Association.

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<sup>8</sup> Faden and Citrome (2024). A systematic review of clozapine for aggression and violence.

<sup>9</sup> Shaheen (2023). The effect of clozapine on violence in mental illness.

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- C. Environmental Impact. Not applicable.
- D. Economic Impact. Not applicable
- E. Certification

The undersigned certifies, that to the best knowledge and belief of the undersigned this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Signature: Gilbert Honigfeld

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