David Behar, M.D.
206 East Broad Street
Bethlehem, PA 18018

July 29, 2021

Re: Docket No. FDA 2020-P-1073

Dear Dr. Behar:

This responds to your citizen petition dated March 9, 2020 (Petition), requesting that the Food and Drug Administration (FDA or Agency): (1) decommission the Clozapine REMS Program; (2) remove the requirement that health care providers be certified in order to prescribe clozapine; and (3) remove language in the package insert regarding mandatory blood testing and replace it with language deferring entirely to the discretion of the healthcare provider.

FDA has considered the information in your Petition, as well as other information available to the Agency. For the reasons set forth below, your Petition is denied.

I. BACKGROUND

A. REMS

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355-1) authorizes FDA to require a Risk Evaluation and Mitigation Strategy (REMS) if FDA determines that it is necessary to ensure that the benefits of the drug outweigh its risks. A REMS is a required risk management strategy that employs tools beyond prescribing information to ensure that the benefits of a drug outweigh its risks. A REMS may require a Medication Guide (or patient package insert) to provide risk information to patients[1] and/or a communication plan to disseminate risk information to health care providers.[2] FDA may also require certain Elements to Assure Safe Use (ETASU) when such elements are necessary to mitigate specific serious risks associated with a drug.[3] The ETASU may include, for example, requirements that health care providers who prescribe the drug have particular training or experience, that patients using the drug be monitored, or that the drug be dispensed to patients with evidence or other documentation of safe-use conditions.[4]

Certain REMS with ETASU may also include an implementation system through which the applicant is able to monitor and evaluate implementation of the ETASU and work to improve

[1] Section 505-1(e)(2) of the FD&C Act.
[2] Section 505-1(e)(3) of the FD&C Act.
[3] Section 505-l(f)(1) of the FD&C Act.
[4] Section 505-l(f)(3) of the FD&C Act.

their implementation.[5] Finally, REMS generally must have a timetable for submission of assessments of the strategy.[6] FDA can require a REMS at the time of initial approval of a new drug application (NDA) or, should FDA become aware of new safety information[7] about a drug and determine that a REMS is necessary to ensure that the benefits of the drug outweigh its risks, after the drug has been approved.[8] When FDA determines that a modification of a REMS is necessary to ensure that the benefits of a drug outweigh its risks, to minimize the burden on the health care delivery system of complying with the REMS, or to accommodate different, comparable aspects of the ETASU of an abbreviated new drug application (ANDA) and the applicable listed drug, FDA has authority to require that the application holder submit a proposed modification to a REMS under section 505-1(g) of the FD&C Act.

B. Clozapine

Clozapine is a tricyclic dibenzodiazepine derivative. It is an atypical antipsychotic drug approved for treatment-resistant schizophrenia and to reduce the risk of recurrent suicidal behavior in patients with schizophrenia or schizoaffective disorder. Clozapine is indicated for patients with severe schizophrenia who fail to respond adequately to standard antipsychotic drug treatment. Clozapine carries a boxed warning[9] for severe neutropenia, defined as an absolute neutrophil count (ANC) less than (<) 500/µL.[10] This is a serious condition that is associated with an increase in the risk of serious and potentially fatal infections. Risk of neutropenia appears greatest during the first 18 weeks of treatment and then declines. The mechanism by which clozapine causes neutropenia is unknown and is not dose-dependent.

Current labeling[11] for clozapine provides guidelines for ANC monitoring. For patients in the general population,[12] prescribers are to obtain a complete blood count (CBC), including the ANC value, prior to initiating treatment with clozapine to ensure the presence of a normal baseline

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[5] Section 505-1(f)(4) of the FD&C Act.
[6] Section 505-1(d) of the FD&C Act.
[7] Section 505-1(b)(3) of the FD&C Act.
[8] Section 505-1(a)(2) of the FD&C Act.
[9] A boxed warning is ordinarily used to highlight for prescribers one of the following situations: (1) there is an adverse reaction so serious in proportion to the potential benefit from the drug that it is essential that it be considered in assessing the risks and benefits of using the drug, or (2) there is a serious adverse reaction that can be prevented or reduced in frequency or severity by appropriate use of the drug. See 21 CFR 201.57(c)(1) and FDA's Guidance for Industry *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format* (October 2011). We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fdaguidance-documents.
[10] Previous versions of clozapine labeling referred to the risk of agranulocytosis, which is the absence of granulocytes (neutrophils, basophils, and eosinophils). Neutrophils constitute the majority of granulocytes and the presence or absence of other granulocytes is not important to the existence of the risk. To improve and standardize understanding, "severe neutropenia," which signifies a neutrophil count of less than 500/µL, replaces the previous term, agranulocytosis, in the current labeling. Additionally, previous versions of clozapine labeling used cubic millimeters (mm^3) as the unit of measure for ANC. Current labeling uses microliters (µL). These units of measure are equivalent. This petition response uses microliters (µL) throughout.
[11] Current labeling can be found at https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/019758s088lbl.pdf.
[12] Current clozapine labeling provides separate ANC monitoring guidelines for patients with benign ethic neutropenia, a condition observed in certain ethic groups whose average ANC values are lower than standard laboratory ranges for neutrophils.

neutrophil count. Patients in the general population with an ANC equal to or greater than (≥) 1500/µL are considered within the normal range and are eligible to initiate treatment. Weekly ANC monitoring is required for all patients during the first 6 months of treatment. If a patient's ANC remains equal to or greater than 1500/µL for the first 6 months of treatment, monitoring frequency may be reduced to every 2 weeks for the next 6 months. If the ANC remains equal to or greater than 1500/µL for the second 6 months of continuous therapy, ANC monitoring frequency may be reduced to once every 4 weeks thereafter.

Although the original labeling for clozapine called for permanent discontinuation of clozapine if patients' ANC dropped below a certain level, the current labeling provides for patients to be rechallenged, and prescribers to make individualized treatment decisions if they determine that the risk of psychiatric illness is greater than the risk of rechallenge, for example, in patients for whom clozapine may be the antipsychotic of last resort.[13] The labeling states that if a patient will be rechallenged, the clinician should consider the ANC thresholds provided in the labeling, the patient's medical and psychiatric history, a discussion with the patient and his/her caregiver about the benefits and risks of rechallenge, and the severity and characteristics of the neutropenic episode.

C. The Clozapine REMS Program

Clozapine is subject to a REMS to ensure that the benefits of clozapine outweigh the risk of severe neutropenia. The goal of the REMS is to mitigate the risk of severe neutropenia associated with the use of clozapine by: (1) educating prescribers and pharmacists about the risk of severe neutropenia and appropriate monitoring requirements; (2) informing patients about the risk and appropriate monitoring; (3) ensuring compliance with the monitoring schedule prior to dispensing clozapine; (4) ensuring the prescriber documents a risk-benefit assessment when ANC falls below the acceptable range; and (5) enrolling patients in a registry to establish long-term safety of clozapine.

The REMS requires that prescribers who prescribe clozapine for outpatient use certify in the program, enroll their patients in the program, assess patients' ANCs, and submit them to the program.[14]

The REMS also requires that pharmacies certify in the program and take certain actions before dispensing clozapine, including verifying through the REMS Program that the patient is enrolled, and that the ANC is within the acceptable range described in the labeling, or that the prescriber has authorized the continuation of clozapine treatment for patients with an ANC that falls below

[13] This labeling change was approved on September 15, 2015. See the Agency's safety announcement, "FDA Drug Safety Communication: FDA modifies monitoring for neutropenia associated with schizophrenia medicine clozapine; approves new shared REMS program for all clozapine medicines," available at https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-modifies-monitoring-neutropenia-associated-schizophrenia-medicine

[14] Today the Clozapine REMS is being modified to require submission of laboratory results to the REMS program monthly using a Patient Status Form instead of more frequently when the patient's monitoring frequency is weekly or bi-weekly.

the acceptable range.[15]

II. DISCUSSION

Your Petition asks the Agency to decommission the Clozapine REMS Program, remove the requirement that health care providers be certified in order to prescribe clozapine, and remove language in the package insert regarding mandatory blood testing, replacing it with language deferring entirely to the discretion of the healthcare provider. In support of these requests, your Petition asserts that (1) the blood monitoring requirement in the Clozapine REMS Program originated as a Medicare fraud scheme; (2) the Clozapine REMS Program is not warranted because the incidence rate of agranulocytosis is lower than that associated with other drugs with box warnings for agranulocytosis that are not subject to REMS; (3) the requirement for regular monitoring of ANC deters patients from using clozapine; and (4) the REMS requirements constitute unconstitutional discrimination against patients with mental illness, present an undue burden, and violate the Americans with Disabilities Act. Petitioner also requests that FDA "effect creation of a national registry for clozapine patients having benign ethnic neutropenia" and implement the proposed labeling change by direct final rulemaking (Petition at 9).
The labeling and REMS for clozapine originally required a specific schedule for monitoring ANC and permanent discontinuation of clozapine in the event of the ANC dropping below a certain threshold. The labeling underwent a significant modification in 2015 and a new, shared REMS Program was approved, which provided for more prescriber discretion and flexibility in assessing the specific risk/benefit profile for each patient and making appropriate, individualized treatment decisions. With the current labeling and REMS requirements, the Agency believes it has struck the right balance between providing for discretion in prescribing to benefit patients and ensuring that the serious risk associated with clozapine is adequately mitigated. FDA does not agree that the labeling should be changed to leave ANC monitoring entirely to the discretion of the healthcare providers for the reasons set out more fully below. Likewise, the Agency does not agree that the REMS requirements, including the requirement for prescriber certification, should be discontinued, as these requirements are necessary to ensure the benefits of clozapine outweigh its risks.

A. The Pricing Sandoz Employed for Clozapine in the 1990's is Not Relevant To the Required Certification and Monitoring in the REMS

Your Petition states that the Clozapine REMS Program should be decommissioned due, in part, to "the historical rationale behind the blood monitoring requirement" (Petition at 2). Your Petition states that the requirement for blood monitoring in the United States was a result of a pricing scheme by the manufacturer, Sandoz, when the drug was first introduced to the U.S. market.

This asserted set of facts, however, was not relevant to the Agency's approval of the ANC monitoring requirements in the labeling and the determination that a REMS was necessary to

[15] Complete information about the REMS requirements, including the REMS document, can be found on FDA's Approved Risk Evaluation and Mitigation Strategies (REMS) web page, available at https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=RemsDetails.page&REMS=351.

mitigate the risk of severe neutropenia. The Agency required labeling with a boxed warning with ANC monitoring guidelines and reference to a restricted distribution system to ensure monitoring when clozapine was approved and then ultimately required a REMS for clozapine because it determined that these measures were necessary to assure safe use of clozapine.[16] The manner in which the manufacturer sold and priced the product was not relevant to this determination.

B. The Clozapine REMS Program is Necessary to Ensure the Benefits of Clozapine Outweigh the Risk of Severe Neutropenia

Your Petition asserts that the low incidence of fatal side effects associated with clozapine do not warrant the ANC monitoring requirements in the labeling and the REMS (Petition at 2). Your Petition argues that the incidence rates of agranulocytosis associated with clozapine are relatively low compared to other prescription drug products that carry the risk of agranulocytosis or neutropenia but have not been determined by the Agency to require a REMS (Petition at 4).

As a threshold matter, your Petition is inaccurate in its description of the monitoring requirements in the labeling of clozapine, which are central to the Clozapine REMS Program (Petition at 3). Patients in the general population can start clozapine treatment when their ANC is ≥ 1500/ μL, not ≥ 2000/μL, as the Petition states. Mild neutropenia is defined in clozapine's labeling as 1499/μL > ANC ≥ 1000/μL, not 2000/μL > ANC ≥ 1500/μL. Severe neutropenia is defined in clozapine's labeling as ANC < 500/μL, not ANC < 1000/μL. For patients with benign ethnic neutropenia (BEN), a lower ANC at initiation and while getting clozapine treatment is acceptable.[17] In addition, your Petition states that clozapine must be withheld from patients whose ANC drops below certain levels (Petition at 3), but as explained above, the labeling contemplates rechallenge in patients with severe neutropenia if the prescriber determines that the benefits outweigh the risks for that patient, and the REMS provides for prescriber authorization of dispensing clozapine to patients with low ANC if they determine the benefits of clozapine treatment outweigh the risk of severe neutropenia and provide a treatment rationale to the REMS program. Your Petition therefore mischaracterizes the extent to which the REMS limits use of the drug.

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[16] Clozaril (clozapine) was first approved on September 26, 1989, for the management of severely ill schizophrenic patients who fail to respond adequately to standard antipsychotics. At the time, Clozaril was only available through a distribution system that ensured weekly white blood count (WBC) testing prior to delivery of the next week's supply of medication. This distribution system was considered in the approval of the product and included in labeling. Clozapine NDAs and ANDAs approved between 1989 and 2007 each had a registry for the monitoring and databasing of WBC counts for all clozapine-treated patients to help prevent clozapine-induced agranulocytosis. The Food and Drug Administration Amendments Act of 2007 (FDAAA) enacted section 505-1 of the FD&C Act, which authorizes FDA to require a REMS. Following FDAAA's enactment, FDA determined that clozapine had a deemed REMS in effect due to its restricted distribution system. On September 3, 2009, FDA documented deficiencies identified in the clozapine restricted distribution system, and on September 15, 2015, FDA approved the single, shared Clozapine REMS Program, which includes all clozapine manufacturers.

[17] We note that your Petition requests the creation of a national registry for clozapine patients having benign ethnic neutropenia without further discussion or support (Petition at 9). Contrary to the representations in the Petition, clozapine is acceptable for treatment in patients with BEN and the labeling includes recommendations specific to patients with BEN who are treated with clozapine. The Clozapine REMS already includes a requirement that the sponsors maintain a registry for all patients. Accordingly, we do not further discuss the request for a registry.

Your Petition's characterization of the incidence rates of agranulocytosis associated with clozapine is also inaccurate. Your Petition states that "without monitoring, agranulocytosis occurs during the first few months of treatment in about 1% of patients who take clozapine" (Petition at 3). The Agency conducted a systematic review of the literature to identify original studies evaluating clozapine use and agranulocytosis incidence. Of the 214 articles identified, 10 met FDA's criteria for inclusion.[18] Nine of these studies were conducted in populations where clozapine patients were regularly monitored for agranulocytosis. The single study conducted prior to the widespread adoption of clozapine monitoring estimated agranulocytosis incidence as 2.6% per year of treatment (de la Chapelle et al. 1997). Studies conducted in populations where clozapine patients' neutrophil counts were monitored regularly reported lower incidence of agranulocytosis. Cumulative incidence of agranulocytosis among clozapine patients undergoing regular blood monitoring was less than 1% in most studies, ranging from 0.38% to 1.15% (Alvir et al. 1993; Atkin et al. 1996; Copolov et al. 1998; Honigfeld et al. 1998; Kang et al. 2006; Lambertenghi Deliliers 2000; Mena et al. 2019; Miller and Cutten 1997; Munro et al. 1999). Accordingly, the Petition's estimated rate of about 1% during the initial months of clozapine treatment is appropriate for patients undergoing regular hematologic monitoring, but for patients without regular monitoring this estimate is likely low. Importantly, the difference between these statistics supports the value of regular ANC monitoring in preventing severe neutropenia.

Moreover, in determining the need for a REMS the Agency considers not only the incidence rate of the risk, but also the severity. While a high frequency of adverse events may necessitate a REMS to mitigate this risk, FDA may also require a REMS for an infrequent adverse event, if the adverse event is particularly severe.[19] A risk such as severe neutropenia, which can lead to death, warrants measures to mitigate it, particularly when there is support for the effectiveness of these measures in preventing this serious outcome (Honigfeld, G., et al., 1998).

To support the argument that the Clozapine REMS Program is not warranted, your Petition refers to "at least seventy other prescription medications that also carry a black box warning for drug-induced agranulocytosis or neutropenia, but which are not subject to a REMS program" (Petition at 4). Your Petition specifically cites palbociclib and methicillin as comparisons. In addition to considering the severity of the risk, FDA considers a number of other factors in determining the need for a REMS for a particular drug, including the actions needed to mitigate the risk and the specialties of the healthcare providers who may prescribe, dispense or administer the drug.[20] Palbociclib is used for treatment of advanced or metastatic breast cancer in oncology practices where ANC monitoring is routine, and providers are experienced in the diagnosis and

[18] The review excluded articles not published in English, case reports, reviews, editorials, and studies conducted in pediatric populations. It also excluded articles that did not directly estimate agranulocytosis incidence among clozapine users, studies with fewer than five agranulocytosis cases, studies where the number of cases or population at risk were merely estimated, and duplicate studies reporting on the same population.
[19] For further information, see FDA's April 2019 guidance for industry *REMS: FDA's Application of Statutory Factors in Determining When a REMS Is Necessary*. We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fdaguidance-documents.
[20] *Id*.

management of neutropenia.[21] Methicillin, which is no longer marketed in the United States, is an antibiotic administered intravenously in hospitals for acute infections, for which ANC monitoring is an essential part of care. A hospital setting is also appropriate for the management of neutropenia.

In contrast, ANC monitoring is neither routinely performed nor readily available in many psychiatric practices where clozapine is likely to be prescribed, and, generally, most psychiatrists and associated personnel are not usually trained and not likely to have experience in the diagnosis and management of neutropenia. Additionally, patients with schizophrenia are a vulnerable population because of psychotic symptoms and cognitive impairment associated with this disorder that render them unreliable to promptly report symptoms of an infection that may indicate neutropenia.[22] Your Petition does not provide the names or classes of drugs other than palbociclib and methicillin with box warnings for agranulocytosis or neutropenia that are not subject to REMS.

Each decision to require a REMS is based on the specific circumstances surrounding that drug, including the specialists likely to prescribe the drug. For clozapine, the Agency considered the severity of the risk of severe neutropenia, which can lead to serious and sometimes fatal infections, as well as the indicated patient population and the prescribing population. Based on the totality of these circumstances, the Agency determined that a REMS program for clozapine was necessary to ensure that the ANC monitoring, which can detect and prevent severe neutropenia and the serious, sometimes fatal, infections that can occur as a result, is performed (Honigfeld et al. 1998).

C. The Petition's Cited Studies Do Not Support the Assertion That the Clozapine REMS Program Deters Patients From Taking Clozapine

Your Petition asserts that the Clozapine REMS Program should be removed because it presents a "significant deterrence in patients' willingness to take clozapine due to the onerous blood monitoring requirement" (Petition at 2). The evidence provided in your Petition, however, does not support this conclusion.

Your Petition cites one study, Taylor (2000), in support of your allegation that individuals with schizophrenia are deterred from using clozapine due to FDA's REMS program for clozapine. The study was conducted in 2000, well before the creation of the Clozapine REMS Program. Further, the study was conducted in patients attending clozapine clinics in the United Kingdom. The study does not reflect any impacts of the REMS program for clozapine, which was approved in 2015 and applies to patients in the United States. Even if the study results in Taylor (2000) could be extrapolated to patients in the United States, they would not support the claims in your Petition. The study found that most patients did not find blood monitoring to be significantly

[21] It is also important to note that although the incidence of all grade neutropenia is reported in the clinical trials in the palbociclib labeling as 80% in one study and 83% in the other, only 10% or 11% of patients experienced grade 4 neutropenia (<500/ /μL).

[22] See guidance at p.7 ("For drugs intended for use in an outpatient setting, FDA considers the degree to which patients can be expected to reliably recognize symptoms as being associated with a drug and to take necessary actions to address adverse events")

difficult and that only 1.6% of surveyed patients responded that "blood tests made them want to stop taking clozapine" (Taylor et al. 2000; Mistry and Osborn 2011 (summarizing the Taylor study as concluding that "most patients did not find blood monitoring a significant difficulty and the majority believed that the benefits of clozapine outweighed its potential side-effects")). The results from Taylor (2000) undercut your allegation that regular blood testing prevents individuals with mental illness from receiving clozapine.

D. The Clozapine REMS Program Appropriately Considers the Risks of Discontinuation of Clozapine

Your Petition argues that the sudden interruption of clozapine treatment "can be catastrophic" and that "the current regulations mandating cessation of clozapine treatment based solely upon WBC and ANC counts without concern for other factors, including the potentially severe negative consequences to patients of such cessation are not sufficiently refined to be considered thoughtful, responsible regulations" (Petition at 7-8). Although it is true that sudden discontinuation of clozapine treatment can be detrimental to patients, your Petition's argument is flawed in several important respects. First, much of the Petition's description of the effects of cessation of clozapine treatment is inaccurate or misleading. Second, the Petition ignores the severity of the risk of severe neutropenia which the REMS aims to mitigate, and third, the REMS does not mandate sudden discontinuation of clozapine as described by the Petition.

1. Much of the Petition's description of the effects of clozapine discontinuation are inaccurate or misleading

Your Petition reports the following immediate, acute effects of sudden discontinuation of clozapine (Petition at 7) and states that these effects remit quickly with the resumption of clozapine: bad flu-like symptoms with headaches and vomiting lasting a week; delirium; the return of original psychotic symptoms; the return of suicidal ideas; abnormal movements. None of the data referenced by the Petition indicate that bad flu-like symptoms, headaches, or suicidal ideas are caused by sudden discontinuation of clozapine. Published case reports cited by the Petitioner describe symptoms consistent with cholinergic rebound, such as vomiting and diarrhea, associated with discontinuation of clozapine (Ahmed et al. 1998; Stanilla et al. 1997). These case reports also describe delirium after stopping clozapine. Although it is plausible that suddenly stopping clozapine caused these events, because case reports do not include a control or other counterfactual comparison, they cannot establish a causal link. Some, but not all, of these events remitted quickly with resumption of clozapine. Also, case reports provide no information on how frequently these events occur after clozapine discontinuation, which is an important factor in determining the clinical importance of these events.

In addition, your Petition states that discontinuation of clozapine can lead to brain damage and deterioration in the quality of remission, with a need for an increased dose of clozapine, taking longer to work and decreased effectiveness (Petition at 8). One of the studies you cite examined the correlation between the duration of untreated illness (DUI), which was defined as the time from prodromal symptom onset to admission for treatment of psychosis, and gray matter density in various brain regions on MRI scans in 82 patients with a first episode of psychotic illness (Bangalore et al. 2009). The study found an inverse correlation between DUI and gray matter

density, suggesting that structural changes in the brain may be occurring during the early phase of illness and may be greater the longer a patient is untreated. You apparently interpret this finding to indicate that brain damage may be a consequence of stopping clozapine treatment. This inference, however, is not supported by the data presented. First, this was a cross-sectional study, with no baseline MRI scan for comparison. Thus, it cannot be concluded that any findings on MRI scans developed during the prodromal phase of illness; the findings may have existed prior to onset. Second, even if it could be shown that the MRI changes had been progressing over the course of untreated illness, there is no indication that treatment with clozapine or other antipsychotic drugs would slow, halt, or reverse these changes; these drugs may only provide symptomatic relief. Third, this study analyzed the effects of untreated illness in treatment naïve patients, excluding patients using any other antipsychotic drug for longer than 2 weeks at any point in their lives. The study sample may not be representative in terms of brain structure and function of clozapine patients who stop treatment. Even patients who stop clozapine shortly after initiation are very likely to have had extensive exposure to other antipsychotic drugs, since Clozapine is generally only used with patients who have not responded to other drugs. Fourth, as stated by the authors, the DUI is typically 1 to 3 years. This duration is much longer than that which would occur in clozapine patients who interrupt treatment for a short period because of an abnormal blood test or side effects. For these reasons, this study does not support the Petition's claim that stopping clozapine treatment produces brain damage.

Several other studies cited in your Petition are limited in their probative value. One study's findings are consistent with the hypothesis that discontinuation of clozapine leads to a deterioration in the quality of subsequent remission and the need for a higher clozapine dose (Miodownik et al. 2006). However, as acknowledged by the authors, limitations of this study were its retrospective design, small number of patients, and lack of a validated scale for measuring remission quality. Another study led the Petitioner to conclude that stopping clozapine produces a decrease in functioning and an increase in psychiatric hospitalization time (Atkinson et al. 2007). This study, too, is limited by a retrospective design and small sample size and is inadequate to draw the conclusions made in the Petition.

2. The potential detrimental effects of clozapine discontinuation as a result of low ANC must be balanced against the risk of severe neutropenia

Although abrupt discontinuation of clozapine treatment may have negative consequences, including the return of symptoms of the disease that may have been ameliorated by the treatment, it is important to consider this risk in the context of the risk of continued clozapine treatment when a patient's ANC drops too low. Developing severe neutropenia can lead to serious, sometimes fatal infections -- a risk that will, in most cases, be greater than the risk of adverse consequences associated with discontinuation of clozapine, such as headache, diarrhea, vomiting, or abnormal movements, many of which can be managed with anticholinergic drugs.

REMS with ETASU by their very nature may impose some burden on stakeholders because they often require certain actions by providers, pharmacies, and/or patients to assure safe use of the drug. FDA is mindful of the potential burden and takes steps to minimize it whenever possible. The risks of potential interruption in clozapine treatment for patients was a significant factor in the decision to modify the labeling and REMS in 2015. Incorporating more appropriate ANC

monitoring criteria for BEN patients in the labeling and REMS allowed the opportunity for clozapine treatment for more patients. In addition, the modifications to the labeling and REMS increased prescriber discretion by allowing patients to be rechallenged. However, the Agency believes that removal of the requirements for regular ANC monitoring altogether would fail to adequately mitigate the risk of severe neutropenia.

3. The Clozapine REMS Program provides for prescriber authorization of continued clozapine treatment despite low ANC

Your Petition's contention that the Clozapine REMS Program should be decommissioned because of the risks of discontinuation of treatment rests on the erroneous assertion that the REMS automatically forces discontinuation of treatment with an ANC below a certain threshold (Petition at 8). As explained above, however, the REMS provides for prescribers to continue clozapine in patients who experience neutropenia if they determine the benefits of the drug outweigh the risk of serious and potentially fatal infections due to neutropenia. The REMS requires that ANC monitoring take place at certain intervals so that prescribers and patients can promptly identify decreases in ANC and can stop treatment to avoid the serious consequences of severe neutropenia. But prescribers can choose to authorize continued treatment in general population patients whose ANC is less than 1000/μL and BEN patients whose ANC is less than 500/μL by contacting the REMS program if they determine that the benefits outweigh the risks.

E. The Clozapine REMS Program Does Not Violate the Constitution or the Americans with Disabilities Act

Your Petition alleges that the Clozapine REMS Program constitutes disparate-treatment discrimination against individuals with mental illness by "prohibiting such groups of individuals from being prescribed what often is *the only* effective medication available to treat or control their symptoms." (Petition at 6). The result, you argue, is that individuals with mental illness suffer a disparate impact because they are prohibited from using a treatment without a "compelling reason" for the prohibition. Your Petition also alleges that FDA's Clozapine REMS Program is unconstitutional because it places an "undue burden" in the path of patients seeking treatment. Your petition analogizes to *Whole Woman's Health* v. *Hellerstedt* and *Planned Parenthood of Southeastern Pennsylvania* v. *Casey* to support your claims. You also allege that the Clozapine REMS is in violation of Title II of the Americans with Disabilities Act (ADA) (Petition at 7).

FDA disagrees with your claims that the Clozapine REMS Program discriminates against individuals with mental illness or that it has a disparate impact by "prohibiting" them from being prescribed or using clozapine, and your petition provides no support for those assertions. (Petition at 6). As explained above, the Clozapine REMS does not "prohibit" prescribing clozapine or its use. The REMS authority provides FDA a way to approve drugs that otherwise would not meet the approval standards because their risks outweigh their benefits. Rather than preventing individuals with mental illness from being prescribed clozapine, the Clozapine REMS Program facilitates the use of clozapine with the additional safety requirements necessary to ensure that the benefits of the drug outweigh the risks. As described above, the study you cite in support of your allegation that individuals with schizophrenia have trouble accessing clozapine

due to FDA's REMS program actually undercuts this assertion (see Section II.C. above). Your citations to case law in support of your disparate impact arguments are inapposite, as these cases discuss disparate impact in the context of alleged violations of specific federal statutes not at issue here.[23]

The Clozapine REMS is rationally related to a legitimate interest in protecting the public from the risks of a drug that, without a REMS in place, do not outweigh the benefits.[24] As explained above, FDA determines that a REMS is necessary based on the specific circumstances surrounding the particular drug, which can include the patient population and the prescribing population.

FDA also disagrees with your claim in the Petition that FDA's Clozapine REMS Program is unconstitutional because it presents an "undue burden" for patients seeking treatment. Courts have applied the "undue burden" standard when government policy could infringe an individual's fundamental rights.[25] Your Petition has not identified a fundamental right that could be burdened by FDA action. Courts have previously held that there is not a fundamental right to obtain a particular treatment.[26] The "undue burden" standard articulated in *Casey* and *Whole Woman's Health* does not apply here, where no fundamental rights are at risk of infringement.

In addition, your ADA claim is not supported by the statutory language of Title II of the ADA. The Clozapine REMS Program cannot violate Title II of the ADA because Title II of the ADA applies neither to FDA nor to the clozapine application holders. Title II of the ADA prohibits discrimination on the basis of disability in services, programs, and activities provided by a "public entity."[27] Title II of the ADA defines "public entity" to mean "any State or local government;" "any department, agency, special purpose district, or other instrumentality of a

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[23] In *Texas Dep't of Hous. & Cmty. Affs. v. Inclusive Communities Project, Inc.*, 576 U.S. 519 (2015), the Court examined whether disparate-impact liability exists under the Fair Housing Act, while in *Griggs v. Duke Power Co.*, 401 U.S. 424 (1971), the Court looked at whether certain employment requirements were in violation of Title VII the Civil Rights Act.

[24] *See Tennessee v. Lane*, 541 U.S. 509, 522 (2004) (applying rational basis test to claims of discrimination based on disability).

[25] See *Whole Woman's Health* v. *Hellerstedt*, 136 S.Ct. 2292, 2311 (2016); *Planned Parenthood of Southeastern Pennsylvania* v. *Casey*, 505 U.S. 833, 876 (1992).

[26] See *Abigail Alliance for Better Access to Developmental Drugs* v. *von Eschenbach,* 495 F.3d 695, 711 (D.C. Cir. 2007) (rejecting a right to procure and use experimental drugs). In its holding, the D.C. Circuit pointed to other courts which had "rejected arguments that the Constitution provides an affirmative right of access to particular medical treatments reasonably prohibited by the government." (Id. at 710.) See e.g., *Mitchell* v. *Clayton*, 995 F.2d 772, 775 (7th Cir. 1993) ("most federal courts have held that a patient does not have a constitutional right to obtain a particular type of treatment or to obtain treatment from a particular provider if the government has reasonably prohibited that type of treatment or provider"); *N.Y. State Ophthalmological Society* v. *Bowen,* 854 F.2d 1379, 1389 (D.C. Cir. 1988) ("We disagree that the constitutional right to privacy comprehensively protects all choices made by patients and their physicians or subjects to 'strict scrutiny' all government interference with choice of medical treatment. There is no basis under current privacy case law for extending such stringent protection to every decision bearing, however indirectly, on a person's health and physical well-being.")

[27] Title II of the ADA provides that "no qualified individual with a disability shall, by reason of such disability, be excluded from participation in or be denied the benefits of the services, programs, or activities of a public entity, or be subjected to discrimination by any such entity." (See 42 U.S.C. 12132.)

State or States or local government;" and "the National Railroad Passenger Corporation, and any commuter authority."[28] Neither FDA nor the clozapine application holders meets this definition.

III. CONCLUSION

As described above, FDA has determined that the patient monitoring described in the labeling and the prescriber certification required by the REMS are necessary to ensure that the benefits of clozapine outweigh its risks.[29] FDA modifies the Clozapine REMS when it determines it necessary either to continue ensuring the benefits outweigh the risks or to minimize burden on the healthcare delivery system, as it did in 2015 to provide for the rechallenge of patients and more discretion for prescribers. Although we are denying the requests in your Petition, we note that today we are further minimizing the burden on the healthcare delivery system by modifying the REMS to require submission of laboratory results to the REMS program monthly using a Patient Status Form instead of more frequently when the patient's monitoring frequency is weekly or bi-weekly. By analyzing periodic assessments of the Clozapine REMS, FDA will continue to evaluate the program and require modifications if necessary.

For the reasons stated above, the Petition is denied.

Sincerely,

Douglas C. Throckmorton -S

Digitally signed by Douglas C. Throckmorton -S
Date: 2021.07.27 11:10:04 -04'00'

Patrizia Cavazzoni, M.D.
Director
Center for Drug Evaluation and Research

[28] 42 U.S.C. 12131(1).
[29] Accordingly, FDA does not intend to make the requested changes by direct final rule.

REFERENCES

Ahmed, S, KN Chengappa, VR Naidu, RW Baker, H Parepally, and NR Schooler, 1998, Clozapine Withdrawal-Emergent Dystonias and Dyskinesias: A Case Series, J Clin Psychiatry, 59(9):472-477.

Alvir, JM, JA Lieberman, AZ Safferman, JL Schwimmer, and JA Schaaf, 1993, Clozapine-Induced Agranulocytosis–Incidence and Risk Factors in the United States, N Engl J Med, 329(3):162-167.

Atkin, K, F Kendall, D Gould, H Freeman, J Liberman, and D O'Sullivan, 1996, Neutropenia and Agranulocytosis in Patients Receiving Clozapine in the UK and Ireland, Br J Psychiatry, 169(4):483-488.

Atkinson, J, P Douglas-Hall, C Fischetti, A Sparshatt, and DM Taylor, 2007, Outcome Following Clozapine Discontinuation: A Retrospective Analysis, J Clin Psychiatry, 68(7):1027-1030.

Bangalore, S, DD Goradia, J Nutche, VA Diwadkar, KMR Prasad, and MS Keshavan, 2009, Untreated Illness Duration Correlates With Gray Matter Loss in First-Episode Psychoses, Neuroreport, 20(7):729-734.

Copolov, DL, WR Bell, WJ Benson, NA Keks, DC Strazzeri, and GF Johnson, 1998, Clozapine Treatment in Australia: A Review of Haematological Monitoring, Med J Aust, 168(10):495-497.

de la Chapelle, A, C Kari, M Nurminen, and S Hernberg, 1977, Clozapine-Induced Agranulocytosis. A Genetic and Epidemiologic Study, Hum Genet, 37(2):183-194.

Honigfeld, G, F Arellano, J Sethi, A Bianchini, and J Schein, 1998, Reducing Clozapine-Related Morbidity and Mortality: 5 Years of Experience With the Clozaril National Registry, J Clin Psychiatry, 59(3 Suppl):3S-7S. Concluding that regular monitoring of the ANC can detect and reduce the incidence of severe neutropenia.

Kang, BJ, MJ Cho, JT Oh, Y Lee, BJ Chae, and J Ko, 2006, Long-Term Patient Monitoring for Clozapine-Induced Agranulocytosis and Neutropenia in Korea: When Is It Safe to Discontinue CPMS?, Hum Psychopharmacol, 21(6):387-391.

Lambertenghi Deliliers, G, 2000, Blood Dyscrasias in Clozapine-Treated Patients in Italy, Haematologica, 85(3):233-237.

Mena, CI, RA Nachar, NA Crossley, and AA González-Valderrama, 2019, Clozapine-Associated Neutropenia in Latin America: Incidence Report of 5380 Chilean Users, Int Clin Psychopharmacol, 34(5):257-263.

Miller, PR and AE Cutten, 1997, Haematological Side Effects of Clozapine: Patient Characteristics, N Z Med J, 110(1041):125-127.

Miodownik, C, V Lerner, A Kibari, D Toder, and H Cohen, 2006, The Effect of Sudden Clozapine Discontinuation on Management of Schizophrenic Patients: A Retrospective Controlled Study, J Clin Psychiatry, 67(8):1204-1208.

Mistry, H and D Osborn, 2011, Underuse of Clozapine in Treatment-Resistant Schizophrenia, Advances in Psychiatric Treatment, epub ahead of print January 6, 2011, doi:10.1192/apt.bp.110.008128. Summarizing the Taylor study as concluding that "most patients did not find blood monitoring a significant difficulty and the majority believed that the benefits of clozapine outweighed its potential side-effects."

Munro, J, D O'Sullivan, C Andrews, A Arana, A Mortimer, and R Kerwin, 1999, Active Monitoring of 12,760 Clozapine Recipients in the UK and Ireland: Beyond Pharmacovigilance, Br J Psychiatry, (175):576-580.

Stanilla, JK, J deLeon, and GM Simpson, 1997, Clozapine Withdrawal Resulting in Delirium With Psychosis: A Report of Three Cases, J Clin Psychiatry, 58(6):252-255.

Taylor, D, L Shapland, G Laverick, J Bond, and J Munro, 2000, Clozapine–A Survey of Patient Perception, Psychiatric Bulletin, (24):450-452.