

September 3, 2014

Dockets Management Branch  
Food and Drug Administration  
Department of Health and Human Services, Room 1-23  
12420 Parklawn Drive  
Rockville, MD 20857

Dear Commissioner:

**Citizen Petition**

This petition, submitted pursuant to 21CFR10.30, requests that the FDA amend the Clozapine Risk Evaluation and Mitigation Strategy (REMS) to accommodate for the condition of benign ethnic neutropenia (BEN).

**A. Action Requested**

Amend the Clozapine REMS to accommodate BEN.

Current REMS permits beginning Clozapine only if white blood cell count (WBC) is  $>3500\text{mm}^3$ . Therapy must be interrupted if the WBC falls to between  $2000\text{mm}^3$  and  $3000\text{mm}^3$  or absolute neutrophil count (ANC) falls to between  $1000\text{mm}^3$  and  $1500\text{mm}^3$ . Therapy must be stopped if the WBC drops below  $2000\text{mm}^3$  or ANC drops below  $1000\text{mm}^3$ .

Amended Clozapine REMS would permit a patient with treatment-resistant schizophrenia, who has been diagnosed with BEN by a hematologist, to adhere to the REMS adapted for BEN such that Clozapine can be started if the WBC is  $>3000\text{mm}^3$  and therapy must be interrupted if the WBC drops below  $2500\text{mm}^3$  or ANC drops below  $1000\text{mm}^3$ .

**B. Statement of Grounds**

1. African-American adults have lower WBC counts and ANC's than Caucasians at baseline. This is a benign phenomenon and does not put them at higher risk for agranulocytosis. The Clozaril REMS in the U.K. and Ireland has different ranges for patients with BEN which prevents the need to stop clozapine unnecessarily. The FDA does not make these allowances which may be partly why fewer African Americans are initiated or maintained on clozapine in the United States.
2. This Citizen's Petition is being written to request that the FDA consider amending the Clozapine Risk Evaluation and Mitigation Strategy (REMS) to more closely resemble the United Kingdom's 2002 adaptation which accommodates for the condition of benign ethnic neutropenia (BEN).

This change in the United States would permit many more citizens of African and Arab descent, who have refractory schizophrenia, have access to clozapine treatment.

3. It has been estimated that, because of BEN, about 20% of African Americans would be inappropriately deemed ineligible to begin clozapine. Among African Americans already receiving clozapine treatment, up to 25% have had to have it unnecessarily discontinued.
4. We in Flint, Michigan are running into situations in which we are unable to begin clozapine treatment for African American patients who have ANC's that run low, below the Clozapine Monitoring System guidelines, and appear to have benign ethnic neutropenia.
5. This Citizen Petition is being submitted to request that the Clozapine Risk Evaluation and Mitigation Strategy be changed to reduce racial disparities and permit greater use of clozapine in African American and other ethnic populations.
6. The extensive literature on the BEN syndrome and unique clinical benefits of clozapine will not be reviewed here. A reference list and relevant articles are enclosed. See exhibits #1 - #9.

#### **C. Environmental Impact**

FDA regulations at 21 CFR 10.30 require Petitioner to prepare an environmental assessment under 21 CFR 25.40. However, an environmental assessment is not necessary here. The requests embodied in the instant petition have no environmental implications. Consequently, no environmental assessment is warranted.

#### **D. Economic Impact**

Pursuant to 21 CFR 10.30, information under this section is to be submitted only when requested by the Commissioner following review of the petition.

#### **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 petitioners that are unfavorable to the petition.

#### **F. Conclusion**

For the forgoing reasons, Petitioner requests that this petition be granted and that the Commissioner establish an amended Clozapine REMS for patients with BEN, to permit patients with BEN to receive the benefits of clozapine treatment.



**Todd N. Rosen, MD, FAPA**

*Diplomate, American Board of Psychiatry and Neurology*

**Medical Director, Genesee Health System**

Phone 810.257.3724 Fax 810.257.3731

Please note my new email address: [trosen@genhs.org](mailto:trosen@genhs.org)

Enclosed References/Exhibits:

1. Hsieh MM, Everhart JE, Byrd-Holt DD, Tisdale JF, Rodgers GP: **Prevalence of neutropenia in the U.S. population: Age, sex, smoking status, and ethnic differences.** Ann Intern Med 2007, 146:486-92.
2. Kelly DL, Kreyenbuhl J, Dixon L, Love RC, Medoff D, Conley RR: **Clozapine underutilization and discontinuation in African Americans due to leucopenia.** Schizophr Bull 2007, 33:1221-1224.
3. Kuno E, Rothbard AB: **Racial disparities in antipsychotic prescription patterns for patients with schizophrenia.** Am J Psychiatry 2002, 159:567-572.
4. Rajagopal S. **Clozapine, agranulocytosis, and benign ethnic neutropenia.** Postgrad Med. 2005;81:545-546.
5. Horvitz-Lennon, M, et.al. **The Effect of Race-Ethnicity on Clozapine Outcomes among Medicaid Beneficiaries with Schizophrenia.** Psychiatr Serv. 2013 March 1; 64(3): 230-237.
6. Bray, A. **Ethnic nerutopenia and clozapine.** Australian and New Zealand J of Psychiatry 2008; 42:342-345.
7. Whiskey, E, et.al. **The importance of the recognition of benign ethnic neutropenia in black patients during treatment with clozapine: case reports and database study.** J of Psychopharm 2011. 25(6): 842-845.
8. Fisher, N, et.al. **Treatment with clozapine.** Brit Medical J. Nov 16, 1996. (313): 1262.
9. Denic, S. et.al. **Prevalence, phenotype and inheritance of benign neutropenia in Arabs.** BMC Blood Disorders 2009, 9:3.