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Food and Drug Administration

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The undersigned organizations would like to thank the FDA for informing us of changes in the Clozapine REMS in advance of the November 15, 2021 implementation date. We recognize that clozapine is a medication with unique effectiveness for serious psychiatric illness and that it has unique toxicity concerns. We also wish to emphasize that clozapine can be lifesaving and life sustaining for many patients and that the REMS addresses only one infrequent toxicity.

As our members speak with the new REMS programs and attempt to utilize it, multiple concerns have arisen. We hope that this communication can serve as a basis to proactively initiate changes regarding some issues in the new system and initiate a dialog regarding other issues.

#### **Interim Double Entry**

During the Pharmacy Stakeholder's call, it was noted that the new REMS would not be actually be fully implemented until November 15. The comment was made that clinicians should use both systems together until then. The Clozapine REMS places considerable workload on clinicians in its current and revised form. Prescribers must document in their own medical record system, before using the REMS. It is unreasonable to expect them to document in two additional systems.

#### **Implementation Date**

While November 15 is still several months off, we expect that many pharmacists, designees and prescribers will not register in the new system until shortly before the November 15 change date. The advice to double document will lead even fewer clinicians to use the new system early. Thus, we will be faced with those who don't complete paperwork until November 15 or shortly thereafter. This means, that it is likely that the first post registration set of Patient Status Forms (PSF) will be due on December 22 (37 days after November 15) or shortly thereafter, during the winter holiday season. It is very difficult to reach prescribers during this period as many offices and clinics are closed. This may be compounded by the fact that the first submission of monitoring data appears to require a paper submission which could further delay approvals.

We feel strongly that this implementation date and system will lead to additional work for pharmacists to file exemptions or, more likely, increase the potential for unfilled prescriptions. The impact of unfilled clozapine prescriptions can be devastating for patients who similarly may have difficulty reaching prescribers during this period. It is essential that this implementation date be delayed until after January 1, 2022. Alternatively, pharmacists should be allowed to fill prescriptions regardless of where the PSF is in the authorization process until after January 1, 2022. There is some precedence for such an alternative given the exemption from normal monitoring that occurred during the pandemic.

### **Lack of Data Transfer**

Many clinicians depended on the historical data maintained in the current REMS and in previous manufacturer maintained clozapine monitoring systems. It is unreasonable to deny prescribers of this data that they entered. Furthermore, the lack of historical data could result in harm to patients in some circumstances. The FDA must intervene with the manufacturers to make this data available to prescribers.

Another potentially serious consequence of the lack of data transfer between REMS is the lack of a transfer of the “do not rechallenge” designation for patients. This “do not rechallenge” list was deemed so important that it predated any REMS for clozapine. This is an important component of the clozapine REMS and one that our organizations thinks should be retained.

### **The Patient Status Form and Need for Bulk Data Submission**

The PSF that our organizations have obtained is five pages long. Many prescribers and clinics see multiple patients on clozapine. If a clinic sees twenty clozapine patients each week, it is unreasonable for them to have to print 100 pages and then fax 100 pages of PSFs. We understand that clinicians will be able to submit data online, but this is still not an ideal solution. The best solution is to separate the clinical decision part of the form from the monitoring part of the form and develop a form where a clinician can submit monitoring results on multiple patients at one time. This would greatly reduce workload and confusion. Furthermore, any PDF versions of forms should be fillable forms.

### **Registration Requirements and Email Addresses**

The health professional registration process for the new REMS has already proven problematic. Requirements for DEA numbers for professionals that don't prescribe controlled substances are unreasonable. Residents often don't have their own DEA numbers which hinders registration and restricts the pool of clozapine prescribers. In the current REMS, designees could request registration and be approved by the prescriber. Now, the prescriber will have to make the request. This is a more time-consuming process. Furthermore, there are limits on roles and the number of designees. This just does not work in busy clinics. We request that the vendor resolve these issues immediately to avoid disruptions in patient care.

Many clinicians practice in multiple locations. Particularly in rural areas, a prescriber may travel to different areas and clinics on different days of the week or month. For these reasons, the requirement that a prescriber have a new email address for each site is unreasonable. This adds to prescriber burden, means the prescriber must monitor and keep track of multiple email addresses and may lead the prescriber to avoid prescribing the drug at some locations with few patients. This was an issue with the old REMS and is being carried over to the new REMS. This issue must also be addressed immediately.

### **Lag Regarding Data Submission**

For some time, many thought leaders have questioned the need for the Clozapine REMS. Now that data submission can lapse for 37 days (even longer for patients on every two or monthly prescription fills), the REMS data submission does not reduce risk. The PFS is completed after an adverse event and outcome is over. Given this fact, we are uncertain how the changed REMS “reinforce(s) medication use behaviors and actions that support the safe use of” clozapine. Instead, the changed REMS increases the burden on those caring for the seriously mentally ill population. Furthermore, it neglects some of the other serious and potentially fatal side effects of clozapine.

During much of the current pandemic, health professionals were allowed to use their own judgement regarding the monitoring of clozapine. They practiced judicious care and monitoring and referred to the product labeling as necessary to assure patient safety. There is no suggestion that any pandemic-related changes in behavior led to increased patient harm.

We understand the need for provided education regarding clozapine. We agree that the Elements to Assure Safe Use (ETASU) developed by the FDA continue to include this element. However, it is our opinion that the other elements of the new Clozapine REMS including the patient monitoring component and the prescription authorization element do nothing to improve patient safety. Instead, this system provides data to manufacturers and imposes a workload burden on those caring for vulnerable populations.

### **Conclusion**

In summary, our recommendations are:

1. Restructure the REMS globally to reduce paperwork burden.
2. Delay the Clozapine REMS implementation date until after January 1, 2022. Alternatively, pharmacists should be allowed to fill prescriptions, regardless of status of the PSF authorization, until after January 1, 2022.
3. Ensure data transfer between Clozapine REMS programs.
4. Maintain the “do not rechallenge” designation for patients in the new REMS and ensure that data is maintained from the current REMS system.
5. Patient Status Forms:
  - Provide a method for bulk submission of forms.
  - Separate the clinical decision part of the form from the monitoring part of the form and develop a form where a clinician can submit monitoring results on multiple patients at one time.
  - Ensure that PDF forms are created as fillable forms.
6. Continue the current practice of allowing designees to request registration and be approved by the prescriber.
7. Allow for the use of one email address for prescriber (or designee as requested in #5).
8. Given that the lag in data submission reduces the system’s potential to reduce adverse events and adverse outcomes, remove the requirement for submission of ANCs altogether.

We hope that the transition to this new system will prove to be an opportunity for a discussion between the FDA and all stakeholders aimed at examining the important elements that can be proven to improve patient safety without continuing to burden health professionals and reducing access to this important treatment.

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