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Anna Fine, PharmD, MS
Director, Health Professional Liaison Program
Office of Health & Constituent Affairs
Office of External Affairs
U.S. Food and Drug Administration

Dear Dr. Fine:

It was great to see you at the FDA Network of Experts Open House.

As Deanna and I stated, we had a discussion session on ClozapineREMS at the CPNP Annual Meeting last month. This session was very well attended. Subsequently, we have received a number of comments about the current status of Clozapine REMS following the announcements about the pre-dispensing authorization (PDA). This letter attempts to summarize all of this information.

Mandatory Implementation of the PDA

Many individuals have suggested that there is no need for mandatory implementation of the PDA. The lack of a mandatory PDA during the past six months has not produced any problems for patients to our knowledge. More importantly, our members express the concern that implementation of the mandatory PDA will reduce access to clozapine. Furthermore, many feel this reduced access has the potential to cause greater harm than severe neutropenia when considered on a population basis. Our best guess is that severe neutropenia occurs in less than 0.5% of patients. It may be more likely that patients are harmed by unnecessary interruptions in treatment or the failure of their prescriber or pharmacist to retitrate clozapine after an interruption in treatment. Additional concerns included the potential of increased costs due to these interruptions along with the costs of unnecessary emergency room visits to secure medication and/or treat resultant exacerbations of illness.

An additional concern related to mandatory PDAs relates to ClozapineREMS hours of operation. If PDAs are mandatory, multiple individuals have asked that the Program be open to calls 24 hours a day seven days a week due to the potential for the PDA to interfere with clinical care. To do otherwise would seem imprudent.

A related concern was the amount of time it took for phone and fax data to be added into the system. If the call center is not open, then delays could occur in receiving authorization to dispense if ANCs are reported by fax or means other than direct order entry. Many pharmacists expressed particular concerns over their ability to function in environments where hematology testing and dispensing occurs on the same day.

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Finally, we have received several anecdotal reports from prescribers and community pharmacies expressing concern over the perceived complexity of ClozapineREMS and the PDA system. These concerns have led some independent pharmacies and psychiatrists to cease dispensing and prescribing clozapine.

We strongly urge the FDA to further postpone mandatory PDAs until such time that it can be shown that the risks of such an action are not worse than the potential benefits that may occur from the PDA.

Integration of VA System

Several individuals mentioned that the separate system for the VA places continuity of care at risk. If a patient is in the VA registry and then receives services at a non-VA facility (apparently a common experience in some areas) or is discharged from VA care, the patient will appear to not be registered. This could lead to an interruption in treatment. There were numerous questions as to why the VA is exempt and whether the VA data will be linked to ClozapineREMS before the institution of mandatory PDAs. There was agreement that this situation must be rectified before any mandatory PDA is implemented.

Alternative to Mandatory PDAs and the Current Registry

For all practical purposes, clozapine was largely managed by systems of care prior to ClozapineREMS. While reporting took place to the individual registries, most systems had their own methods and procedures for dealing with clozapine. In fact, this is what the VA is doing. When ClozapineREMS was introduced, its most significant impact was to disrupt these systems that had been developed over decades. Many members proposed that such systems can do a better job of meeting the needs of patients than a centralized monitoring program.

It has been suggested that at a minimum, all hospitals, psychiatric facilities, long term care facilities, clinics associated with hospitals or systems of care and similar entities be exempted from ClozapineREMS. Instead, the FDA should charge each facility/system with developing adequate policies and procedures.

The most significant benefit of this plan is that it would improve access and dramatically reduce the excessive burdens due to the poor design of ClozapineREMS. Additional benefits would include reducing the problems that occur with normal everyday institutional activities such as internal patient transfers, prescriber vacations, changes in resident physician coverage, etc. There is no evidence that the burden placed upon these facilities and systems adds to patient safety.

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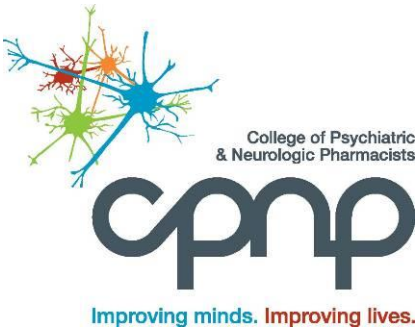


Some have suggested that an aim of ClozapineREMS is to collect data to inform labeling changes that could further reduce monitoring requirements. If this is the case, the FDA could instead require that facilities/systems opting out of ClozapineREMS submit data in a prescribed format periodically as an alternative.

The FDA should strongly consider the alternatives to ClozapineREMS described above.

ClozapineREMS Communication Issues

Considerable concern has been expressed regarding commuications about the plan for PDAs. All entities participating in ClozapineREMS were not made aware of pending changes announced by letters at the same time. Some report waiting six weeks to receive letters that were shared with others earlier. This causes consternation and disrupts team problem solving and planning. Instead, members suggest that all communications for all participants should be on the website.

Prescribers who practice in multiple locations have approached our members with concerns about alerts and communications sent to the wrong location. This results in sharing protected health information with inappropriate parties. There is a need to be able to customize all alerts and communications for each patient.

Several members report that differing information has been given out by ClozapineREMS staff regarding the pharmacist's ability to enter ANCs. CPNP received a report that ClozapineREMS staff have told pharmacists that they have no role except to just "fill the prescription." They have also reportedly refused to discuss clinical issues relating to a patient with a pharmacist when the pharmacist initiated a call on behalf of the prescriber.

Finally, several members indicated that when a request is sent to a prescriber to be their designee, the email request with the letter explaining the request goes back to the requestor and not the prescriber. Multiple individuals also report difficulty keeping ClozapineREMS responses from going into spam systems especially in institutional settings where they may not have control over spam filters.

Restricting all communications to website interactions rather than external channels would avoid HIPAA issues, spam problems, email misdirection and other communication issues.

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ClozapineREMS Website Issues

Many members remain concerned about the continuing inability of pharmacists to see all of a patient's data. Furthermore, there are pieces of data that are difficult or impossible to view during the appropriate website operations. For instance, it is not possible for a designee serving multiple prescribers to see the prescriber currently assigned to a patient. It is similarly difficult to enter data for multiple patients without going back to the dashboard, clicking on pharmacies, choosing *Add Lab* from the drop down menu, clicking *GO*, entering patient specific data, submitting and then returning to the dashboard all over again for the next patient. This is extremely time-consuming, especially when slowdowns in the system lead to lags in the system refreshing screens.

When dealing with searches for specific patients, the system provides no indication of why a patient is not found. In many cases the patient is in the system. Frequently failure to locate a patient is due to a typographical error in any one of five fields. However, the system does not suggest possible errors or aid the user by pointing out that a specific field is not compatible with the system record. In previous systems, there was an ability to see a list of patients and easily enter the values for an entire list of patients with a single draw date. It was also easier to assure that all values were entered correctly.

One particular problem that was predicted prior to the first release of the website was that patients move all of the time. Problems with incorrect zip codes frequently result in "patient not enrolled" messages. Using a dynamic variable such as a zip code could cause problems if mandatory PDAs are implemented. Multiple users report that this has required multiple telephone calls to the ClozapineREMS Program.

ClozapineREMS is prone to errors that result from eligibility checks. When performing eligibility checks for multiple patients, new labs for subsequent patients have sometimes been saved under the previous patient. One pharmacist opines that this is due to issues with cookies.

Continued Areas of Confusion

There is continued lack of clarity on how to handle situations in hospitals, emergency rooms, urgent care, psychiatric hospitals with emergency department equivalent beds, crisis facilities.

The definition of what constitutes a "current" ANC is also a matter of confusion. Individual callers have been given varying instructions on this issue by different ClozapineREMS staff. Some members report being told that an ANC must have been obtained within the last seven days regardless of monitoring frequency. Others have been told it varies with the monitoring frequency. This information should be available on the data entry page to clarify for clinicians using the system.

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Pharmacists also report that ClozapineREMS staff have told them they will no longer be able to enter ANCs once the mandatory PDA is implemented. This requires clarification.

The Pharmacist's Role

In the past we have discussed the role that pharmacists play in the management of clozapine patients. This is particularly true among pharmacists practicing in hospitals and other organized systems of care. Pharmacists are being frequently requested to register patients, change monitoring frequency or enter a patient as having BEN. There was unanimous agreement that despite the language in the recently release "PDA letters," pharmacists in non-retail settings must be given this authority. Failure to do so simply adds unnecessary burdens to health systems and prescribers. In many settings, the pharmacist is more likely to have internet access in the clinic or hospital setting than the prescriber. Not allowing the pharmacist to perform these tasks can restrict access. Again, there is no evidence that restricting these activities adds to patient safety. Already, there are reports of prescribers just turning over their access to the pharmacist so they don't have to bother with ClozapineREMS. Furthermore, in many settings, the pharmacists performing these activities have specific clinical privileges based on collaborative drug therapy management agreements.

We strongly believe that ClozapineREMS continues to present unnecessary burdens on pharmacists and prescribers without evidence that it reduces risk. We do know that mandatory implementation of PDAs will introduce a barrier to access to clozapine at a time when systems and other government agencies are seeking to improve access. We ask that the implementation of mandatory PDAs be postponed (preferably cancelled) until such time as all of these matters are resolved. We hope that the FDA will consider the suggestions we have made above.

Thank you again for listening and the courtesies that you have afforded us in our previous conversations.

Sincerely,

Raymond C. Love, PharmD, BCPP, FASHP
President

cc: Christopher Thomas, PharmD, BCPP
President Elect
Deanna Kelly, PharmD, BCPP
Incoming President Elect

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