

### BEFORE STARTING CLOZAPINE TREATMENT

- > Before starting treatment with clozapine, the baseline absolute neutrophil count (ANC) must be:
  - At least 1500/ $\mu$ L for the general population, or
  - At least 1000/ $\mu$ L for patients with documented benign ethnic neutropenia (BEN)
- > It is no longer necessary to check the National Non-Rechallenge Master File (NNRMF) before starting treatment.
  - The NNRMF is no longer available. All patients who were listed in the NNRMF were transferred into the Clozapine REMS Program. These patients are identified with a red flag  in the Clozapine REMS Program.

### MONITORING AND DURING TREATMENT

#### LABS

- > Prescribers must submit ANC according to the patient's monitoring frequency (MF) on file with the Clozapine REMS Program:
  - For weekly MF, ANC must be submitted within 7 days of the lab draw\* date
  - For every two weeks MF, ANC must be submitted within 15 days of the lab draw\* date
  - For monthly MF, ANC must be submitted within 31 days of the lab draw\* date

\*Assumes the lab draw date is day 0
- > White blood cell (WBC) counts are not accepted. If you have a WBC count and differential, you may use the ANC calculator on the Clozapine REMS Program Website at [www.clozapinerems.com](http://www.clozapinerems.com) to determine the ANC.
- > An ANC is normal if it is greater than or equal to 1500/ $\mu$ L for the general population, or greater than or equal to 1000/ $\mu$ L for patients with BEN.

#### MONITORING FREQUENCY

- > Patients may transition to less frequent ANC monitoring based on their history of continuous clozapine therapy and normal ANCs.
  - Weekly ANC monitoring is required for all patients during the first six months of treatment.
  - If the patient's ANC remains in the normal range for the first six months of therapy, MF may be reduced to once every two weeks.
  - If the patient's ANC continues to remain in the normal range for the second six months of treatment, ANC MF may be reduced to once monthly.
- > Monitoring frequency is calculated based on the patient's lab history in the Clozapine REMS Program. It is critical that all labs be submitted to the Clozapine REMS Program according to the patient's MF to ensure that the patient's monitoring frequency does not revert to a more frequent schedule.
  - The Clozapine REMS Program made every effort to consolidate ANC data for patients with laboratory data in multiple individual manufacturer registries to create complete patient records. Patients with complete profile information in the individual manufacturer registries were migrated to the Clozapine REMS Program successfully, but may have had different monitoring frequencies across multiple individual manufacturer registries and/or had a significant gap in ANC data when patient data was consolidated from the multiple individual manufacturer registries.
    - In accordance with the clozapine Prescribing Information, if the patient had consistent ANCs submitted over the previous 12-month period, the patient was migrated with a monthly MF.
    - If a patient's ANCs were inconsistently submitted to the registries in the previous 12-month period and there was a timeframe longer than 56 days between blood draw dates, the patient was migrated with a weekly MF.
  - The guidelines outlined above for assigning a new MF are consistent with the Prescribing Information.
  - If a prescriber needs to change a patient's MF, the prescriber may do so via the Prescriber Dashboard on the Clozapine REMS Program Website. The prescriber or prescriber designee may also update a patient's MF by calling the Clozapine REMS Program Contact Center at 844-267-8678.
  - During the phased implementation period, the Clozapine REMS Program will not deny clozapine dispensing based on MF data. However, once the REMS Program is fully implemented, the MF is utilized to determine if a patient's ANC is current. Therefore, accuracy of the MF is important as a factor in determining if a pharmacy will be authorized to dispense clozapine to the patient.

#### TREATMENT INTERRUPTIONS

- > Treatment interruptions are now recommended at lower ANC thresholds than in previous versions of the Prescribing Information.
  - For general population patients, interrupt treatment if neutropenia is suspected to be clozapine-induced for ANC less than 1000/ $\mu$ L.
  - For patients with documented BEN, interrupt treatment if neutropenia is suspected to be clozapine-induced for ANC less than 500/ $\mu$ L.
  - See Table 1 in the *Clozapine and the Risk of Neutropenia: A Guide for Healthcare Providers* or Tables 2 and 3 in the clozapine Prescribing Information for more detailed treatment guidance.
- > Prescribers may use clinical judgment to continue treatment with clozapine for patients with moderate or severe neutropenia if they determine that the benefits of clozapine therapy outweigh the risks. The prescriber must provide a "Treatment Rationale" in the Clozapine REMS Program to avoid treatment interruptions.
  - A prescriber can provide a *Treatment Rationale* via the Prescriber Dashboard on the Clozapine REMS Program Website or by calling the Clozapine REMS Program Contact Center at 844-267-8678.

#### BEN PATIENTS

- > Patients with documented BEN have specific treatment guidelines in the clozapine Prescribing Information (see Table 1 in the *Clozapine and the Risk of Neutropenia: A Guide for Healthcare Providers* or Table 3 in the clozapine Prescribing Information for details).

#### HOSPICE PATIENTS

- > Patients in hospice may be excluded from certain program requirements (see Section 8.8 of the clozapine Prescribing Information).

### DISCONTINUING CLOZAPINE TREATMENT

- > Four weeks of weekly monitoring for patients who are discontinuing clozapine treatment is no longer required.
- > The duration and frequency of ANC monitoring is dependent on that patient's last ANC and clinical status (see Section 2.4 in the clozapine Prescribing Information for more details).