

CLOZAPINE (CLOZARIL®, FAZACLO®)

INDICATIONS

- 1) For use in patients with refractory schizophrenia or schizoaffective disorder, defined as failure on two antipsychotics from two different chemical families given for sufficient time (6-12 weeks) at a sufficient dose (1000 mg/day of chlorpromazine equivalents).
- 2) For use in schizophrenic or schizoaffective patients who cannot tolerate other antipsychotics.
- 3) Psychosis associated with other organic conditions, (who have failed two antipsychotics, or who cannot tolerate other antipsychotics)
- 4) Manic disorders with psychosis (in patients who have failed two antipsychotics)
- 5) Reduction in the risk of aggression or recurrent suicidal behavior in patients with schizophrenia or schizoaffective disorder

PRECAUTIONS TO CONSIDER

Contraindications

Absolute:

- 1) History of anaphylactic reaction or similarly severe significant hypersensitivity to the medication prescribed
- 2) Myeloproliferative disorders
- 3) History of clozapine-induced agranulocytosis or severe granulocytopenia
- 4) Concomitant use of agents that may cause bone marrow suppression, including carbamazepine (Tegretol®, Carbatrol®, Equetro®)
- 5) Uncontrolled epilepsy
- 6) Severe CNS depression
- 7) Paralytic ileus

Relative:

- 1) History of drug induced agranulocytosis or leukopenia
- 2) Breast cancer
- 3) History of neuroleptic malignant syndrome
- 4) Narrow angle glaucoma
- 5) Impaired hepatic function
- 6) Prostatic hypertrophy
- 7) Parkinson's disease
- 8) Severe cardiovascular diseases
- 9) History of seizure
- 10) Diabetes Mellitus

PRECAUTIONS TO CONSIDER (continued)

Precautions

Alcoholism (active), recent or current blood dyscrasias, angina, hypotension, congestive heart failure, arrhythmias, glaucoma, obesity, urinary retention, patients at risk for paralytic ileus, pregnancy/nursing mothers, dementia-related psychosis, phenylketonurics (Fazaclo®)

Pregnancy and Breast-Feeding

See precautions. FDA Pregnancy Category B.

Drug Interactions of Major Significance

- 1) Concomitant use of CNS depressants
- 2) Antithyroid agents
- 3) Concomitant use of agents that cause EPS (including droperidol, prochlorperazine, promethazine, metoclopramide, amoxapine, metyrosine, pimozide, reserpine)
- 4) Concomitant use of hypotension producing agents
- 5) Levodopa
- 6) Concomitant use of agents that cause bone marrow suppression
- 7) Clozapine is a major substrate of CYP 1A2 and a moderate inhibitor of CYP 2D6.
- 8) Strong inhibitors or inducers of Cytochrome P450 (1A2)

SEE TABLE A: Cytochrome P450 Drug Metabolism/Inhibition

Age-Specific Considerations

Safety and efficacy have not been established in children under the age of 16. Geriatric patients may be more susceptible to orthostatic and anticholinergic effects.

Side Effects Which Require Medical Attention

- 1) Anticholinergic effects
- 2) Visual changes
- 3) Tardive dyskinesia or other late-onset EPS
- 4) Hypotension
- 5) Rashes, photosensitivity and altered pigmentation
- 6) Early symptoms of agranulocytosis (fever, sore throat, weakness)
- 7) Fluctuating vital signs
- 8) Altered consciousness
- 9) Drooling
- 10) Hepatitis
- 11) Seizure
- 12) Fever

PRECAUTIONS TO CONSIDER (continued)

Side Effects Which Require Medical Attention (continued)

- 13) Cardiomyopathy/myocarditis - Symptoms of myocarditis including unexplained fatigue, dyspnea, tachypnea, fever, etc.
- 14) Pulmonary embolism or DVT
- 15) Hyperglycemia
- 16) Clinically significant weight gain
- 17) Hypercholesterolemia or hypertriglyceridemia

PATIENT MONITORING

Patient Monitoring Parameters

- 1) CBC as indicated by guidelines established by the manufacturer
- 2) Pregnancy test – as clinically indicated
- 3) BMI and measurements – when a new antipsychotic is initiated, at every visit (monthly for inpatients) for 6 months after the new antipsychotic is initiated, and quarterly when the antipsychotic dose is stable.
- 4) Fasting plasma glucose level or hemoglobin A_{1c} – before initiating a new antipsychotic, then yearly.

If a patient has significant risk factors for diabetes and for those that are gaining weight – before initiating a new antipsychotic, 4 months after starting an antipsychotic, and then yearly.

- 5) Lipid screening [total cholesterol, low- and high-density lipoprotein (LDL and HDL) cholesterol, and triglycerides] – Every 2 years or more often if lipid levels are in the normal range, every 6 months if the LDL level is > 130 mg/dl

If no lipid screening has been done within the last 2 years, then a lipid profile should be obtained within 30 days of initiation of the drug.

- 6) Sexual function inquiry – inquire for evidence of galactorrhea/gynecomastia, menstrual disturbance, libido disturbance or erectile/ejaculatory disturbance yearly

If a patient is receiving an antipsychotic known to be associated with prolactin elevation, then at each visit (quarterly for inpatients) for the first 12 months after starting an antipsychotic or until the medication dose is stable and then yearly.

- 7) Prolactin level – if there is evidence of galactorrhea/gynecomastia, menstrual disturbance, libido disturbance or erectile/ejaculatory yearly.
- 8) EPS Evaluation (examination for rigidity, tremor, akathisia) – before initiation of any antipsychotic medication, then weekly for the first 2 weeks after initiating treatment with a new antipsychotic or until the dose has been stabilized and weekly for 2 weeks after a dose increase.
- 9) Tardive dyskinesia evaluation – every 3 months and as clinically indicated.
- 10) Vision questionnaire – ask whether the patient has experienced a change in vision and should specifically ask about distance vision and blurry vision – yearly

PATIENT MONITORING (continued)

Patient Monitoring Parameters (continued)

- 11) Ocular evaluations – yearly for patients older than age 40 years; every 2 years for younger patients
- 12) EKG – baseline, annually and as clinically indicated (e.g., myocarditis, unexplained fatigue, tachypnea, etc.)
- 13) Troponin and C-reactive protein as clinically indicated for suspected myocarditis

Dosing

See DSHS/DADS Drug Formulary for dosage guidelines.

Exceptions to maximum dosage must be justified as per medication rule.