# VRAYLAR (CARIPRAZINE)

**Brand name:** Vraylar
**Generic:** cariprazine

**Manufacturer:** Allergan
**Distributor:** Actavis Pharma, Inc
**Approval date:** September 17, 2015

**Drug class:** Atypical antipsychotic

**Indications:** Schizophrenia, acute treatment of manic or mixed episodes associated with bipolar I disorder

**Mechanism of action:** Partial agonist at D2 and 5HT1A and antagonist at 5HT2A

**Boxed warning:** Increased mortality in elderly patients with dementia related psychosis

**Dosage form/strength:** Capsule (1.5mg, 3mg, 4.5mg, 6mg)

**Administration:** Can be given orally with or without food

- **Dosing**
  - Schizophrenia
    - Start at 1.5mg/day
    - Recommended 1.5 – 6mg/day
  - Bipolar mania
    - Start at 1.5mg/day
    - Recommended 3 – 6mg/day
  - Dosing above 6mg does not show any benefit and increases the risk of dose-related adverse effects
- **Adverse reactions (incidence greater than 5%)**
  - Schizophrenia – 6 week trial
    - Extrapyrimidal symptoms, akathisia, headache, somnolence, insomnia
    - Mean change in weight after 6 weeks was 0.8 – 1kg
    - Blood glucose similar to placebo
    - Lipids similar to placebo
  - Bipolar mania – 3 week trial
    - Extrapyrimidal symptoms, dyspepsia, vomiting, somnolence, restlessness, nausea, constipation, abdominal pain, headache, dizziness, insomnia, restlessness
    - Mean change in weight was 0.2 – 0.6kg
    - Blood glucose similar to placebo
    - Lipids similar to placebo
- **Warnings/precautions**
  - Similar to other antipsychotics, Cariprazine carries the risk of cerebrovascular adverse reactions, neuroleptic malignant syndrome, leucopenia, neutropenia, seizures, cognitive and motor impairment, metabolic changes, body temperature dysregulation,dysphagia, and tardive dyskinesia
  - Adverse effects may also take several weeks to appear due to cariprazine and its major metabolites taking time to accumulate
- **Pharmacokinetics**
  - Cariprazine has two major active metabolites which are desmethyl cariprazine (DCAR) and didesmethylcariprazine (DDCAR) which are equipotent to cariprazine

- DCAR reaches steady state in 1 to 2 weeks while DDCAR reaches steady state at 4 to 8 weeks
- Half-life for cariprazine: 2-4 days
- Half-life for DDCAR: 1-3 weeks
- Absorption
  - Peak plasma concentrations are reached between 3 to 6 hours
  - High fat meals do not significantly affect $C_{max}$ or AUC
- Distribution
  - 91 – 97% protein bound
- Metabolism
  - Extensive CYP3A4 metabolism. Also metabolized by CYP2D6 to a lesser extent
- Elimination
  - 21% excreted in urine with 1.2% unchanged in urine

- **Pharmacodynamics**
  - At three times the maximum dose, cariprazine does not prolong QT interval to a significant level
- **Dosing adjustments**
  - Hepatic
    - No dosage adjustment necessary for mild to moderate impairment (Child-Pugh score between 5 and 9)
    - Not recommended for use in patients with severe impairment (Child-Pugh score between 10 and 15)
  - Renal
    - No dosage adjustment with mild to moderate impairment (CrCl >30ml/min
    - Not recommended in CrCl <30ml/min
- **Drug interactions**
  - Cariprazine undergoes metabolism by CYP3A4. Strong inhibitors or inducers of CYP3A4 may produce changes in serum concentrations of Cariprazine
    - Examples of strong inhibitors which may increase serum cariprazine levels
      - Itraconazole
      - Ketoconazole
    - Examples of strong inducers which may decrease serum cariprazine levels
      - Rifampin
      - Carbamazepine
- **Pregnancy/breastfeeding**
  - No available data on humans but animal data shows fetal harm. Rat studies showed malformations, lower pup survival, and developmental delays. Cariprazine was not teratogenic in rabbits.
  - No studies have been conducted on the presence of cariprazine in human milk but is was present in rat milk
- **Clinical trials**
  - Schizophrenia
    - Three different 6 week, randomized, double blind, placebo controlled trials in patients aged 18 to 60 years old
    - Primary efficacy measure: positive and negative syndrome scale (PANNS)
    - Secondary efficacy measure: Clinical Global Impressions Severity (CGI-S)
    - Study 1
      - 711 patients
      - 3 doses of Cariprazine (1.5, 3, or 4mg) with active control risperidone. All doses and active control were superior to placebo on the PANNS and CGI-S
    - Study 2
      - 604 patients
      - 2 doses of Cariprazine (3 or 6mg) with active control aripriprazole.

            - All doses and active control were superior to placebo on the PANNS and CGI-S
        - Study 3
            - 439 patients
            - 2 flexible doses of Cariprazine (3 to 6mg or 6 to 9mg)
            - All doses were superior to placebo on the PANNS and CGI-S
        - Dose related increase of adverse reactions, especially above 6mg. Maximum recommended dose is 6mg/day
    - Place in therapy/considerations
        - Does not have an IM formulation
        - Risk for drug interactions
        - Shown to be effective for schizophrenia and bipolar mania and/or mixed episodes
        - Long half-life when compared to other atypical antipsychotics such as ziprasidone or lurasidone
        - No significant QT prolongation
        - Low weight gain comparable to agents like ziprasidone
        - Lipid and glucose changes are similar to placebo

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**References**


1. "Label: CARIPRAZINE- Cariprazine Capsule, Gelatin Coated." *DailyMed*. 15 Sept. 2015. Accessed: 6 Oct. 2015.
2. "Cariprazine (cariprazine)." *Cariprazine New FDA Drug Approval*. Web. 6 Oct. 2015. <http://www.centerwatch.com/drug-information/fda-approved-drugs/drug/100094/cariprazine-cariprazine>. Accessed: 6 Oct. 2015.
3. Product Information: VRAYLAR(R) oral capsules, cariprazine oral capsules. Actavis Pharma, Inc, Parsippany, NJ, 2015.