Brexpiprazole (Rexulti ®)
FDA approved July 2015

Brexpiprazole is an atypical antipsychotic indicated for

- Treatment of schizophrenia
- Use as an adjunctive therapy to antidepressants for the treatment of MDD

Mechanism

- Serotonin-dopamine activity modulator, acts as a partial agonist for serotonin 5-HT_{1A} and dopamine D_2 receptors and as an antagonist at serotonin 5-HT_{2A} and noradrenaline alpha1B/2C receptors

How supplied: Tablets - 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, and 4 mg

Dosage:

Indication	Starting Dose	Recommended Dose	Maximum Dose
MDD	0.5 mg/d or 1 mg/d	2 mg/d	3 mg/d
Schizophrenia	1 mg/d	2 to 4 mg/d	4 mg/d

- Dose adjustment needed in
  - Renal or hepatic impairment
  - Known CYP2D6 poor metabolizers
  - Concomitant use with CYP3A4 or CYP2D6 inhibitors or strong CYP3A4 inducers

Administration: Administer once daily with or without food

Pharmacokinetics:

Bioavailability	**95%**
Tmax	Within 4 hours
Half-life	91 hours
Steady-state concentrations	Within 10-12 days
Metabolism	Primarily hepatic by CYP3A4 and CYP2D6
Elimination	Mainly feces and urine

Adverse Reactions: Most common adverse reactions were

- MDD: Weight increased and akathisia (≥5% and at least twice the rate for placebo)
- Schizophrenia: Weight increased (≥4% and at least twice the rate for placebo)

Warnings and Precautions

- Black box warnings regarding dementia-related psychosis as other atypical antipsychotics as well as a warning for increased risk of suicidal thoughts in young patients taking antidepressants
- Cerebrovascular adverse reactions in elderly patients with Dementia-Related Psychosis: Increased incidence of cerebrovascular adverse reactions (e.g. stroke, transient ischemic attack)
- Neuroleptic Malignant Syndrome: Manage with immediate discontinuation and close monitoring
- Tardive dyskinesia: Discontinue if clinically appropriate
- Metabolic changes: Monitor for hyperglycemia/DM, dyslipidemia & weight gain
- Leukopenia, neutropenia, and agranulocytosis: Perform CBC in patients with pre-existing low WBC or h/o leukopenia / neutropenia. Consider discontinuing Rexulti if a clinically significant decline in WBC occurs in absence of other causative factors
- Orthostatic hypotension and syncope: Monitor HR / BP & warn patients with known cardiovascular or cerebrovascular disease, and risk of dehydration or syncope
- Seizures: Use cautiously in patients with a h/o seizures or with conditions that lower seizure threshold

Use in specific populations

- Pregnancy: May cause extrapyramidal and/or withdrawal symptoms in neonates with 3rd trimester exposure
- Safety and efficacy have not been established in pediatric patients

Clinical trials

- MDD – Brexpiprazole was compared to placebo in two 6-week, randomized, double blind trials in a total of 980 adults (18-65 yo) that had not responded adequately to prior antidepressant therapy
    - In one trial, mean improvements in the primary end point, the Montgomery-Asberg Depression Rating Scale (MADRS) scores were significantly greater with brexpiprazole 2 mg/d than with placebo (8.4 vs 5.2 points)
    - In the other trial, improvement was numerically greater with brexpiprazole 3 mg/d and 1 mg/d than with placebo (8.3 and 7.6 vs 6.3 points), but statistical significance was not established
- Schizophrenia – Brexpiprazole was compared to placebo in two 6-week, randomized, double blind trials in a total of 1076 adults (18-65 yo)
    - In one trial, mean improvements in the primary end point of the Positive and Negative Syndrome Scale (PANSS) scores for brexpiprazole were significantly greater with both 2 mg/d (20.7 points) and 4 mg/d (19.7 points) than with placebo (12.0 points)
    - In a 2nd trial, improvement was significantly greater with 4 mg/d (20.0 points), but not with 2 mg/d (16.6 points), compared to placebo (13.5 points)
- Adverse effects occurring in ≥5% of subjects taking brexpiprazole and more frequently than in those taking placebo in at least one clinical trial included akathisia, weight gain, headache, and somnolence. Mean weight gain over 6 weeks was 1.0-1.3 kg greater with brexpiprazole 2 mg/d compared with placebo

Role in Therapy

- Brexpiprazole is a partial agonist/antagonist, similar to aripiprazole but with different binding profile to dopamine D_2, serotonin5-$HT_{1A,}$ 5-HT_{2A} and noradrenaline alpha 1B/2C receptors
- Brexpiprazole was more effective than placebo in short-term trials in reducing symptoms of schizophrenia and depression; it is FDA approved for both indications
- Direct comparisons with other antipsychotics are lacking, and long-term safety is unknown
- Brexpiprazole appears to be generally well tolerated with relatively low side effect profile; it appears to have decreased akathisia but increased weight gain compared to aripiprazole, see chart below

Drug	Diabetes	Weight Gain	Extrapyramidal Symptoms	QTc Interval Prolongation	Elevated Prolactin
Aripiprazole	+/−	+	++	+/−	−
Asenapine	+	++	++	+	++
Brexpiprazole*	+	++	+	−	+/−
Clozapine	++++	++++	+/−	+	+/−
Iloperidone	++	++	+/−	++	+/−
Lurasidone	+/−	+/−	++	+/−	+/−
Olanzapine	++++	++++	+	+	+
Paliperidone	++	+++	+++	+	+++
Quetiapine	++	+++	+/−	+	+/−
Risperidone	++	+++	+++	+	+++
Ziprasidone	+/−	+/−	−	++	+

Formulary Recommendation:

- Add to formulary as PA required; Tier 2 in CA/CMC
- Approval criteria:
    - two previous documented trials of generic atypical antipsychotics in schizophrenia
    - one previous documented trial of generic atypical antipsychotic in adjunctive treatment of major depression (in addition to antidepressants)