PDL DRUG REVIEW

Proprietary Name: Rexulti®
Common Name: brexpiprazole
PDL Category: Antipsychotics-Atypical

Comparable Products	Preferred Drug List Status
Abilify	Preferred Step 2

Summary

Indications and Usage: For adjunctive treatment of major depressive disorder (MDD) AND treatment of schizophrenia. Rexulti® is not approved for the treatment of patients with dementia-related psychosis. The safety and efficacy of use in children younger than 18 years with the other indications have not been established. While there is no pregnancy category listed for this product, the risk summary indicates that neonates whose mothers are exposed to antipsychotics, like Rexulti®, during the 3rd trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms. It is recommended to monitor neonates for extrapyramidal and/or withdrawal symptoms and manage appropriately.

Dosage Forms: Tablets: 0.25mg, 0.5mg, 1mg, 2mg, 3mg, 4mg

Recommended Dosage: *Adjunct for MDD:* 0.5-1mg QD, then titrate to target dose of 2mg to a max of 3mg. *Schizophrenia*: 1mg QD days 1-4 to then titrate to 2mg QD day 5-7 then 4mg QD on day 8 per clinical response and tolerability.

The maximum recommended dose is 2mg for MDD and 3mg for schizophrenia in patients with moderate to severe hepatic impairment and for patients with moderate, moderate, or end-stage renal impairment.

Drug Interactions: Reduce the dose of Rexulti® if use concomitantly with strong CYP3A4 inhibitors (such as itraconazole, clarithromycin, or ketoconazole), if use with strong CYP2D6 inhibitors (such as paroxetine, fluoxetine, or quinidine), CYP2D6 poor metabolizers, known CYP2D6 poor metabolizers taking a strong or moderate CYP3A4 inhibitor, or if use with both CYP3A4 and CYP2D6 inhibitors (such as itraconazole plus quinidine or fluconazole plus paroxetine). Increase the dose of Rexulti® if use concomitantly with strong CYP3A4 inducers (such as rifampin or St. John's wort).

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Rexulti®) minus reported % incidence for placebo in schizophrenia trials. Please note that an incidence of 0% means the incidence was the same or that the active drug was less than placebo.* The most frequently reported adverse events included dyspepsia (1%), diarrhea (1%), weight increased (2%), blood creatinine phosphokinase increased (1%), akathisia (1%), tremor (2%), sedation (1%), and EPS-related adverse events excluding akathisia (1%).

Rexulti® has a boxed warning regarding increased mortality in elderly patients with dementia-related psychosis when treated with antipsychotic drugs, as well as an increased risk of suicidal thoughts and behaviors.

Rexulti® should be used with caution in those with a history of seizures or with conditions that potentially lower the seizure threshold.

Weight gain is reported with most antipsychotics. In schizophrenia clinical trials with Rexulti®, the 4mg dose had a mean change from baseline of +1.2kg as compared with +0.2kg with the placebo group. In addition, 10% of the 4mg group had a ≥7% increase in body weight at any visit as compared with 4% of the placebo group. Other metabolic changes such as hyperglycemia and dyslipidemia were also assessed. Shifts in fasting glucose were similar between Rexulti® and placebo, as well as changes in fasting total cholesterol, LDL-cholesterol, and HDL cholesterol.

Leukopenia and neutropenia have both been reported in clinical trials and/or post-marketing reports with Rexulti®. It is recommended to monitor for clinically significant neutropenia and discontinue treatment with severe neutropenia.

Contraindications: Known hypersensitivity to brexpiprazole or any component of the compound

Manufacturer: Otsuka America Pharmaceuticals

Analysis: Brexpiprazole, the active ingredient of Rexulti®, is an atypical antipsychotic with efficacy that may be mediated through a combination of partial agonist activity at serotonin 5-HT1A and dopamine D2 receptors, and antagonist activity at serotonin 5-HT2A receptors. Four randomized, double-blind, placebo-controlled 6-week studies were performed to assess the safety and efficacy as adjunctive treatment of MDD and as treatment for schizophrenia (2 studies for each indication).

For the MDD studies, Rexulti® 2mg was used in study 1 and Rexulti® 1mg or 3mg was used in study 2. The primary endpoint was the change from baseline to week 6 in the Montgomery-Asberg Depression Rating Scale (MADRS), a 10-item clinician-related scale used to assess the degree of depressive symptomatology (0=no symptoms, 60=worst symptoms). At randomization, the MADRS total score was 27. In both studies, Rexulti® 2mg and 3mg tablets (plus antidepressants) were superior to placebo (plus antidepressants) for reducing the mean MADRS total score. Results are shown in the table below.

	Trial 1		Trial 2		
Primary efficacy endpoint: MADRS	Rexulti® 2mg	placebo	Rexulti® 1mg	Rexulti® 3mg	placebo
Mean baseline Score	26.9	27.3	26.5	26.5	26.5
Least-square (LS) mean change from baseline	-8.4	-5.3	-7.6	-8.3	-6.3
Placebo-subtracted difference	-3.2	-	-1.3	-2.0	-

The schizophrenia trials used Rexulti® 2mg or 4mg, and the primary endpoint was the change from baseline to week 6 in the Positive and Negative Syndrome Scale (PANSS) total score (ranges from 30 which is the best to 210 which is the worst). Results suggested that Rexulti® 2mg and 4mg tablets were superior to placebo on the PANSS total score in study 1; only Rexulti® 4mg tablets was superior to placebo in study 2. Results are shown in the table below.

	Trial 1			Trial 2		
Primary efficacy endpoint: PANSS total score	Rexulti® 2mg	Rexulti® 4mg	placebo	Rexulti® 2mg	Rexulti® 4mg	placebo
Mean baseline Score	95.9	94.7	95.7	96.3	95.0	94.6
Least-square (LS) mean change from baseline	-20.7	-19.7	-12.0	-16.6	-20.0	-13.5
Placebo-subtracted difference	-8.7	-7.6	-	-3.1	-6.5	-

Place in Therapy: Rexulti® is an atypical antipsychotic indicated for the treatment of schizophrenia and as adjunctive treatment for MDD. It was found to be superior to placebo for these indications (but not the 1mg when assessed as adjunctive treatment for MDD). There are currently no comparator studies with other atypicals.

There is no evidence at this time to support that Rexulti® is more efficacious or safer than the currently available, more cost effective medications, per data from the registration trials in the package insert. It is therefore recommended that Rexulti® remain non-preferred and require prior authorization and be available to the few who are unable to tolerate or have failed on any preferred medications.

PDL Placement:

- ☐ **Preferred**
- ☒ **Non-Preferred Step 3**
- ☐ **Preferred with Conditions**

References

[1] Rexulti [package insert]. Rockville, MD: Otsuka America Pharmaceutical, Inc; 2015.