Pr REXULTI® brexpiprazole tablets

CANMAT RECOMMENDS 1ST LINE ADJUNCTIVE THERAPY OPTION BREXPIPRAZOLE

For patients with an inadequate response to antidepressant treatment during the current episode of MDD[1,2]*

PrREXULTI® is indicated for use as an adjunct to antidepressants for the treatment of major depressive disorder (MDD) in adult patients with an inadequate response to prior antidepressant treatments during the current episode.[3]

RESEARCH ARTICLE

Efficacy and safety of adjunctive brexpiprazole 2 mg in major depressive disorder: A phase 3, randomized, placebo-controlled study in patients with inadequate response to antidepressants

Michael E. Thase, MD; James M. Youakim, MD; Aleksandar Skuban, MD; Mary Hobart, PhD; Carole Augustine, MA; Peter Zhang, PhD; Robert D. McQuade, PhD; William H. Carson, MD; Margaretta Nyilas, MD; Raymond Sanchez, MD; and Hans Eriksson, MD[4]

CANMAT: Canadian Network for Mood and Anxiety Treatments.

* See guidelines for complete recommendations.

Simple once-daily dosing options for your patients

Recommended dosing with a flexible titration schedule[3]

Option A

1. Initiate with

1 week

1 week

2. Achieve recommended target dose/Maximum dose of

Option B

1. Initiate with

1 week

2. Achieve recommended target dose/Maximum dose of

Adapted from Product Monograph

[Pr]REXULTI® is taken orally, with or without food.

- Dosage increases should occur at weekly intervals based on the patient's clinical response and tolerability. Periodically reassess to determine the continued need and appropriate dose for treatment.
- The required length of adjunctive treatment with REXULTI is unknown. When prescribed as an adjunct to antidepressants in the treatment of MDD, REXULTI should be used for the shortest period of time that is clinically indicated.

Please consult the Product Monograph for full dosing information.

Important safety information

Clinical use:

When considering the use of REXULTI as adjunctive treatment in MDD, clinicians must take into account the safety concerns associated with antipsychotic drugs, a class of drugs to which REXULTI belongs. Safety concerns of this class include: weight gain; hyperlipidemia; hyperglycemia; tardive dyskinesia; and neuroleptic malignant syndrome. REXULTI should only be prescribed in patients with MDD by clinicians who are aware of the importance and are experienced in the early detection and management of the safety issues associated with this class of drugs.

The efficacy and safety of REXULTI in the adjunctive treatment of MDD were demonstrated in 6-week, double-blind, placebo-controlled trials in adult patients. Therefore, the required length of adjunctive treatment with REXULTI is not known. When prescribed as an adjunct to antidepressants in the treatment of MDD, REXULTI should be used for the shortest period of time that is clinically indicated. It is not known whether efficacy in adjunct treatment is due to REXULTI alone or from combined treatment with an antidepressant.

- The safety and efficacy of REXULTI have not been systematically evaluated in MDD patients ≥65 years of age. Use caution when treating geriatric patients.
- REXULTI is not indicated in pediatric patients (<18 years) and its use is not recommended in this population.

The PYXIS trial

Objective

To assess the efficacy, tolerability profile and safety profile of PrREXULTI® (fixed-dose 2 mg/day) as adjunctive therapy to antidepressant treatments in patients with MDD and an inadequate response to antidepressants.[4]*

1–4 weeks

SCREENING

Inclusion criteria[3]

- Adult patients
- MDD (DSM-IV-TR criteria), with or without symptoms of anxiety
- Inadequate response (patient-reported) to 1–3 prior antidepressant treatment(s) in current episode

8 weeks

PROSPECTIVE PHASE (SINGLE-BLIND)

Antidepressant + placebo

- Antidepressant treatments used in prospective treatment phase:
  - Escitalopram
  - Fluoxetine
  - Paroxetine CR
  - Sertraline
  - Duloxetine
  - Venlafaxine XR
- Inadequate response during 8 weeks of prospective antidepressant treatment defined as:
  - HAMD-17 improvement of <50% from baseline and HAMD-17 score ≥14 at week 8
  - CGI-I ≥3 at week 8

Patients showed an inadequate response to various antidepressant treatments before the randomized phase[2]

Selected baseline patient demographics[4]

	Antidepressant + REXULTI (n=188)	Antidepressant + placebo (n=191)
Age (mean)	44.1 years	45.2 years
Female sex	69.1%	71.7%
Duration of current episode	13.5 months	13.7 months
Recurrent episodes	88.8%	89.5%
Number of lifetime episodes	3.8	3.8
MADRS Total score	26.6	27.1
SDS Mean score	6.0	6.3

Adapted from Thase *et al.*

An adjunctive treatment for Major Depressive Disorder with demonstrated efficacy

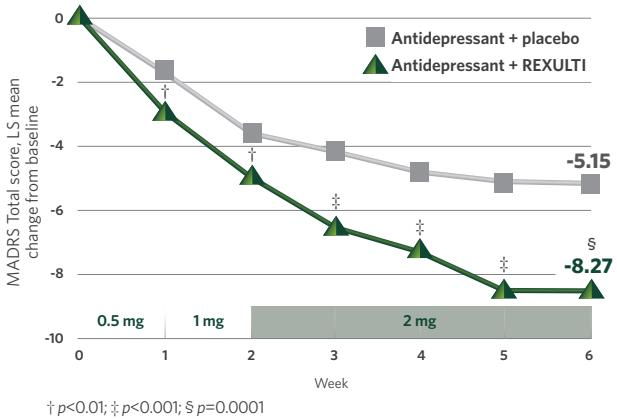
A randomized, double-blind, 6-week fixed-dose study in patients with inadequate response to antidepressant monotherapy[3]

6 weeks

RANDOMIZED PHASE (DOUBLE-BLIND)

Primary Endpoint

Improved depression symptoms, as measured by MADRS at week 6 (clinician-rated)[3,4]



† $p<0.01$; ‡ $p<0.001$; § $p=0.0001$

3.12-point
greater reduction for patients treated with antidepressant + PrREXULTI® vs. antidepressant + placebo at week 6

Baseline MADRS Total score, antidepressant + placebo: 27.14, n=191; antidepressant + REXULTI: 26.61, n=187

Adapted from Product Monograph and Thase *et al.* (incl. Supplementary Material)

Depressive symptoms were measured using the Montgomery-Åsberg Depression Rating Scale (MADRS) Total score, a physician-administered questionnaire that rates patients' symptoms on a scale from 0 to 6 across 10 items, with higher values reflecting more severe symptoms:

- **Apparent sadness**
- **Reported sadness**
- **Inner tension**
- **Reduced sleep**
- **Reduced appetite**
- **Concentration difficulties**
- **Lassitude**
- **Inability to feel**
- **Pessimistic thoughts**
- **Suicidal thoughts**

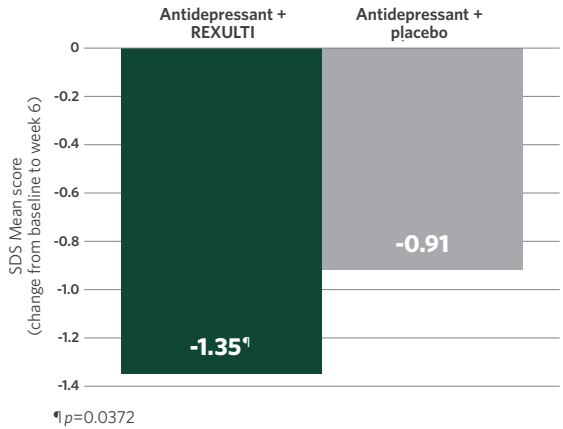
DSM-IV-TR: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision; CR: controlled-release; XR: extended-release; HAMD-17: 17-item Hamilton Depression Rating Scale; CGI-I: Clinical Global Impression of Improvement; MADRS: Montgomery-Åsberg Depression Rating Scale; LS: least squares; SDS: Sheehan Disability Scale.

* Defined as <50% improvement from baseline on the HAMD-17, a HAMD-17 score ≥14 at week 8, and a CGI-I ≥3.

The efficacy of [Pr]REXULTI® in the adjunctive treatment of MDD was evaluated in over 187 patients.[3]

Key Secondary Endpoint

Demonstrated improvement in functioning at week 6[3,4]



Statistically significant greater improvement in SDS Mean score for patients treated with antidepressant + REXULTI (2 mg/day) than with antidepressant + placebo at week 6

Adapted from Product Monograph and Thase *et al.* Supplementary Material

As measured by the Sheehan Disability Scale (SDS), a 3-item self-rated instrument used to assess functional impairment in three domains, with higher values reflecting greater impairment:[3,5]

- **Work/School**
- **Social life**
- **Family life**

The social life and family life domains showed improvement for patients taking antidepressant + REXULTI (2 mg/day) vs. antidepressant + placebo ($p<0.05$) while the work/school domain did not.

	Antidepressant + REXULTI	Antidepressant + placebo	*P*-value
Work/School	-1.09	-0.90	0.4771
Social life	-1.54	-1.04	0.0323
Family life	-1.33	-0.73	0.0129

Adapted from Thase *et al.* Supplementary Material

Demonstrated safety profile

Safety and tolerability profile[3]

Treatment-emergent adverse events (TEAEs) with incidence of ≥5% in any antidepressant + PrREXULTI® dose group (1 to 2 mg) and greater than antidepressant + placebo group in short-term phase 3 clinical trials[3]			
	Antidepressant + REXULTI (mg/day)		Antidepressant + placebo (n=819)
	1 mg (n=226)	2 mg (n=380)	
Akathisia	4%	8%	3%
Fatigue	3%	2%	1%
Headache	9%	4%	6%
Nasopharyngitis	7%	3%	3%
Restlessness	2%	6%	1%
Somnolence	4%	5%	1%
Tremor	4%	2%	1%
Weight increase	7%	7%	2%

Adapted from Product Monograph

Most cases of akathisia were assessed as mild or moderate in severity, and, in the fixed-dose studies, were dose-dependent. Discontinuations due to akathisia were reported only for REXULTI-treated patients (0.3% for antidepressant + REXULTI 2 mg/day).

Selected adverse events in short-term (6 weeks) Phase 3 clinical trials[3]

Weight change

	Antidepressant + REXULTI (mg/day)		Antidepressant + placebo (n=819)
	1 mg (n=225)	2 mg (n=379)	
Mean change in weight	+1.3 kg	+1.6 kg	+0.3 kg
Incidence of ≥7% weight increase	4.9%	4.5%	1.8%

Adapted from Product Monograph

Antipsychotic drugs have been associated with metabolic changes, including weight gain. Clinical monitoring of weight is recommended.

Important safety information

Most serious warnings and precautions:

Increased mortality in elderly patients with dementia: Elderly patients with dementia treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of 13 placebo-controlled trials with various atypical antipsychotics (modal duration of 10 weeks) in these patients showed a mean 1.6-fold increase in the death rate in the drug-treated patients. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature.

Other relevant warnings and precautions:

- Body temperature regulation
- Risk of falls and somnolence
- Contains lactose
- Orthostatic hypotension
- Risk of QT prolongation
- Evaluate patients for a history of drug abuse
- Driving and operating machinery
- Reports of hyperglycemia and diabetic ketoacidosis
- Weight gain
- Dyslipidemia
- Hyperprolactinemia
- Priapism
- Risk of leukopenia/neutropenia
- Venous thromboembolism
- Serious hypersensitivity reactions
- Neuroleptic malignant syndrome
- Tardive dyskinesia
- Risk of seizures/convulsions
- Risk of suicide
- Risk of impulse-control disorders/compulsive behaviours
- Severe cutaneous adverse reactions
- Dysphagia
- Should not be used during pregnancy or breast-feeding
- Caution when used in geriatric patient populations due to potential increased risk of cerebrovascular adverse events, including fatalities
- Monitoring and laboratory tests: blood glucose, fasting lipid profile and body weight, complete blood count (CBC), white blood cell (WBC) and differential counts, prolactin and blood pressure, should be monitored at baseline and periodically throughout treatment

For more information:

Please consult the Product Monograph at www.rexultimonograph.ca for important information relating to adverse reactions, drug interactions, and dosing information, which have not been discussed in this piece. The Product Monograph is also available by calling us at **1-877-341-9245**.

Select features of the PYXIS trial

- A prospective phase where patients showed an **inadequate response to antidepressant treatment**.
- Efficacy evaluated in over 187 patients who fulfilled the DSM-IV-TR criteria for MDD, with or without symptoms of anxiety and with demonstrated inadequate response to 1–3 prior antidepressants in the current episode and an inadequate response during the prospective antidepressant trial phase.
- Significantly **greater reduction in depressive symptoms** as measured by MADRS Total score was observed in antidepressant + PrREXULTI® 2 mg/day compared to antidepressant + placebo at week 6.
- **Greater functional improvements** were shown with antidepressant + REXULTI vs. antidepressant + placebo in SDS Mean score (key secondary endpoint). Findings for the work/school domain vs. antidepressant + placebo were not statistically significant.

References: 1. Lam RW, Kennedy SH, Adams C, *et al.* Canadian Network for Mood and Anxiety Treatments (CANMAT) 2023 Update on Clinical Guidelines for Management of Major Depressive Disorder in Adults. *Can J Psychiatry.* 2024;1-47. **2.** CANMAT. Data on File. CANMAT Letter to PAAB. **3.** REXULTI Product Monograph. Otsuka Pharmaceutical Co., Ltd. **4.** Thase ME, Youakim JM, Skuban A *et al.* Efficacy and safety of adjunctive brexpiprazole 2 mg in major depressive disorder: A phase 3, randomized, placebo-controlled study in patients with inadequate response to antidepressants. *J Clin Psychiatry.* 2015;76(9):1224–1231 (incl. supplementary). **5.** Sheehan DV. Sheehan Disability Scale (SDS) – Overview. 1983.

Otsuka Lundbeck

OTS-REX-00104E

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REVIEWED BY PAAB

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