DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

Kateshia Brooks, Director
Otsuka Pharmaceutical Development and Commercialization, Inc.
2440 Research Blvd
Rockville, MD 20850

RE: NDA 205422
REXULTI® (brexpiprazole) tablets, for oral use
MA 772, 791

Dear Kateshia Brooks:

The Office of Prescription Drug Promotion (OPDP) of the U.S. Food and Drug Administration (FDA) has reviewed the promotional communications, a direct-to-consumer (DTC) television advertisement (TV ad), titled "REXULTI MDD 2023-B TV Ad - See the Signs" (11US22EBC0039) and DTC banner (banner), titled "2023 MDD Consumer Campaign Desktop Display Banners A" (11US23EBC0168) for REXULTI® (brexpiprazole) tablets, for oral use (Rexulti), submitted by Otsuka Pharmaceutical Development and Commercialization, Inc., (Otsuka) under cover of Form FDA 2253. The TV ad and banner make false or misleading claims and representations about the efficacy of Rexulti. Thus, the TV ad and banner misbrand Rexulti within the meaning of the Federal Food, Drug and Cosmetic Act (FD&C Act) and make its distribution violative. 21 U.S.C. 352(a), (n); 321(n); 331(a). *See* 21 CFR 202.1(e)(5). This violation is especially concerning because major depressive disorder (MDD), a debilitating and chronic illness, is a significant public health concern, and the promotional communications create a misleading impression regarding the effectiveness of Rexulti, a drug with multiple serious, potentially life-threatening or irreversible risks.

Background

Below are the indication and summary of the most serious and most common risks associated with the use of Rexulti.[1] According to the INDICATIONS AND USAGE section of the FDA-approved prescribing information (PI) (in pertinent part):

> Rexulti is indicated for:
>
> - Adjunctive treatment of major depressive disorder (MDD) in adults . . .

The PI for Rexulti contains boxed warnings regarding increased mortality in elderly patients with dementia-related psychosis and increased risk of suicidal thoughts and behaviors in patients aged 24 years and younger. Rexulti is contraindicated in patients with a known

[1] This information is for background purposes only and does not necessarily represent the risk information that should be included in the promotional communication(s) cited in this letter.

hypersensitivity to brexpiprazole or any of its components. In addition, the PI for Rexulti includes warnings and precautions regarding cerebrovascular adverse reactions including stroke in elderly patients with dementia-related psychosis, neuroleptic malignant syndrome, tardive dyskinesia, metabolic changes, pathological gambling and other compulsive behaviors, leukopenia, neutropenia, and agranulocytosis, orthostatic hypotension and syncope, falls, seizures, body temperature dysregulation, dysphagia, and potential for cognitive and motor impairment. The most common adverse reactions reported with Rexulti as an adjunctive treatment for major depressive disorder were weight increased, somnolence, and akathisia.

False or Misleading Claims about Efficacy

Prescription drug advertisements and labeling (promotional communications) misbrand a drug if they are false or misleading with respect to efficacy. The determination of whether a promotional communication is misleading includes, among other things, not only representations made or suggested in the promotional communication, but also the extent to which the promotional communication fails to reveal facts material in light of the representations made or with respect to consequences that may result from the use of the drug as recommended or suggested in the promotional communication.

The TV ad includes the following claim (in pertinent part):

- "When added to an antidepressant, REXULTI was proven to reduce depression symptoms 62% more than the antidepressant alone." (Voiceover, frames 8-9)

The banner also includes the following claims (in pertinent part):

- "When added to an antidepressant, Rexulti was proven to provide a 62% greater reduction in depression symptoms" (Frame 3)
- "When added to an antidepressant, Rexulti was proven to provide a 62% greater reduction in depression symptoms vs. the antidepressant alone." (Frame 4)

These claims overstate the efficacy of the drug by misrepresenting the efficacy profile of Rexulti. Specifically, these claims misleadingly suggest that a patient can expect to experience a 62% reduction (i.e., an improvement) in depression symptoms when added to an antidepressant (ADT) alone. However, this 62% reduction claimed is far greater than the reduction of 11.9% calculated based on the data from Study 1 for the 2 mg dose promoted in the TV ad and banner based on the population-level summary of the treatment effect, which is the difference in the changes from baseline in depression symptoms (as measured by the Montgomery-Asberg Depression Rational Scale [MADRS[2]] total score) between the two groups based on the prespecified primary analysis.

[2] The MADRS is a 10-item clinician-related scale used to assess the degree of depressive symptomatology, with 0 representing no symptoms and 60 representing worst symptoms.

According to the CLINICAL STUDIES, Adjunctive Treatment of Major Depressive Disorder section of the PI, the primary endpoint evaluated in the two studies supporting Rexulti's use in the treatment of MDD was change from baseline to Week 6 in the MADRS. We note that the mean MADRS total score was 27 at randomization. According to Table 12, in Study 1, the least-squares mean change from baseline for the primary endpoint was -8.4 for the Rexulti (2 mg/day) + ADT treatment group compared to -5.2 for placebo + ADT, with a placebo-subtracted difference of -3.2 (95% unadjusted confidence interval [CI]: -4.9, -1.5). Therefore, upon comparison with mean baseline, the placebo-subtracted difference of -3.2 equates to a reduction in depression symptoms of 11.9% from the mean baseline of 27 (3.2 divided by 27), far less than the 62% reduction claimed in the TV ad and banner.

Furthermore, although the TV ad and banner promote the 2 mg tablet, we applied the above analysis from Study 1 to Study 2 to more fully consider the claims made. According to the PI, Study 2 evaluated a 1 mg/day and 3 mg/day dose of Rexulti + ADT versus placebo + ADT for the adjunctive treatment of MDD. Like Study 1, patients in Study 2 did not reach the 62% reduction claimed. According to Table 12, in Study 2, the least-squares mean change from baseline for the primary endpoint was -7.6 for the Rexulti (1 mg/day) + ADT treatment group compared to -6.3 for placebo + ADT, with a placebo-subtracted difference of -1.3 (95% CI: -2.7, 0.1). The placebo-subtracted difference of -1.3 equates to a change of 4.8% from the mean baseline of 27 (1.3 divided by 27). The least-squares mean change from baseline for the primary endpoint was -8.3 for the Rexulti (3 mg/day) + ADT treatment group compared to -6.3 for placebo + ADT, with a placebo-subtracted difference of -2.0 (95% CI: -3.4, -0.5). The placebo-subtracted difference of -2.0 equates to a change of 7.4% from the mean baseline of 27 (2.0 divided by 27). Therefore, as with Study 1, data from Study 2 also demonstrated a significantly lower reduction in depression symptoms from the mean baseline (4.8% and 7.4%, respectively, as measured by MADRS) than the 62% reduction claimed in the TV ad and banner.

OPDP acknowledges that the TV ad and banner include the SUPER "Individual results may vary" (in pertinent part; TV ad, frame 9; banner, frame 4). However, this does not mitigate the misleading impression created by the promotional communications of the magnitude of benefit that patients can expect when taking Rexulti and an ADT.

Conclusion and Requested Action

For the reasons discussed above, the TV ad and banner misbrand Rexulti within the meaning of the FD&C Act and make its distribution violative. 21 U.S.C. 352(a), (n); 321(n); 331(a). *See* 21 CFR 202.1(e)(5).

This letter notifies you of our concerns and provides you with an opportunity to address them. OPDP requests that Otsuka cease any violations of the FD&C Act. Please submit a written response to this letter within 15 working days from the date of receipt, addressing the concerns described in this letter, listing all promotional communications (with the 2253 submission date) for Rexulti that contain representations like those described above, and

explaining any plan for discontinuing use of such communications, or for ceasing distribution of Rexulti.

If you believe that your product is not in violation of the FD&C Act, please include in your submission to us your reasoning and any supporting information for our consideration within 15 working days from the date of receipt of this letter.

The concerns discussed in this letter do not necessarily constitute an exhaustive list of potential violations. It is your responsibility to ensure compliance with each applicable requirement of the FD&C Act and FDA implementing regulations.

Please direct your response to the undersigned at the **Food and Drug Administration, Center for Drug Evaluation and Research, Office of Prescription Drug Promotion, 5901-B Ammendale Road, Beltsville, Maryland 20705-1266**. A courtesy copy can be sent by facsimile to (301) 847-8444. Please refer to MA 772 and 791 in addition to the NDA number in all future correspondence relating to this particular matter. All correspondence should include a subject line that clearly identifies the submission as a Response to Untitled Letter. You are encouraged, but not required, to submit your response in eCTD format. All correspondence submitted in response to this letter should be placed under eCTD Heading 1.15.1.6. Additionally, the response submission should be coded as an Amendment to eCTD Sequence 0596 under NDA 205422. Questions related to the submission of your response letter should be emailed to the OPDP RPM at CDER-OPDP-RPM@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Sapna Shah, PharmD
Team Leader
Division of Advertising & Promotion Review 2
Office of Prescription Drug Promotion

{See appended electronic signature page}

Aline Moukhtara, RN, MPH
Team Leader
Division of Advertising & Promotion Review 1
Office of Prescription Drug Promotion

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SAPNA SHAH
10/31/2023 01:43:07 PM

ALINE M MOUKHTARA
10/31/2023 01:45:27 PM