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205422Orig1s009

OTHER REVIEW(S)

Clinical Outcome Assessment Review Memorandum

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To	Division of Psychiatry
COA tracking number	C2022416
NDA#	205422 S-009
Drug Applicant	Otsuka Pharmaceutical Company, Ltd.
Meeting type	Advice Letter
Indication:	Agitation in Alzheimer's Disease
Care Giver Reported Outcome (ObsRo)	Cohen-Mansfield Agitation Inventory
Clinician Reported Outcomes (ClinRO)	Clinician Global Impression of Change (CGI-C) Clinician Global Impression of Severity (CGI-S)

I. Executive Summary

This memo is in response to the clinical outcome assessment (COA) consult request filed in DARRTS by Division of Psychiatry (DP) on December 13th, 2022 [DARRTS Reference ID # 5093603] for NDA 205422 regarding Rexulti[1] for the treatment of Agitation in Alzheimer's disease (AAD).

This COA consult response is specifically related to DP's request to provide input regarding the CMAI total score as a single measure of agitation, and the clinically meaningful change observed on the CMAI instrument[2] used in pivotal studies 283 and 213, as laid out in the CMAI meaningful change report provided by the Applicant.

Table 1. Proposed COA(s) or COAs Included in Studies 283, 284, 213

COA Name (COA Type)	Concept(s)	Endpoint Position[3]	Copy of COA
CMAI (ObsRO)	Frequency of Agitation	Primary	Appendix A

[1] Brexpiprazole (REXULTI) is an atypical antipsychotic drug exhibiting partial agonist activity at 5-HT1A and D2 and antagonist activity at 5-HT2A which is approved for treatment of schizophrenia and adjunctive treatment of major depressive disorder (MDD).

[2] While CMAI developers do not recommend the use of a total score, DP agreed to its use for this Applicant's program in 2012 at the Applicant's Pre-IND Meeting November 6, 2012.

COA Name (COA Type)	Concept(s)	Endpoint Position[3]	Copy of COA
GGI-S (ClinRO)	Current state of Mental Illness related to Agitation	Secondary	Appendix A
CGI-I (ClinRO)	Current state of Total Improvement in Agitation	Secondary	Appendix A

ClinRO= Clinician-reported outcome; **ObsRO**= Observer-reported outcome

This review concludes the following:

The evidence submitted by the Applicant demonstrates that, in Study 283 and Study 213, patients in the REXULTI 2 mg group and patients in the REXULTI 2 mg/3 mg group, respectively, showed numerically improved Factor 1 (aggressive behavior), Factor 2 (physically non-aggressive behavior), and Factor 3 (verbal agitation) scores compared to the placebo group at Week 12 in a supplementary analysis to examine the magnitude and direction of CMAI subscale response. Additionally, no single factor was found to overly influence the CMAI total score.

Misaligned attributes between the anchor scales and the CMAI along with potential interpretability issues with the CGI-S, lend less confidence in the anchor-based and supplemental analyses (see section IV Global Assessments below). The qualitative data support that a change in the frequency of agitated behaviors is meaningful to caregivers. However, caregivers varied individually regarding the change in the frequency of a specific behavior they would consider to be meaningful, and these findings appeared to be distributed across factors, rather than clustered within a specific Factor (see Appendix B). No qualitative data was provided regarding change considered to be meaningful to patients.

Taking into consideration the limitations of the anchor scales, and upon review of the qualitative and quantitative evidence, it is reasonable to conclude that patients treated with REXULTI 2 mg and REXULTI 2 mg/3 mg experienced a meaningful improvement in the frequency of agitation behaviors compared to those treated with placebo. Conclusions regarding Study 283 efficacy results could not be established.

Recommendations for Future Studies

For future clinical trials in this indication, we recommend that sponsors explore multiple anchors (e.g., current state global impression rating scale, global impression of change scale), including caregivers, to provide an accumulation of evidence to help interpret a clinically meaningful within-patient score change (can also be a range) in the COA endpoint score. The selected anchors should target the concept(s) in the corresponding efficacy endpoints and the recall period should correspond to the assessment interval of the endpoint. Sponsors should submit exact copies of the anchor scales for Agency review and concurrence prior to implementing them in the planned clinical trial(s). Sponsors should also provide evidence for what constitutes a meaningful change on the anchor scale(s).

Other Recommendations:

- Conduct confirmatory factor analysis as recommended by the developers to confirm the proposed factor structure
- Provide considerations for weighting a summed score as recommended by the developers (e.g., use of disruptiveness scale)
- Provide explicit interpretation of scoring

Targeted Clinical Outcome Assessment-Related Labeling Claim(s)

Table 14: Change in CMAI Total Score* from Baseline at Week 12 in Patients with Agitation Associated with Alzheimer's Dementia (Study 6 and Study 7)

Study	Treatment Group	N	Mean Baseline Score (SD)	LS Mean Change (SE)	(b) (4) Difference** (95% CI)
6	REXULTI 1 mg/day	134	70.5 (16.0)	-17.6 (1.3)	0.2 (-3.4, 3.9)
	REXULTI 2 mg/day†	138	71.0 (16.6)	-21.6 (1.3)	-3.8 (-7.4, -0.2)
	Placebo	131	72.2 (17.9)	-17.8 (1.3)	—
7	REXULTI 2 mg/day or 3 mg/day†	225	80.6 (16.6)	-22.6 (1.1)	-5.3 (-8.8, -1.9)
	Placebo	116	79.2 (17.5)	-17.3 (1.4)	—

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: unadjusted confidence interval
*Difference (drug minus placebo) in least-squares mean change from Baseline
†Dosages statistically significantly superior to placebo

(b) (4)

Factor 1 (aggressive behavior), Factor 2 (physically non-aggressive behavior), and Factor 3 (verbal agitation) scores (b) (4) no single factor overly influenced the CMAI total score.

The efficacy of REXULTI in the treatment of agitation associated with Alzheimer's dementia (AAD) was demonstrated in two 12-week, randomized, double-blind, placebo-controlled, fixed-dose studies (Study 6, NCT01862640 and Study 7, NCT03548584).

II. Regulatory Background

- Supplement 9 is a proposal of a new treatment indication (fast track given under IND 155960 in March 2015 to address an unmet medical need).
- Denied breakthrough therapy designation November 2017.
- COR-BLAMEET-05 (Finalized 9/15/17) The Division informed the Applicant that studies 283 and 284 combined results were "not statistically persuasive" and that an sNDA based on these data "would likely result in a refuse to file action." The Division

recommended that the Sponsor conduct a third phase 3 study (12-week, three-arm, fixed-dose, double-blind, placebo-controlled trial including one arm with a higher dose than previously studied (i.e., 3 mg)).

III. Trial Design and Study Endpoints

Studies 283 and 284 were two 12-week, double blind, placebo-controlled studies (331-12-283 and 331-12-284) enrolling a total of 701 individuals with AAD. Trial 331-12-283 was a fixed dose study (1 mg/day and 2 mg/day brexpiprazole) with 432 total subjects; Trial 331-12-284 was a flexible-dose study (0.5 to 2 mg/day brexpiprazole) with 269 subjects. Both studies used the Cohen-Mansfield Agitation Inventory (CMAI) as the primary outcome measure. In Trial 331-12-283, brexpiprazole 2 mg/day was statistically superior to placebo in reducing CMAI scores, but brexpiprazole 1 mg/day was not. In Trial 331-12-284, there was no statistically significant difference between flexibly dosed brexpiprazole and placebo. Post hoc analyses using subjects from study 283 from the 2mg/day brexpiprazole group who exhibited ≥ one aggressive behavior occurring several times per week, demonstrated greater improvement than the intent-to-treat population on the CMAI total score (4.04, p = 0.0255). Post hoc analysis for study 284 demonstrated that the brexpiprazole treatment groups vs. placebo appeared, via numerical improvements, to demonstrate a greater effect on the aggressive behavior factor (BREX: -1.09).[4]

Trial 331-14-213 was a 12-week, double-blind, placebo-controlled phase 3 trial to include patients with a diagnosis of agitation that met the International Psychogeriatric Association's (IPA) provisional consensus definition. Given efficacy was observed in subjects who exhibited sufficient aggressive behavior at Baseline in Trial 331-12-283 and 331-12-284, subjects eligible to enroll in Trial 331-14-213 had to have CMAI Factor 1 aggressive behavior at Baseline,defined as subjects must have ≥ one aggressive behavior occurring several times per week. The schedule of assessments was the similar for each clinical trial (see Table 1).

Table 1. Schedule of COA Assessments Clinical Trials 283, 284 and 213

Table 1. Schedule of clinical outcome assessments for the trials

COA	Visit							
	Screening D-42 to -2	Baseline D0	W2 D15	W4 D29	W6 D43	W8 D57	W10 D71	W12 D85
CMAI	X	X	X	X	X	X	X	X
CGI-S	X	X	X	X	X	X	X	X
CGI-I			X	X	X	X	X	X

Source: Meaningful within-patient change analysis based on the Cohen-Mansfield Agitation Inventory Statistical Analysis Plan (SAP) V2.0, 25 February 2021, p. 9/78.

[4] Source: 21 Sept 2017 Type-C Briefing document Section 10.2.2.2

Reviewer's comment(s)
According to the regulatory background, there were no further communications to the Applicant regarding the acceptability of the CMAI total score as the primary endpoint. However, in other similar reviews to DP, DCOA advised that the developers of the CMAI did not intend to use the total score, indicating it was "not useful" and recommended the use of a composite score (3 Factors), demonstrating significant change in at least 1 factor, and no worsening in the other two (Oct 29, 2015, Chen, DARRTS Reference ID: 3840377). Further, DCOA cautioned that use of a total score creates a risk that changes may not be detected: "If you choose to use the CMAI total score, we would request analyses on individual subscales, and the findings could shape product labeling, if approved." NON-RESPONSIVE

Previous DP Comments to the Applicant related to use of CMAI Total Score:

PIND 115960 Meeting Minutes November 6, 2012, DARRTS Reference ID: 3217349

> ***Question 2: The sponsor would like to explore the feasibility of achieving the proposed indication, using the corresponding primary endpoint: a) The CMAI total score to assess brexpiprazole for the treatment of agitation in patients diagnosed with dementia of the Alzheimer's type. b)*** (b) (4)
>
> ***Does the Agency agree that the choice of primary endpoint is acceptable for achieving the proposed indication?***
>
> *On face, these measures should be acceptable for these different targets, however, as noted in comments for question 1, we recommend that you select the specific entity [i.e., CMAI factor score] you wish to pursue in your development program. Pilot work might be helpful in deciding on which entity to target. Please provide details on who will perform the CMAI ratings and how raters will be trained on using the CMAI.*

IND 115960_Chen, Sept 13, 2017_DARRT Reference ID: 4162355 Comments focused on (b) (4) *rather than use of the CMAI total score.*

Primary Endpoint(s) All Phase 3 Studies:
Change from Baseline to Week 12 in the CMAI total score.

Key Secondary Endpoint All Studies:
Change from Baseline to Week 12 in the Clinical Global Impression Severity of Illness (CGI-S) score, as related to agitation.

IV. COA Description(s)

Cohen Mansfield Agitation Inventory[5] (Appendix A)

[5] Cohen-Mansfield, Jiska, Marcia S. Marx, and Alvin S. Rosenthal. "A description of agitation in a nursing home." Journal of gerontology 44.3 (1989): M77-M84.

This ObsRO consists of 29 items assessing the frequency of agitated behaviors which is administered by trained clinician raters who interview caregivers. The agitated behaviors include physically aggressive behavior (e.g., hitting others), physically non-aggressive behavior (e.g., pacing), verbally aggressive behavior (e.g., swearing), and verbally non-aggressive behaviors (e.g., repetitive sentences). Each behavior is rated on a 7-point scale of frequency with higher ratings corresponding to higher frequency of the agitated behavior. Ratings pertain to the two weeks preceding the administration of the CMAI. The CMAI total score provided by the Applicant was a simple sum of the scores on all 29 items at the time of the assessment. Therefore, the range of possible total scores for each timepoint is 29 to 203 inclusive. If less than 24 items were recorded, the Applicant treated the measure as "unevaluable," if 24 to 28 of the 29 items were recorded, the total score was calculated as the mean of the recorded items multiplied by 29 and then rounded to the first decimal place.

Scoring of CMAI (CMAI Instruction Manual):
The Applicant proposed to use the factor structure proposed by Rabinowitz et al., 2005[6]. Four recognized factors (i.e., subscale domains) contribute to the CMAI total score as follows: Aggressive behaviors (12 items), Physically non-aggressive behaviors (6 items), Verbally agitated behaviors (4 items), and Hiding and hoarding (2 items); Other (5 items).

The developers indicate that totaling the 29 items is "not useful" and recommend:

- Select specific behaviors of interest for analysis (e.g., paces, aimless wandering or general restlessness)
- Select the three factors of agitation for analysis:
    - Aggressive behavior: Hitting, kicking, pushing, scratching, tearing things, cursing or verbal aggression, grabbing (biting, spitting).
    - Physically nonaggressive behavior: Pacing, inappropriate robing or disrobing, trying to get to a different place, handling things inappropriately, general restlessness, repetitious mannerisms.
    - Verbally agitated behavior: Complaining, constant requests for attention, negativism, repetitious sentences or questions, screaming.
- Not all agitative behaviors have the same meaning; aggregate the behaviors in a meaningful way (e.g., hiding things; hoarding things)
- Weight the scores based upon their level of disruptiveness, then total the score

Reviewer's Comment(s):

- *The summed score disallows evaluation of changes in factors/domains*
- *Equal weight is given to each item without respect to disruptiveness or other considerations*
- *The weight of each established factor on the total score is determined by the number of items located within each factor*
- *The frequency of agitated behaviors may vary between factors even within comparable levels of severity of illness*

[6] Rabinowitz, Jonathan, et al. "Factor analysis of the Cohen-Mansfield Agitation Inventory in three large samples of nursing home patients with dementia and behavioral disturbance." The American journal of geriatric psychiatry 13.11 (2005): 991-998.

Rating Instructions (CMAI Instruction Manual):

- If "pacing" occurred rarely at Week 1 and frequently at Week 2: average over the past 2 weeks and rate accordingly.
- If "pacing" would occur but is prevented (e.g., by physical restraints), then:
  - Add a separate category "8 – Would occur if not prevented" (analyze cases separately);
  - Estimate the frequency at which the behavior would occur if not prevented (i.e., hypothetical); or
  - Record the frequency at which it actually occurs when not prevented (observed).

Reviewer's comment(s)

- *A movement of 2 points can vary in meaningfulness, contingent upon the type of behavior and the starting point of frequency. For example, "Hitting" – any change would be meaningful due to the disruption/potential harm caused whereas a change in frequency in "General restlessness" from several times a week to less than once a week may not be meaningful. In other words, if the level of disruptiveness is minimal, the meaningfulness of the change may also be minimal.*
- *This reviewer notes that the disruptiveness scale was not included in the Applicant's implementation of the CMAI, and no weights were used in the CMAI scoring algorithm. Factor 1, aggressive behavior, contains 12 items, Factor 2 physically nonaggressive behavior contains 6 items, and Factor 3, verbally agitated behavior contains 4 items, providing proportional weights of .55, .27, and .18, respectively, when totaling the raw score. This scoring lends greater weight in the CMAI total score to physical aggression, followed by non-physical aggression, and then verbal agitation, respectively, as well as making certain implicit assumptions regarding the relationships among the items and between the subscale factors.*

Global Assessments (Appendix A)

CGI-S – A one-item measure that assesses the amount of mental illness "as related to agitation" in the patient's current state ("at this time"). The item stem is: "Considering your total clinical experience with this particular population, how mentally ill (as related to agitation) is the subject at this time?" Different degrees of mental illness are rated from 0 "not assessed," 1 "normal, not at all ill," 2 "borderline mentally ill," 3 "mildly ill," 4 "moderately ill," 5 "markedly ill," 6 "severely ill," 7, "among the most extremely ill subjects."

Reviewer's comment(s):

- *The attribute being measured using the CGI-S response scale - "mentally ill "- does not align with DSM 5 criteria for AD, which describes agitation as a "behavioral disturbance," opening the CGI-S to misinterpretation.*
- *The recall period used in the CGI-S (i.e., "at this time") is not aligned with the assessment period used to calculate the CMAI total score (i.e., past 14 days). This lack of alignment presents a challenge to interpreting anchor-based analyses using the CGI-S as an anchor scale for the CMAI total score, as the CGI-S reflects only current state (i.e., 1 of the 14 days included in the CMAI total score calculation). This approach implicitly assumes that the agitated behaviors are stable.*

- *The global assessments were not cognitively debriefed to provide evidence of interpretability and consistency across raters.*

CGI-I- A one-item measure that asks the clinician to "rate the total improvement (as related to agitation) **whether or not it is due entirely to drug treatment**. Compared to his/her condition at Baseline, how much has the patient changed?"

0 - Not assessed
1 - Very much improved
2 - Much improved
3 - Minimally improved
4 - No change
5 - Minimally worse
6 - Much worse
7 - Very much worse

Reviewer's comment(s):

- *The implied recall period used in the CGI-I (i.e., current state) is not aligned with the assessment period used to calculate the CMAI total score (i.e., past 14 days). This misalignment presents a similar interpretation challenge as noted in the comment above for the CGI-S.*
- *Multiple reference points for recall (improvement related to agitation, improvement related or not to drug treatment, improvement related to Baseline) may have created interpretation issues or inconsistencies among clinical respondents.*
- *An inspection of the global anchor data by the medical officer primary reviewer indicated that no "0's" (not assessed) were in the raw data, implying that all data were captured for the global anchors for treatment completers.*

V. Summary of Meaningful Change Analyses

The Applicant conducted separate anchor-based analyses using data from Study 283, Study 284 (did not meet trial objective), Study 213, pooled Studies 283 and 284, and pooled studies 283, 284, and 213. It is unclear what the Applicant's final meaningful within-patient change threshold range is as two different ranges were concluded in the Applicant's submission.

- The Applicant's CMAI Meaningful Change Analysis Report Version 3.0 concluded a range of -20 (based on pooled data from Studies 283 and 284) to -25 (based on data from Study 213) point-reduction in the CMAI total score.
- The Applicant's response (April 10. 2023) to FDA's information request (April 3, 2023) concluded a range of -15 to -25 point-reduction in the CMAI total score.

Of note, Study 284 did not meet its trial objective and in Study 283 the treatment differences did not reach statistical significance for either the BREX 1-mg (LSMD = 0.09, p = 0.4440) or BREX 2-mg arm for the key secondary efficacy endpoint, mean change in CGI-S score as related to agitation from Baseline to Week 12 (LSMD = -0.16, p = 0.1566). Further, the target patient population for Study 213 was changed based on the outcome of Studies 283 and 284

and the post hoc analysis of Baseline severity subsets (i.e., patients who exhibited ≥ one aggressive behavior occurring several times per week). Therefore, FDA's evaluation of clinically meaningful within-patient change in the CMAI total score primarily focused on pooled data (across arms) from Study 213. Specifically, anchor-based methods supplemented with empirical cumulative distribution function (eCDF) and probability density function (PDF) curves were used to establish the thresholds, or a range of thresholds, that constitute a clinically meaningful within-patient change in the CMAI total score.

Applicant Analyses of Clinically Meaningful Within-Patient Change[7]

The Applicant conducted the Spearman rank-order correlation between the change from Baseline to Week 12 in CMAI total score and the CGI-S and CGI-I anchors using data from Study 213 (Table 2). Overall, moderately high correlations were observed between the endpoint and anchor scores.

Table 2. Correlations between CMAI total score and change in CGI-S and CGI-I at Week 12 (Study 213)

	Change From Baseline to Week 12 in CGI-S	CGI-C at Week 12
Change From Baseline to Week 12 in CMAI Total Score	0.73	0.73

Source: Reviewer's table, adapted from the Applicant's CMAI Meaningful Change Analysis Report Version 3.0 Outputs for trial 331-14-213, Output 2, Table 2.1.1, page 1077/1649

According to the Applicant's response (April 10, 2023) to FDA's information request (April 3, 2023), a 2-category improvement on the CGI-S and "Much improvement" category on the CGI-I are proposed as target anchor change categories to support the anchor-based analyses. The Applicant stated in the IR response that "*…a 2-point change [improvement] in the CGI-S, which was considered as likely meaningful to the patients and their caregivers. Based on caregiver qualitative research focused on meaningful improvements in agitation behaviors, any reductions in the frequency and severity of agitation behaviors would be a welcome relief and allow for some semblance of normalcy during the course of a very devasting and burdensome condition. The CGI-S is highlighted as a primary anchor for this analysis since the CGI-I, an impression of change, is subject to increased recall error and/or present state bias*."

Reviewer's comment(s): *See reviewer's comment Appendix C, p. 20, which confirms caregivers found improvements in both frequency and severity to be meaningful.*

Discussion

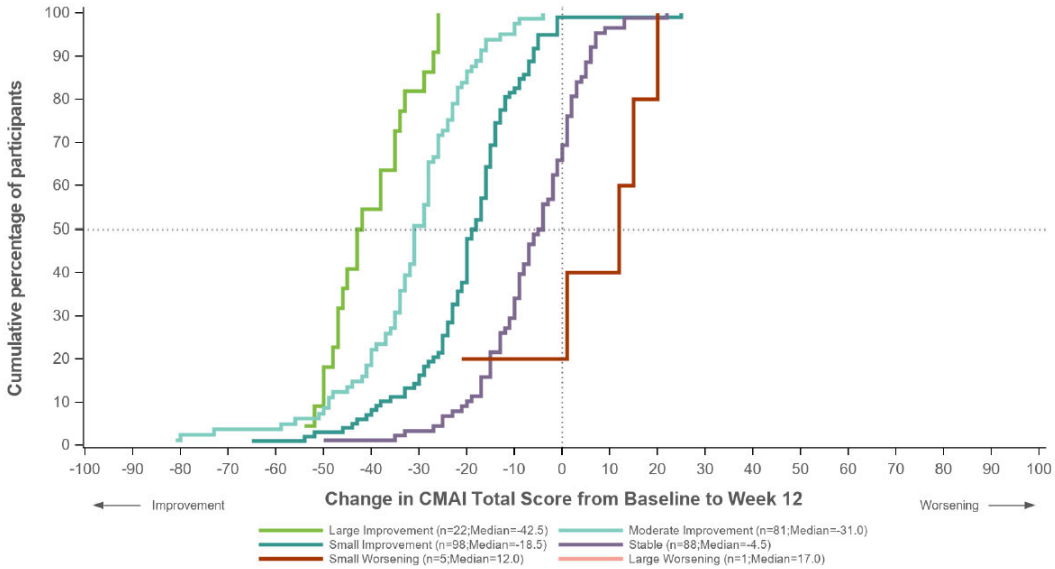
Taking into consideration the aforementioned limitations of the CGI-S and CGI-I anchor scales, the Applicant's proposed target anchor change categories on the CGI-S and CGI-I

[7] CMAI Meaningful Change Analysis Report Version 3.0, 28 September 2022

appear reasonable. As such, a 2-category improvement on the CGI-S and “Much improved” response category on the CGI-I were considered in FDA’s interpretation of clinically meaningful within-patient improvement in the CMAI total score. Additionally, when evaluating a range of meaningful change thresholds, a patient’s Baseline frequency of agitation behaviors should be taken into consideration, as what reporters consider to be a meaningful improvement could be impacted by the patient’s Baseline agitation behavior. However, the Applicant’s analyses did not consider Baseline frequency, which posed a limitation to the interpretation of the anchor-based analysis results.

Refer to Figure 1, below, for the eCDF plot of change in CMAI total score at Week 12 from Baseline by categories of change in CGI-S. In summary, the eCDF plot shows clear separation between the “2-category improvement” (referred to as "Moderate improvement” in the Applicant’s plot) and “1-category improvement” (referred to as “Small improvement” in the Applicant’s plot) as well as “no change” (referred to as “Stable” in the Applicant’s plot) curves. The median change in CMAI total score for patients with a 2-category improvement on the CGIS is -31 points (Table 3), which is a viable choice for a potential meaningful change threshold as it minimizes misclassifying patients who did not experience a meaningful change as experiencing a meaningful change (e.g., patients who remained “stable” on the CGI-S). (Please note, all figures and tables below reflect results from Study 213.)

Figure 1. eCDF, Change in CMAI Total Score at Week 12 From Baseline by Categories of Change in CGI-S (Study 213)

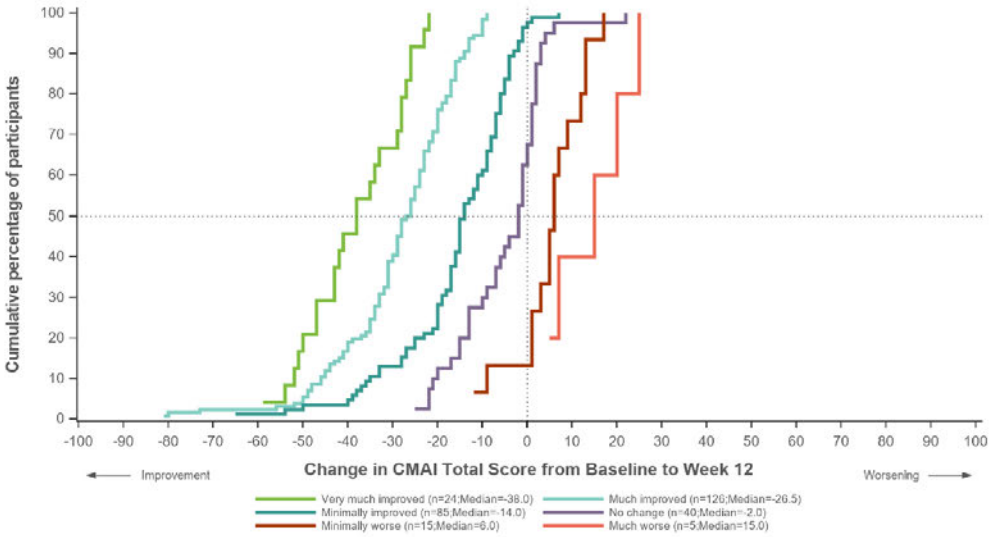


Source: Applicant’s CMAI Meaningful Change Analysis Version 6.0 Outputs for trial 331-14-213, Output 3.1, Figure 3.1.9, page 311

Using the “Much improved” category on the CGI-I (see Figure 2), the median change in CMAI total score is -26.5 points (see Table 4), which appears to be consistent with the results based on CGI-S. Based on this evidence, a reasonable range of meaningful within-patient change threshold range could be 27-point to 31-point improvement in CMAI total score based on data from Study 213.

Figure 2. eCDF, Change in CMAI Total Score at Week 12 From Baseline By CGI-I (Study 213)

Figure 3.1.69: Empirical Cumulative Distribution Function of Change in CMAI Total Score in groups defined by the CGI-I - all categories from Baseline to Week 12



Source: Applicant's CMAI Meaningful Change Analysis Version 6.0 Outputs for trial 331-14-213, Output 3.1, Figure 3.1.69, page 371

Table 3. Descriptive Statistics: Change in CGI-S from Baseline to Week 12 (Study 213)

Table 2.2.1.1: Description of the CMAI according to Change in CGI-S - all categories, from baseline to Week 12, study 331-14-213 (cont'd)

	Change in CGI-S - all categories						
Variable	Large Improvement N=23	Moderate Improvement N=82	Small Improvement N=98	Stable N=88	Small Worsening N=5	Moderate Worsening N=0	Large Worsening N=1
Change in CMAI Total Score							
n (missing)	22 (1)	81 (1)	98 (0)	88 (0)	5 (0)		1 (0)
Mean (SD)	-40.36 (8.75)	-31.95 (13.95)	-19.77 (12.66)	-6.26 (11.27)	5.40 (16.32)		17.00 (.)
Median	-42.50	-31.00	-18.50	-4.50	12.00		17.00
Q1, Q3	-47.00, -34.00	-37.00, -24.00	-25.00, -13.00	-13.00, 1.00	1.00, 15.00		17.00, 17.00
P10, P90	-50.00, -27.00	-49.00, -17.00	-38.00, -6.00	-20.00, 6.00	-21.00, 20.00		17.00, 17.00
Min, Max	-54.00, -26.00	-81.00, -4.00	-65.00, 25.00	-50.00, 22.00	-21.00, 20.00		17.00, 17.00

Source: Applicant's CMAI Meaningful Change Analysis Version 6.0 Outputs for trial 331-14-213, Output 2.2, Figure 2.2.1.1, page 49

Table 4. Descriptive Statistics: Change in CGI-I from Baseline to Week 12 (Study 213)

Table 2.2.1.7: Description of the CMAI according to CGI-I - all categories, from baseline to Week 12, study 331-14-213 (cont'd)

	CGI-I - all categories					
Variable	Very much improved N=24	Much improved N=127	Minimally improved N=85	No change N=40	Minimally worse N=15	Much worse N=6
Change in CMAI Total Score						
n (missing)	24 (0)	126 (1)	85 (0)	40 (0)	15 (0)	5 (1)
Mean (SD)	-38.17 (10.76)	-28.67 (13.30)	-15.72 (12.91)	-5.10 (9.59)	5.13 (7.85)	14.40 (8.47)
Median	-38.00	-26.50	-14.00	-2.00	6.00	15.00
Q1, Q3	-47.00, -28.00	-34.00, -20.00	-20.00, -7.00	-13.00, 1.00	1.00, 12.00	7.00, 20.00
P10, P90	-52.00, -26.00	-46.00, -14.00	-35.00, -3.00	-20.50, 3.00	-9.00, 13.00	5.00, 25.00
Min, Max	-59.00, -22.00	-81.00, -9.00	-65.00, 7.00	-25.00, 22.00	-12.00, 17.00	5.00, 25.00

Source: Applicant's CMAI Meaningful Change Analysis Version 6.0 Outputs for trial 331-14-213, Output 2.2, Figure 2.2.1.7, page 67

To further evaluate the clinical relevance of the observed treatment effect, the eCDF plots of within-patient changes in CMAI total score from Baseline to Week 12 by treatment arm are presented (Figure 3) and show separation between treatment arms based on visual inspection across a wide range of change scores, including in the FDA-proposed meaningful change range of 27-point to 31-point improvement. Taking into consideration the limitations of the anchor scales, it is reasonable to conclude that patients treated with REXULTI 2 mg and REXULTI 2 mg/3 mg in Study 213 experienced a meaningful improvement in the frequency of agitation behaviors compared to those treated with placebo. Of note, in Study 213, the primary efficacy analysis was conducted using the pooled 2mg and 3mg treatment groups.

Figure 3 eCDF, Change in CMAI Total Score at Week 12 From Baseline by Treatment Arm

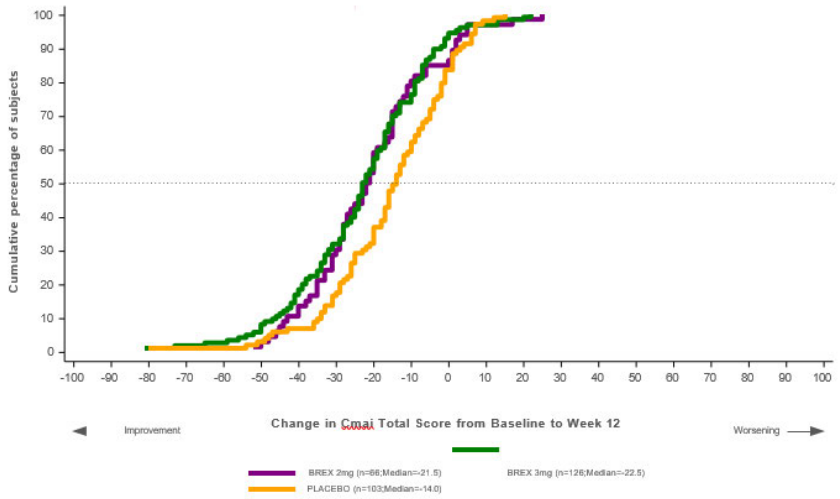


Figure 8: eCDF of the change in CMAI Total score from baseline to Week 12 per treatment arm (separated BREX arms) in the 331-14-213 study

Source: Applicant's CMAI Meaningful Change Analysis Version 3.0 Outputs for trial 331-14-213, Section 6 Results, Figure 8, page 1090/1649

Figure 4. eCDF, Change in CMAI Total Score at Week 12 From Baseline by Treatment Arm (2mg/3mg pooled)

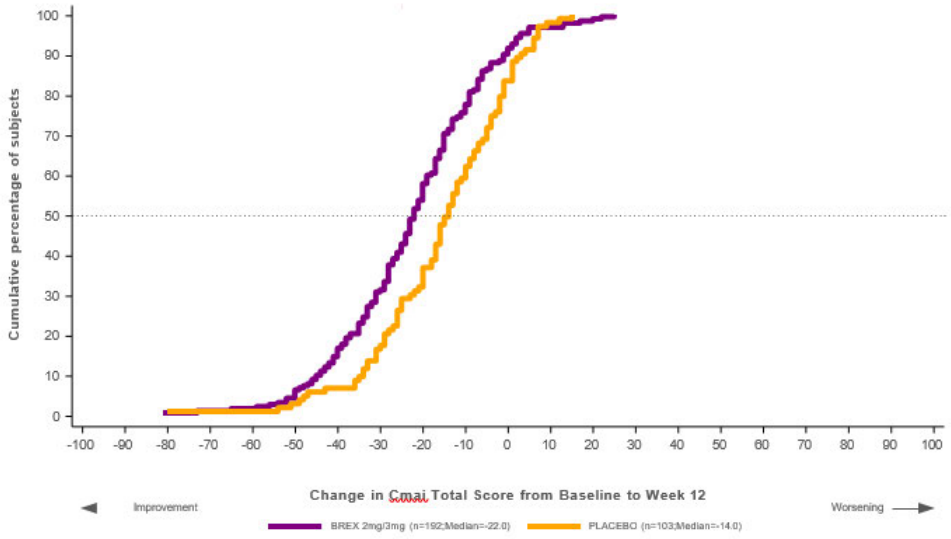


Figure 7: eCDF of the change in CMAI Total score from baseline to Week 12 per treatment arm (combined BREX arms) in the 331-14-213 study

Source: Applicant's CMAI Meaningful Change Analysis Version 3.0 Outputs for trial 331-14-213, Section 6 Results, Figure 7, page 1088/1649

The Applicant further calculated the percent of patients in Study 213 (highlighted in the red box in Table 5 below) who were considered responders (those with a change in CMAI total score greater than a particular threshold) using various thresholds at Week 12, by treatment arms. The Applicant selected the thresholds based on "*-15 (corresponding to the rounded value obtained when looking at a 1-point improvement in the CGI-S), and -20 and -25 (corresponding to the values obtained when looking at a 2-point improvement in the CGI-S, on studies 331-12-283 and 331-12-284 and on study 331-14-213, respectively).*"

Table 5. Percent of Responders in CMAI total Score Using Various Thresholds

Table 4: Percent of responders for the CMAI Total score using various thresholds

	Study 331-12-283				Study 331-12-284		Study 331-14-213			
Threshold Value	BREX 0.5mg N=13	BREX 1mg N=119	BREX 2mg N=120	Placebo N=118	BREX 0.5-2mg N=116	Placebo N=117	BREX 2mg N=66	BREX 3mg N=128	BREX 2-3mg* N=194	Placebo N=103
-15	4 (30.8%)	61 (51.3%)	72 (60.0%)	61 (51.7%)	69 (59.5%)	56 (47.9%)	47 (71.2%)	88 (68.8%)	135 (69.6%)	51 (49.5%)
-20	3 (23.1%)	46 (38.7%)	56 (46.7%)	48 (40.7%)	57 (49.1%)	44 (37.6%)	39 (59.1%)	72 (56.3%)	111 (57.2%)	38 (36.9%)
-25	3 (23.1%)	35 (29.4%)	48 (40.0%)	33 (28.0%)	38 (32.8%)	34 (29.1%)	29 (43.9%)	53 (41.4%)	82 (42.3%)	30 (29.1%)

*Source: CMAI Meaningful Change Analysis Outputs for trial 331-14-213, Output 4, Table 4.1.1; * Combined BREX 2mg and BREX 3mg arms*

Reviewer's comment(s): *The Applicant's responder analysis included a range of values, albeit lower than the FDA-proposed meaningful change range of 27-point to 31-point improvement, further illustrating that within-patient changes in CMAI total score from Baseline to Week 12 by treatment arm separate across a wide range of change scores.*

Issues identified

Issue #1 Limitations in the Selected Anchors

1. The concepts within the primary endpoint and the anchors do not align, creating less confidence with the interpretation of within-patient meaningful change results:
   - **CMAI** measures **Frequency of Agitation Behaviors**
   - **CGI-S** measures **current state of mental illness** related to agitation
   - **CGI-I** measures (**current state of) total improvement in** agitation

2. The recall period of the CMAI (over 2 weeks) does not align with the recall period of the CGI-S (present state) creating interpretation challenges.

3. The attribute being measured using the CGI-S response scale - "mentally ill "- does not align with DSM 5 criteria for AD, which describes agitation as a "behavioral disturbance," opening the CGI-S to possible misinterpretation.

Issue #2: CMAI Total Score and Analyses

1. Use of a total score for CMAI is not recommended by the developers and, thus, would not be appropriate to include in a label claim without confirmation of the magnitude and direction of the primary, three factor change scores; additional label claims or alternative indication statements supported by factor-level analyses may be considerations for future studies, if proposed in the endpoint model and multiple

comparison procedure, and supported by clinically meaningful within-patient change analyses at the factor level.

2. CMAI response options are not distinct:
   - "once or twice a day" and "several times a day" may not be distinct
   - "once or twice a week" and "several times a week" may not be distinct

3. Factor analysis was not conducted to support the use of a CMAI total score: Confirmatory factor analysis is recommended by the instrument developers, as factors are known to vary by sample.

Issue #3: Meaningfulness of Change

1. When evaluating a range of meaningful change thresholds, a patient's Baseline frequency of agitation behaviors should be taken into consideration, as what reporters consider to be a meaningful improvement could be impacted by the patient's Baseline agitation behavior. However, the Applicant's analyses did not consider Baseline frequency, which posed a limitation to the interpretation of the anchor-based analyses results.

2. All meaningful change analyses were conducted post hoc during a period when the Applicant would have access to the results of efficacy analyses such as the responder analyses presented in Table 5. This timing poses a limitation to the interpretation of the anchor-based analysis results.

Appended are:
Appendix A: COAs
Appendix B: Summary of Qualitative Evidence
Appendix C: Summary of Quantitative Evidence
Appendix D: Copy of IR issues to Applicant for Qualitative Evidence
Appendix E: Copy of IR Issued to Applicant for Meaningful Change Analyses
Appendix F: Previous comments provided to DP ahead of mid-cycle meeting February 10, 2023

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/s/

LAURA L SWETT
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DAVID S REASNER
05/01/2023 03:03:55 PM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: April 27, 2023

To: ShinYe (Sandy) Chang, Regulatory Project Manager, Division of Psychiatry (DP)

Shamir Kalaria, DP

Kimberly Updegraff, Associate Director for Labeling, DP

From: Aline Moukhtara, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: OPDP Labeling Comments for REXULTI® (brexpiprazole) tablets, for oral use

NDA: 205422/S-009

Background:
In response to DP's consult request dated February 10, 2023, OPDP has reviewed the proposed Prescribing Information (PI) and Medication Guide for supplement S-009 for REXULTI® (brexpiprazole) tablets, for oral use (Rexulti). This supplement provides for a new indication for the treatment of agitation associated with Alzheimer's dementia .

PI: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DP (Sandy Chang) on April 26, 2023 and are provided below.

Medication Guide: A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed for the proposed Medication Guide and comments were sent under separate cover on April 21, 2023.

Thank you for your consult. If you have any questions, please contact Aline Moukhtara at 301-796-2841 or Aline.Moukhtara@fda.hhs.gov.

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/s/

ALINE M MOUKHTARA
04/27/2023 02:39:08 PM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	April 21, 2023
To:	Shin-Ye (Sandy) Chang, PharmD Senior Regulatory Project Manager **Division of Psychiatry (DP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Sharon Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Laurie Buonaccorsi, PharmD Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Sapna Shah, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	REXULTI (brexpiprazole)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 205422
Supplement Number:	S-009
Applicant:	Otsuka Pharmaceutical Company, Ltd c/o Otsuka Pharmaceutical Development & Commercialization, Inc.

1 INTRODUCTION

On November 10, 2022, Otsuka Pharmaceutical Company, Ltd c/o Otsuka Pharmaceutical Development & Commercialization, Inc. submitted for the Agency's review a Prior Approval Supplement (PAS) – Efficacy to their approved New Drug Application (NDA) 205422/S-009 for REXULTI (brexpiprazole) tablets. With this submission, the Applicant proposes an indication for the treatment of agitation associated with Alzheimer's dementia (AAD).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Psychiatry (DP) on February 10, 2023, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for REXULTI (brexpiprazole) tablets.

2 MATERIAL REVIEWED

- Draft REXULTI (brexpiprazole) tablets MG received on November 10, 2022, and received by DMPP and OPDP on April 18, 2023.
- Draft REXULTI (brexpiprazole) tablets Prescribing Information (PI) received on November 10, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on April 18, 2023 and April 20, 2023.
- Approved REXULTI (brexpiprazole) tablets labeling dated December 27, 2021.
- Approved FETZIMA (levomilnacipran) extended-release capsules, VRAYLAR (cariprazine) capsules, CAPLYTA (lumateperone) capsules, and TRINTELLIX (vortioxetine) tablets comparator labeling dated March 24, 2023, December 16, 2022, April 26, 2022, and September 20, 2021, respectively.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the PI
- removed unnecessary or redundant information

- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

JESSICA M CHUNG
04/21/2023 02:12:54 PM

ALINE M MOUKHTARA
04/21/2023 02:18:54 PM
Signed for Sapna Shah

SHARON R MILLS
04/21/2023 02:21:39 PM

Clinical Inspection Summary

Date	12 Apr 2023
From	Elena Boley, M.D., M.B.A. Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Shin-Ye Chang, PharmD, SRPM Shamir Kalaria, PharmD, PhD, Clinical Analyst Jean Kim, MD, Team Leader Bernard Fischer, MD, Deputy Division Director Tiffany Farchione, MD, Division Director Division of Psychiatry
NDA #	NDA 205422-S9
Applicant	Otsuka Pharmaceutical Development & Commercialization, Inc.
Drug	Rexulti (brexpiprazole [OPC-34712]), 2 mg and 3 mg tablets
NME	No
Proposed Indication	Treatment of adults with agitation associated with Alzheimer's dementia (AAD)
Consultation Request Date	13 Dec 2022
Summary Goal Date	26 Apr 2023
Action Goal Date	10 May 2023
PDUFA Date	10 May 2023

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Drs. Martin, Patel, Mantero-Atienza, Kozhuharov, Petrovic as well as the contract research organization (CRO), (b) (4), and the sponsor, Otsuka Pharmaceutical Development & Commercialization, Inc., were inspected in support of NDA 205422-S9. The inspections covered Protocols 331-12-283, 331-12-284, and 331-14-213. Despite some minor protocol deviations and issues with deviation management by the sponsor, the studies overall appear to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication.

II. BACKGROUND

NDA 205422-S9 was submitted in support the use of brexpiprazole tablets for the treatment of adults with agitation associated with Alzheimer's dementia (AAD). The three Phase 3 clinical studies supporting the application were the following:

- Protocol 331-12-283: "A Phase 3, 12-week, Multicenter, Randomized, Double-blind, Placebo-controlled Trial to Evaluate the Efficacy, Safety, and Tolerability of 2 Fixed Doses of Brexpiprazole (OPC-34712) in the Treatment of Subjects with Agitation Associated with Dementia of the Alzheimer's Type"

- Protocol 331-12-284: "A Phase 3, 12-week, Multicenter, Randomized, Double-blind, Placebo-controlled Trial to Evaluate the Efficacy, Safety, and Tolerability of Flexible Dosing of Brexpiprazole (OPC-34712) in the Treatment of Subjects with Agitation Associated with Dementia of the Alzheimer's Type"

- Protocol 331-14-213: "A Phase 3, 12-Week, Multicenter, Randomized, Double-blind, Placebo-controlled, 2 Arm, Fixed-dose Trial to Evaluate the Efficacy, Safety, and Tolerability of Brexpiprazole (OPC-34712) in the Treatment of Subjects with Agitation Associated with Dementia of the Alzheimer's Type"

Protocol 331-12-283

This study was a Phase 3, multinational, multicenter, randomized, double-blind, placebo-controlled trial in adult participants aged 55 to 90 years of age with a diagnosis of probable Alzheimer's disease, with agitation symptom onset 2 weeks prior to screening. The primary objective was to compare the efficacy of 2 fixed doses (1 mg/day and 2 mg/day) of brexpiprazole with placebo in subjects with agitation associated with dementia of the Alzheimer's type, as assessed by the Cohen-Mansfield Agitation Inventory (CMAI) after 12 weeks of treatment.

Eligible participants were males and females aged 55 to 90 years of age (inclusive), who were living in either an institutionalized setting (residential) or in a noninstitutionalized setting (community) where the subject was not living alone. Enrolled participants had a diagnosis of probable Alzheimer's disease according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria and onset of symptoms of agitation at least 2 weeks prior to the screening visit.

Participants were required to have had a previous MRI or CT scan of the brain (performed after the onset of the symptoms of dementia) with findings consistent with a diagnosis of Alzheimer's dementia (if no previous MRI or CT, one was performed during screening). Each subject was determined by the investigator to have the capacity to provide informed consent during the screening period and throughout the course of the trial. Additionally, each participant was required to have a caregiver who could spend a minimum of 2 hours per day for 4 days per week with the subject to assess changes in the subject's condition. Eligible participants also were to have a Mini-Mental State Examination (MMSE) score of 5 to 22, inclusive, and a total score (frequency × severity) of 4 on the agitation/aggression item of the Neuropsychiatric Inventory Nursing Home (NPINH) (for institutionalized subjects) or the Neuropsychiatric Assessment for Noninstitutionalized Patients based on the NPI-NH (NPI/NPI-NH) (for noninstitutionalized subjects) at their screening and baseline visits. Subjects were required to be capable of self-locomotion or locomotion with an assistive device.

Finally, per the investigator's judgment, after subjects were evaluated for reversible factors (e.g., pain, infection, polypharmacy) and a trial of nonpharmacological interventions, subjects were to require pharmacotherapy for the treatment of agitation. Major exclusion criteria included a history of stroke, well-documented transient ischemic attack, pulmonary or cerebral embolism, or AXIS I disorders. See protocol for full listing of exclusion criteria.

The study was comprised of three periods: a screening period, a double-blind treatment period, and a post-treatment safety follow-up period. The total duration of the study was 16 weeks.

During the screening period, subject eligibility was reviewed by an external quality oversight group, Clinical Surveillance & Training. After approval of subject eligibility was obtained, subjects were randomized in a 1:1:1:1 fashion to receive one of three doses of brexpiprazole (0.5 mg/day, 1 mg/day, or 2 mg/day) or placebo. All subjects assigned to a brexpiprazole treatment group received 0.25 mg/day as a starting dose. By Week 4, each subject had to be titrated to their assigned dose of brexpiprazole or matching placebo and continue that dose through Week 12/End of Treatment. Subjects unable to tolerate their assigned dose of brexpiprazole (or matching placebo) were withdrawn from the trial. Down-titration was not allowed.

Subjects were evaluated at Baseline, Day 3, and every 2 weeks through Week 12/End of Treatment. Clinicians administered the CMAI (a questionnaire that measures the frequency of 29 agitated behaviors) with the participation of a previously identified caregiver.

During the 30-day follow-up period, all subjects were assessed in person or by phone. Those who completed the treatment period and the follow-up evaluation were eligible to enroll in a 2-month observational rollover study, Trial 331-13-211.

Protocol 331-12-284

Eligibility criteria were similar to Study 331-12-283.

Study 331-12-284 had a similar study design to Study 331-12-283 (see above), except study 331-12-284 consisted of one flexible-dose group (0.5 to 2 mg/day) and a placebo group. Subjects were randomized in a 1:1 fashion to receive either brexpiprazole 0.25 mg/day or matching placebo. Dosing was increased to 0.5 mg/day at the Day 3 visit and then to 1 mg/day at the Week 2 visit. If 1 mg/day was not tolerated, the dose could be decreased to 0.5 mg/day and re-increased to 1 mg/day as tolerated. If 1 mg/day was tolerated, the dose could be further increased to 2 mg/day at the Week 4 Visit. Dose decreases and increases were always to occur in a stepwise manner and could occur at any time (scheduled or unscheduled visits). Subjects assigned to the placebo group took matching placebo for the full treatment period. Subjects unable to tolerate 0.5 mg/day of brexpiprazole (or matching placebo) were discontinued from the trial.

Protocol 331-14-213

Study 331-14-213 had a similar study design to Study 331-12-283 (see above), except study 331-14-213 consisted of one fixed-dose group (target dose of 2 mg/day or 3 mg/day) and a placebo group.

Eligibility criteria were similar to the eligibility criteria for Study 331-12-283. However, additional eligibility criteria, unknown to the site investigators, were included in a blinded addendum to the protocol and included subjects meeting the criteria for CMAI Factor 1 agitation (≥1 aggressive behavior(s) occurring several times per week, or ≥ 2 aggressive behaviors occurring once or twice per week, or ≥3 aggressive behaviors occurring less than once per week).

After approval from Clinical Surveillance & Training, subjects were randomized in a 2:1 fashion to receive brexpiprazole or matching placebo. Subjects in the brexpiprazole group were further randomized in a 1:2 fashion to receive 2 mg/day and 3 mg/day. Dosing was increased for all subjects to 1 mg/day and then 2 mg/day of brexpiprazole or matching placebo after the Week 2 Visit. After the Week 4 visit, those randomized to the 3 mg/day brexpiprazole group had their dose increased to 3 mg/day. All treatment was continued through Week12/End of Treatment. Down-titration was not allowed at any time during the trial. Subjects unable to tolerate brexpiprazole at their assigned dose (or matching placebo) were discontinued.

Subjects who completed the 12-week double-blind treatment period may have been eligible to enter a 12-week open-label extension trial.

The ***primary efficacy endpoint*** for all three studies was the change from baseline to Week 12 in the CMAI Total Score.

The ***safety endpoint of interest*** to the review division was deaths, with special attention to those related to cardiovascular adverse events.

Details relevant to Study 331-12-283

Study 331-12-283 was conducted at 81 centers that screened subjects in 7 countries worldwide (Croatia, Germany, Serbia, Spain, Russia, Ukraine, and the United States). The first subject was enrolled on July 11, 2013, and the last subject completed final visit on March 15, 2017. Of the 433 subjects that were randomized, 377 subjects (87.1%) completed the study. The original protocol was dated February 18, 2013, there were four protocol amendments, and the final protocol was dated September 10, 2015.

Details relevant to Study 331-12-284

Study 331-12-284 was conducted at 62 centers that screened subjects in 9 countries worldwide (Bulgaria, Canada, Finland, France, Russia, Slovenia, Ukraine, the United Kingdom, and the United States). The first subject was enrolled on October 28, 2013, and the last subject completed final visit on March 30, 2017. Of the 270 subjects that were randomized, 238

subjects (88.1%) completed the study. The original protocol was dated May 6, 2013, there were three protocol amendments, and the final protocol was dated September 10, 2015.

Details relevant to Study 331-14-213

Study 331-14-213 was conducted at 123 centers that screened subjects in 7 countries worldwide (Bulgaria, Hungary, Serbia, Slovakia, Spain, Ukraine, and the United States). The first subject was enrolled on May 16, 2018, and the last subject completed final visit on June 1, 2022. Of the 345 subjects that were randomized, 342 subjects (99.1%) completed the study. The original protocol was dated February 15, 2018, there were five protocol amendments, including two amendments to the blinded addendum, and the final protocol was dated September 14, 2020.

Rationale for Site Selection

The clinical sites for inspection were chosen primarily based on the regional distribution of subjects, the numbers of enrolled subjects, site-specific efficacy results, and the results of an analysis that identified three individual sites that each drove the overall efficacy results. Foreign sites were selected for inspection because there were insufficient domestic data (i.e., subjects from the US comprised only 32% of the safety population in the three studies combined).

III. RESULTS (by site):

1. **Gnyandev Patel, M.D.**
   Site #118
   Protocol: 331-12-283
   Site # 114
   Protocol: 331-14-213
   3300 E. South St., Suite 206
   Lakewood, CA 90805 US
   PDUFA Inspection Dates: February 6-10, 2023

At this site for Protocol 331-12-283, 39 subjects were screened, 24 were randomized, and 18 subjects completed the study. Of the 6 subjects who did not complete the study, 3 subjects met protocol-specified withdrawal criteria (subjects (b) (6), and (b) (6)), 2 subjects discontinued due to adverse events (subjects (b) (6) and (b) (6), both in the brexpiprazole 1 mg treatment group, cerebrovascular accident/lacunar infarct and worsening agitation, respectively), and the remaining subject withdrew consent (subject (b) (6), assigned to the brexpiprazole 0.5 mg treatment group).

At this site for Protocol 331-14-213, 24 subjects were screened, 15 were randomized, and 14 subjects completed the study. Subject (b) (6) discontinued due to the serious adverse event of altered mental status and had been assigned to the brexpiprazole 3 mg treatment group. The narrative for this serious AE is in the application.

The inspection evaluated the informed consent for all screened subjects in both studies. In addition, the study records for all 24 randomized subjects in Protocol 331-12-283 and all 15 randomized subjects in Protocol 331-14-213 were evaluated for protocol adherence, adverse event reporting, concomitant medications, and eligibility. Other records reviewed during the inspection included, but were not limited to, the study protocol and amendments; institutional review board (IRB) submissions, approvals, and correspondence; source records, including medical records; primary efficacy endpoint data and safety data; protocol deviations; drug accountability logs; monitor logs and follow-up letters; and other regulatory documentation (e.g., Form FDA 1572s).

Adverse events were reviewed for both studies. There was no evidence of under-reporting of adverse events. During the inspection, the paper source records were reviewed for Protocol 331-12-283, and the electronic source data contained on a USB provided to the site by the sponsor were reviewed for Protocol 331-14-213. For both studies, the raw data for each of the 29 items in the CMAI at Baseline and Week 12 were verified against the data line listings provided by the sponsor for all randomized subjects. No discrepancies were noted.

2. **Emilio Mantero-Atienza, M.D.**
   Site #121
   Protocol: 331-12-283
   Premier Clinical Research Institute, Inc.
   3100 NW 72nd Ave., Suite 125
   Miami, FL 33122 US
   PDUFA Inspection Dates: February 27 to March 3, 2023

At this site for Protocol 331-12-283, 30 subjects were screened, 16 were randomized, and 15 subjects completed the study. Subject (b) (6), assigned to the placebo group, did not complete the study due to withdrawal of consent.

The inspection evaluated the study records for all 30 screened subjects. Records reviewed during the inspection included, but were not limited to, the study protocol and amendments; institutional review board (IRB) submissions, approvals, and correspondence; subject eligibility criteria; informed consent process and forms; source records, including medical records; primary efficacy endpoint data and safety data; adverse event reporting; protocol deviations; drug accountability logs; monitor logs and follow-up letters; and other regulatory documentation (e.g., Form FDA 1572s).

There was no evidence of under-reporting of adverse events. During the inspection, the paper source records were reviewed, and the raw data for each of the 29 items in the CMAI at Baseline and Week 12 were verified against the data line listings provided by the sponsor for all 16 randomized subjects. No discrepancies were noted.

3. Jovanka Petrovic, M.D.
Site #502
Protocol: 331-14-213
Special Hospital for Psychiatric Diseases
Cara Lazara 253
Kovin 26220
Serbia
PDUFA Inspection Dates: February 27 to March 3, 2023

At this site for Protocol 331-14-213, 17 subjects were screened, 11 were randomized, and 10 subjects completed the study. Subject (b) (6), assigned to the brexpiprazole 3 mg group, was randomized but then lost to follow up prior to Week 12.

The inspection evaluated the study records for the 17 screened subjects. Records reviewed during the inspection included, but were not limited to, the study protocol and amendments; independent ethics committee approvals; subject eligibility criteria; informed consent process and forms; source records, including medical records; primary efficacy endpoint data and safety data; adverse event reporting; protocol deviations; drug accountability logs; monitor logs and follow-up letters; and other regulatory documentation.

There was no evidence of under-reporting of adverse events. During the inspection, the paper source records were reviewed, and the raw data for each of the 29 items in the CMAI at Baseline and Week 12 were verified against the data line listings provided by the sponsor for all 10 randomized subjects who completed the study. No discrepancies were noted.

4. Manuel Franco Martin, M.D.
Site #192
Protocol: 331-12-283
Hernán Cortés 40
Zamora 49021
Spain
PDUFA Inspection Dates: March 6-10, 2023

At this site for Protocol 331-12-283, 23 subjects were screened, 13 were randomized, and 12 subjects completed the study. Subject (b) (6), assigned to the placebo group, was randomized but then withdrawn by the investigator prior to Week 12.

The inspection evaluated the study records for all 13 randomized subjects. Records reviewed during the inspection included, but were not limited to, the study protocol and amendments; independent ethics committee approvals; subject eligibility criteria; informed consent process and forms; source records, including medical records; primary efficacy endpoint data and safety data; adverse event reporting; protocol deviations; drug accountability logs; monitor logs and follow-up letters; and other regulatory documentation.

There was no evidence of under-reporting of adverse events. During the inspection, the paper source records were reviewed, and the raw data for each of the 29 items in the CMAI at

Baseline and Week 12 were verified against the data line listings provided by the sponsor for the 12 randomized subjects who completed the study through Week 12. No discrepancies were noted.

5. Hristo Kozhuharov, M.D.
Site #801
Protocol: 331-12-284
15 "Republika" Blvd
Varna 9020
Bulgaria
PDUFA Inspection Dates: March 13-17, 2023

At this site for Protocol 331-12-284, 10 subjects were screened, 9 subjects were randomized, and all 9 subjects completed the study.

The inspection evaluated the study records for the 9 randomized subjects. Records reviewed during the inspection included, but were not limited to, the study protocol and amendments; independent ethics committee approvals; subject eligibility criteria; informed consent process and forms; source records, including medical records; primary efficacy endpoint data and safety data; adverse event reporting; protocol deviations; drug accountability logs; monitor logs and follow-up letters; and other regulatory documentation (e.g., Form FDA 1572s).

Adverse events were reviewed for all subjects. There was no evidence of under-reporting of adverse events. During the inspection, the paper source records were reviewed. The raw data for each of the 29 items in the CMAI score at Baseline and Week 12 were verified against the data line listings provided by the sponsor for all randomized subjects. No discrepancies were noted.

During the screening period, subject (b) (6) was started on a new medication, glicazide. Clinical Surveillance & Training was not notified and, as a result, their determination that the subject was eligible for randomization was based on incomplete information. If Clinical Surveillance & Training had been notified that a new medication had been started, this subject likely would have been determined to be ineligible for the study.

Reviewer's comment: This isolated event is unlikely to have impacted the study's efficacy results.

The inspection found that subject (b) (6), who was assigned to the brexpiprazole group, took a prohibited anticonvulsant medication (gabapentin) during the study.

Reviewer's comment: Neither adverse event (left bundle branch block nor lumbosacral radiculopathy) that was reported for Subject (b) (6) was a serious adverse event, was considered related to the study drug, or elicited a change in study drug dose. This oversight appears not to have compromised subject safety.

The inspection found that Subject (b) (6), who was assigned to the brexpiprazole group, was

mistakenly given a kit containing the placebo treatment at the Week 2 visit. Because subjects were evaluated every 2 weeks, it is likely that this subject received 2 weeks of placebo treatment.

Reviewer's comment: Data from this subject is unlikely to impact the efficacy results. However, if a single kit of placebo had any effect on the overall results, it would be to minimize the difference between the two groups.

6. Otsuka Pharmaceutical Development & Commercialization, Inc.
Protocol: 331-12-283
Protocol: 331-12-284
Protocol: 331-14-213
2440 Research Blvd,
Rockville, Maryland 20850
PDUFA Inspection Dates: February 14-27, 2023

The inspection of the sponsor focused on the control, oversight, and management of Protocols 331-12-283, 331-12-284, and 331-14-213, with particular attention to the six investigator sites that were selected for inspection (sites #118, #121, and #192 from Protocol 331-12-283, site #801 from Protocol 331-12-284, and sites #114 and #502 from Protocol 331-14-213). An additional focus was the processes and procedures related to protocol deviation classification, documentation, and tracking.

Study records reviewed included records related to the roles and responsibilities of sponsor and their service providers; the organization and its personnel; selection and monitoring of clinical investigators; quality control and assurance activities, including selection of monitors, monitoring procedures and activities, and sponsor audits; standard operating procedures; safety and adverse event reporting; data collection and handling; record retention, financial disclosure, electronic records and signature compliance; test article accountability; relevant communication and correspondence; and registration of studies on ClinicalTrials.gov.

The inspection found that the sponsor did not appear to have adequate processes and procedures in place for tracking protocol deviation classification and documenting the rationale behind protocol deviation classification revisions (i.e., major to minor or vice versa). Additionally, the sponsor's final Protocol Deviation Decision Workbook, which was consistent with the submitted protocol deviation data, was recorded in a document format (Excel) with no capability to provide an audit trail.

Reviewer's comment: Although the sponsor's oversight of the protocol deviation documentation practices was lacking, there was no evidence to suggest that the protocol deviation classification revisions were not made in a protocol-specified manner.

On January 18, 2023, the review division sent an information request to the sponsor requesting updated datasets because they noticed the tables in the clinical study report (CSR) contained major protocol deviation data that differed from data contained in the submitted data sets for Studies 331-12-283 and 331-12-284. When the field investigator asked about this, the sponsor explained that after database lock and following an investigation and reconciliation of existing

protocol deviations, they discovered that some protocol deviations were missing from the submitted data set. The sponsor changed and then re-ran the relevant program and identified all missing deviations. These deviations were then added to the database and included in tables in the CSR and protocol deviation listings. The sponsor updated their standard operating procedures and implemented a new process for Protocol 331-14-213. They also provided updated protocol deviation trackers for each study.

Reviewer's comment: The sponsor successfully identified the discrepancy, completed an investigation, and reconciled the protocol deviations. They addressed the cause by correcting the relevant program and ultimately submitted complete data sets for the protocol deviations to the Agency. They appropriately updated their standard operating procedures and implemented a new process for study 331-13-213. The corrective and preventative actions by Otsuka appear to be adequate.

7. (b) (4)

Protocol: 331-12-283
Protocol: 331-12-284
Protocol: 331-14-213
(b) (4)

PDUFA Inspection Dates: (b) (4)

The inspection of the (b) (4), the CRO, focused on site monitoring and sponsor/CRO oversight of the six investigator sites that were selected for inspection (sites #118, #121, and #192 from Protocol 331-12-283, site #801 from Protocol 331-12-284, and sites #114 and #502 from Protocol 331-14-213).

The sponsor transferred regulatory responsibilities to (b) (4) to perform critical clinical trial activities. (b) (4) was responsible for providing services related to 1) source data review; 2) selection of clinical investigators; 3) investigator meeting content; 4) clinical trainings; 5) site monitoring (blinded); 6) IP management; 7) medical monitoring; 8) drug safety (not including form completion); 9) data management; and 10) project management.

The inspection covered roles and responsibilities; the organization and its personnel; registration of studies on ClinicalTrials.gov; oversight of the clinical trial conduct, selection of clinical investigators and monitoring procedures and activities; (b) (4) quality management system; drug accountability; adverse event reporting; process for managing protocol deviations; data collection, handling, and management; record retention; and financial disclosure. Records reviewed during the inspection included the study master files, standard operating procedures related to the studies, site monitoring, handling of adverse events, data collection, determining if the CRO discovered any non-compliant sites, and how the CRO tried to bring these sites into compliance. Information was also obtained concerning procedures for selection of clinical investigators, selection of monitors, monitoring procedures and frequency, interactive web response system, contract services used, and other sponsor/monitor related activities.

Similar to the sponsor inspection, inquiries regarding the discovery that some deviations were

missing from the major protocol deviation listing were made at the CRO inspection, and requests were sent to the sponsor via the CRO. Please see above regarding the inspection of Otsuka.

{See appended electronic signature page}

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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Pharmacovigilance and Epidemiology

Integrated Safety Memorandum

Date:	March 13, 2023
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Product Name:	Rexulti (brexpiprazole)
Subject:	Hospitalization and Death in Patients 65 years of Age and Older
Application Type/Number:	NDA 205422
Submission Number:	S-009
Applicant:	Otsuka America Pharmaceuticals, Inc.
TTT Record ID:	2022-3081

1 INTRODUCTION

This Office of Surveillance and Epidemiology (OSE) integrated memorandum includes an evaluation of Rexulti (brexpiprazole) and serious adverse events (SAEs) with an outcome of hospitalization or death in patients aged 65 years and older reported in the FDA Adverse Event Reporting System (FAERS) and literature reports, as well as drug utilization data for brexpiprazole. The Division of Psychiatry (DP) requested this evaluation in preparation for the planned Advisory Committee meeting in April 2023.

1.1 BACKGROUND

1.1.1 Consult History

On November 10, 2022, Otsuka America Pharmaceuticals, the Applicant, submitted a supplemental new drug application (sNDA) 205422-S009 for brexpiprazole oral tablets to support an indication for the treatment of agitation associated with Alzheimer's dementia. No medication is currently approved by FDA for behavioral and psychological symptoms of dementia (BPSD), including symptoms of agitation. The pooled safety findings in the clinical development program reported six deaths in the pooled brexpiprazole group and one death in the pooled placebo group. The Applicant assessed causality of death as unrelated to brexpiprazole in all cases of death.[1]

Because of the imbalance of mortality in patients receiving brexpiprazole in the development program for the treatment of agitation associated with Alzheimer's dementia in addition to the BOXED WARNING of Increased Mortality in Elderly Patients with Dementia-Related Psychosis that all antipsychotics have in their labeling[2], DP consulted the Division of Pharmacovigilance (DPV) on December 16, 2022, to conduct a review of FAERS and the medical literature for SAEs with brexpiprazole leading to hospitalization or death in patients aged 65 years and older. Specifically, DP was interested in the following SAEs: worsening of memory and cognition, serious cardiovascular adverse events (CVAEs), respiratory infections, falls, and extrapyramidal (EPS) adverse events.

1.1.2 Boxed Warning: Increased Mortality in Elderly Patients with Dementia-Related Psychosis

On May 18, 2001, Janssen Pharmaceuticals notified the Division of Neuropharmacological Drug Products (former name of DP) of six cases of cerebrovascular accidents (CVAs) in a clinical trial of older adults with dementia receiving risperidone, an atypical antipsychotic in the same class as brexpiprazole, for the treatment of BPSD. Two of the CVA cases resulted in death.[3] Subsequently, further data analysis led to the addition of a WARNING for Cerebrovascular Adverse Events, Including Stroke, in Elderly Patients with Dementia to the labeling for risperidone in 2003 **(See Appendix A)**.[4] Other atypical antipsychotics, including olanzapine and aripiprazole, subsequently had a similar WARNING for Cerebrovascular Adverse Events, Including Stroke, in Elderly Patients with Dementia added to their labeling **(See Appendices B and C)**.[5,6] The accruing clinical trial safety data of antipsychotic use in patients with dementia showed disproportionately higher rates of death in patients receiving antipsychotics relative to patients receiving placebo, therefore, generating a need for further investigation of a possible pharmacological class effect.

DP completed a review and evaluation of clinical data investigating mortality and antipsychotic drug use for the treatment of BPSD on July 27, 2005.[7] The review systematically assessed all the available data from randomized placebo-controlled trials of antipsychotics in patients with BPSD to determine effect on mortality. At the time of the review, antipsychotics with randomized controlled data for treating BPSD included aripiprazole, olanzapine, risperidone, ziprasidone, quetiapine, and haloperidol. The analysis included 17 studies totaling 5377 patients, with 3611 patients receiving an antipsychotic and 1766 patients receiving placebo. The analysis concluded that the use of atypical antipsychotics in the treatment of patients with BPSD increased the risk of death between 1.6 to 1.7 times compared to patients treated with placebo. A Public Health Advisory was issued and all six atypical antipsychotics approved by the FDA at the time (i.e., clozapine, risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole) had the following BOXED WARNING added to their labeling (example from the olanzapine labeling):[8]

Increased Mortality in Elderly Patients with Dementia-Related Psychosis — Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks) in these patients revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that seen in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. 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. ZYPREXA (olanzapine) is not approved for the treatment of patients with dementia-related psychosis (*see* WARNINGS).

Two observational studies published in 2007 demonstrated similar findings that patients treated for BPSD with conventional antipsychotics had an increase in mortality relative to patients treated with placebo.[9,10] Although FDA found both studies to have methodological limitations, the lack of a unique mechanism for an increase in mortality and inability to substantially rule out an increase in mortality with conventional antipsychotics led FDA to recommend labeling all antipsychotics with the BOXED WARNING in 2008.[11] Currently, all antipsychotics, including brexpiprazole, have a BOXED WARNING for Increased Mortality in Elderly Patients with Dementia-Related Psychosis.

1.1.3 Mechanisms of Increased Death with Antipsychotic Use in Patients with Dementia

There is no agreed upon underlying mechanism for why antipsychotics are associated with increased mortality when used in patients with dementia. Initially, an increase in the risk of CVAs secondary to alpha-adrenergic blockade, was deemed to be the most plausible cause based on findings from the use of risperidone in patients with BPSD.[12] As clinical data accrued, a diverse range of causes for death were identified including cardiac (e.g., congestive heart failure [CHF], myocardial infarction [MI], CVA, sudden cardiac death), respiratory (e.g., pulmonary embolism [PE], chronic obstructive pulmonary disease [COPD], aspiration), and infectious causes (urinary tract infection [UTI], pneumonia, sepsis).[7,11]

1.2 RELEVANT PRODUCT LABELING AND REGULATORY HISTORY

FDA approved brexpiprazole on July 10, 2015 for the treatment of schizophrenia in patients ages 13 years and older. Brexpiprazole is also indicated as an adjunctive therapy to antidepressants for the treatment of major depressive disorder (MDD) in adults. It is available as 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, and 4 mg tablets. The initial, recommended, and maximum doses by indication are listed below in **Table 1**.[13]

Table 1. Initial, Recommended, and Maximum Doses for Brexpiprazole by Indication			
Indication	**Starting Dose**	**Recommended Dose**	**Maximum Dose**
Schizophrenia (Adults)	1 mg/day	2 to 4 mg/day	4 mg/day
Schizophrenia Pediatric (13-17 years)	0.5 mg/day	2 to 4 mg/day	4 mg/day
MDD (Adults)	0.5 mg/day or 1 mg/day	2 mg/day	3 mg/day

As part of their sNDA submission, the Applicant has proposed the following modification to the BOXED WARNING:[1]

(b) (4)

The current labeling for brexpiprazole includes the following BOXED WARNING:

(b) (4)

The current labeling for brexpiprazole also includes the following information relevant to older adult patients or patients with dementia.[13]

5 WARNINGS AND PRECAUTIONS

5.1 INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group.

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. (b) (4)

5.3 Cerebrovascular Adverse Reactions Including Stroke in Elderly Patients with Dementia-Related Psychosis

In placebo-controlled trials in elderly patients with dementia, patients randomized to risperidone, aripiprazole, and olanzapine had a higher incidence of stroke and transient ischemic attack, including fatal stroke. (b) (4)

8 USE IN SPECIFIC POPULATIONS

8.5 Geriatric Use

(b) (4)

Other atypical antipsychotics[a] include an additional reference to patients with Alzheimer's type dementia in WARNINGS and PRECAUTIONS under Dysphagia,[14-20] specifically:

> Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in patients with

[a] Ziprasidone, risperidone, quetiapine, paliperidone, olanzapine, lurasidone, and aripiprazole

advanced Alzheimer's dementia. [ANTIPSYCHOTIC NAME] and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

In contrast, the brexpiprazole labeling omits specific mention of both pneumonia and Alzheimer's dementia as noted below.[13]

5.13 DYSPHAGIA

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Antipsychotic drugs, including REXULTI, should be used cautiously in patients at risk for aspiration.

2 METHODS AND MATERIALS

2.1 CAUSALITY CRITERIA

DPV assessed all FAERS and literature reports that described any adverse event in patients 65 years of age or older for a causal relationship with brexpiprazole using the World Health Organization-Uppsala Monitoring Centre (WHO-UMC) system as shown below in **Table 2**.[21] We categorized the reports as probable, possible, unlikely, or unassessable based on the strength of evidence for a causal association as shown in **Table 2**.

Table 2. Causality Classification and Criteria Based on the WHO-UMC System

Causality term	Assessment Criteria
Probable	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely	• Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations
Unassessable	• More data for proper assessment needed • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified

2.2 FAERS SEARCH STRATEGY

DPV searched the FAERS database with the strategy described in **Table 3**.

Table 3. FAERS Search Strategy*	
Date of search	January 3, 2023
Time period of search	All reports through December 31, 2022
Search type	*RxLogix PV Reports Quick Query*
Product terms	Active Moiety: brexpiprazole
MedDRA search terms (Version 25.1)	All adverse events
Case Outcome	Hospitalization or Death
Patient Age (Years)	Age 65 and above‡
* See **Appendix D** for a description of the FAERS database. ‡ Includes patients with a reported age 65 and above in the structured age data field or free text narrative in reports with null age in the structured field. Abbreviations: FAERS =FDA Adverse Events Reporting System, MedDRA=Medical Dictionary for Regulatory Activities	

2.3 LITERATURE SEARCH STRATEGY

DPV searched the medical literature for case reports describing adverse events associated with brexpiprazole in patients over the age of 65. The strategy is described in **Table 4**.

Table 4. Literature Search Strategy	
Date of search	January 17, 2023
Database	Embase, PubMed
Search terms	Embase: ('brexpiprazole'/exp OR brexpiprazole) AND ('case finding'/de OR 'case report'/de OR 'case study'/de OR 'case series' OR 'case report' OR 'case':ti,ab) AND [aged]/lim PubMed: brexpiprazole Filters: Case Reports, Aged: 65+ years
Years included in search	January 1, 1996 through January 17, 2023

2.4 PERIODIC SAFETY REPORTS

In addition to our review of FAERS and the medical literature, DPV screened periodic safety reports covering January 2019 to July 2022, specifically the Applicant's assessment of SAFETY in the elderly, to identify SAEs of interest not captured in FAERS or in the medical literature.

2.5 DRUG UTILIZATION

The Drug Use Team in the Division of Epidemiology II assessed the extent of brexpiprazole use among patients aged 65 years or older, its relative use among all patients, as well as possible reasons for use, to contextualize the adverse event reports from the FAERS database. We used proprietary databases available to the Agency to conduct the utilization analyses. Full database descriptions and limitations are included in **Appendix E**.

2.5.1 Determination of setting of care

To determine the setting of care where brexpiprazole tablets were primarily used, we obtained brexpiprazole manufacturer sales distribution data to various U.S. settings of care in 2022 using the IQVIA™ National Sales Perspective (NSP) database.

2.5.2 Patient utilization data

To assess the extent of brexpiprazole utilization in the older patient population, we obtained the annual estimated number of patients who received a dispensed prescription for brexpiprazole from U.S. outpatient retail pharmacies, stratified by patient age (0 – 64, 65+ years), 2017 – 2022, from the IQVIA Total Patient Tracker™ (TPT) database. Of note, these data are inclusive of all indication.

2.5.3 Office-based healthcare provider survey data

To provide insight into the possible reasons for brexpiprazole use, we obtained diagnoses data associated with brexpiprazole use as reported by U.S. office-based healthcare providers, stratified by patient age (0 – 64, 65+ years) from the Syneos Health Research and Insights LLC., Treatment Answers™ with Pain Panel database, 2017 – 2022, cumulative. We captured diagnoses data based on International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10 CM) diagnosis codes. This database provides survey data from a sample of 3,500 office-based healthcare providers, including 115 pain specialists, reporting on patient activity one day per month. The survey data are used to provide insight into prescriber intent or prescribing habits for disease conditions but are not directly linked to or may not result in a dispensed prescription.

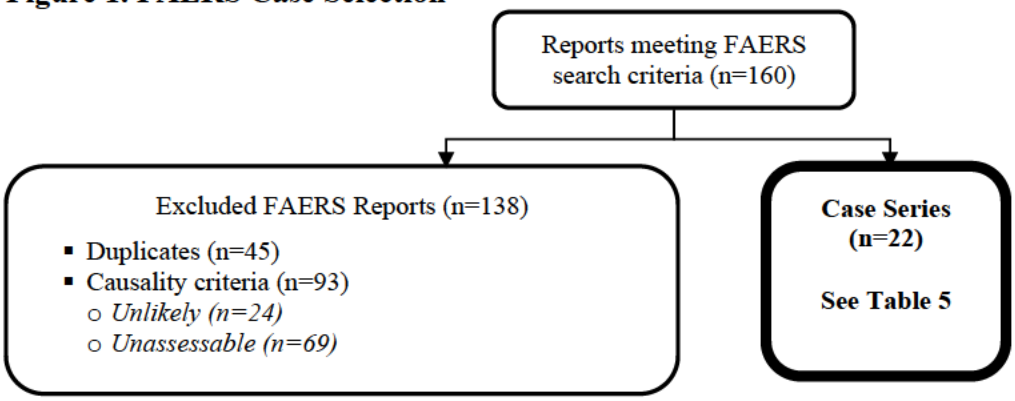
3 RESULTS

3.1 FAERS

DPV identified 160 reports coded with the outcome of death or hospitalization with brexpiprazole use in patients 65 years of age and older. After deduplication, we identified a total of 115 reports for which we reviewed and assessed the causality using the causality criteria in Section 2.1.

Out of the 115 reports, we identified 22 cases that were assessable and had SAEs deemed possibly related to brexpiprazole. These 22 cases were included in the case series (See **Figure 1**).

Figure 1. FAERS Case Selection



Descriptive characteristics of the 22 FAERS cases included in our series are provided in **Table 5**.

Table 5. Descriptive Characteristics of Death and Hospitalization FAERS Cases for Brexpiprazole in Patients Aged 65 years and Older, Received by FDA Through December 31, 2022

		N=22
Sex	Male	9
	Female	13
Age	65 to <70 years	5
	70 to <80 years	14
	80 to <90 years	2
	≥90 years	1
	Mean	74.7 years
	Median	73.6 years
	Range	65-94 years
Country	Japan	16
	United States	6
Report type	Expedited	21
	Direct	1
Initial FDA Received Year	2017	1
	2018	7
	2019	6
	2020	3
	2021	3
	2022	2
Reason for use*	Delusion	1
	Delusional disorder	2
	Dementia Alzheimer's type	3
	Depressive delusion	1
	Major depression	4
	Schizophrenia	9
	Not reported	2
Serious outcome(s)†	Death	5
	Life Threatening	3

Table 5. Descriptive Characteristics of Death and Hospitalization FAERS Cases for Brexpiprazole in Patients Aged 65 years and Older, Received by FDA Through December 31, 2022		
	N=22	
	Hospitalization	19
	Disability	1
	Other serious	12

* A case can have more than one reason for use

† For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, or other serious important medical events. A case can have more than one serious outcome.

Cases with a possible causal association related to brexpiprazole use are grouped by similar events (e.g., cardiovascular, respiratory) and discussed in more details in Sections 3.1.1-3.1.6. The three cases that reported using brexpiprazole for Alzheimer's dementia were from clinical studies and involved the development of aspiration pneumonia. These cases are reviewed in more detail in Sections 3.1.3. We also identified 10 reports in FAERS of accidents or injuries, including falls and fractures; however, we assessed these reports as either unassessable or unlikely due to brexpiprazole use. The majority of reports coded with the PT *Fall* were missing case information to establish a direct time relationship between drug intake and the fall.

Table 6 includes the characteristics of the five fatal cases with SAEs possibly related to brexpiprazole use. These cases are described in more detail in Sections 3.1.1, 3.1.4, and 3.1.6.

Table 6. Summary of Fatal Cases with a Serious Adverse Event Possibly* Related to Brexpiprazole in Patients Aged 65 Years and Older, Received by FDA Through December 31, 2022 (n=5)

FAERS Case #	Patient Age (years)/Sex	Reason for Use	Dose†	Adverse Events Possibly Related to Brexpiprazole	Presence of Potential Contributing Medications	Presence of Potential Contributing Disease States	Cause of Death
18618418	89/Male	Dementia Alzheimer's type	2 mg	Pneumonia aspiration	No	Dementia	Unknown
16965973	74/Male	Schizophrenia	2 mg	Pneumonia aspiration	Yes (olanzapine, suvorexant, ramelteon)	No	Pneumonia
21486653	78/Female	Unknown	NR	Toxicity	Yes (multiple)	NR	Suspected suicide
17528871	75/Male	Schizophrenia‡	2 mg§	Drug-induced liver injury, Hepatic failure	Yes (valproate)	Yes (sepsis)	Hepatic failure, Sepsis
15236766	85/Female	Schizophrenia	2 mg	Urinary tract infection, Sepsis	Yes (clocapramine, asenapine, suvorexant)	Yes (malnutrition, anemia, and multiple previous episodes of pneumonia	Abnormal nutritional condition

Table 6. Summary of Fatal Cases with a Serious Adverse Event Possibly* Related to Brexpiprazole in Patients Aged 65 Years and Older, Received by FDA Through December 31, 2022 (n=5)							
						and an intestinal obstruction)	
*See Section 2.1 and Table 2 for a definition and criteria for possible causality †Maximum daily dose of brexpiprazole used by the patient ‡Patient had a past medical history of Dementia Alzheimer's type §Patient reported to be receiving 2 mg/day of brexpiprazole, but the narrative does not indicate the dose was increased above 1 mg/day NR=Not reported							

3.1.1 Respiratory Events of Interest

We identified five cases of pneumonia possibly associated with brexpiprazole use either leading to hospitalization or death. There were two deaths, though only one death was attributed to pneumonia, and there were three non-fatal cases that led to hospitalization. In three cases, brexpiprazole was used for the treatment of neuropsychiatric symptoms associated with Alzheimer's dementia in clinical studies by the Applicant. These cases are summarized below:

FAERS Case #18618418, Version #6, MCN JP-OTSUKA-2020_031557, Initial FDA received date December 15, 2020, 15-Day, Japan, Death, Hospitalization
PTs: *Pneumonia aspiration, Marasmus*

An 89-year-old male with Alzheimer's disease started brexpiprazole in the open-label 14-week extension study 331-102-00184 (NCT03724942). He had previously received brexpiprazole as a study drug in a double-blind clinical trial for agitation associated with dementia of the Alzheimer's type for 3 months prior to the open-label study. His medical history was significant for hypertension and hyperlipidemia. He was also taking valsartan, nifedipine, donepezil, and pravastatin. Brexpiprazole was titrated from a 0.5 mg/day starting dose to 2 mg/day over 14 days. He then experienced oversedation and decreased oral intake, and the brexpiprazole dose was decreased to 1 mg/day 7 days later. There was some initial improvement in sedation, but he was noted to be experiencing daytime drowsiness, salivation, and increased swallowing time 9 days after reducing brexpiprazole to 1 mg/day, and 27 days after reducing the dose he had a temperature of 38 degrees Celsius and was given an antipyretic with resolution of fever. He was ultimately diagnosed with aspiration pneumonia 1 week later (43 days after the dose increase of brexpiprazole to 2 mg/day and 36 days after the dose reduction to 1 mg/day) with fever, worsening arousal, dysphagia, and decreased intake. Brexpiprazole was discontinued on the same day. He was treated with tazobactam. White blood cell (WBC) count was within the normal range 1 week later, and the patient's pneumonia was considered resolving. He did continue to display periodic hypoxia, pyrexia, wheezing, and decreased responsiveness. The patient died just over 1 month after discontinuing brexpiprazole. No autopsy was performed. Cause of death was attributed to decreased physical function and debility due to aging.

FAERS Case #19367465, Version #1, MCN JP OTSUKA-2021_018242, Initial FDA received date June 2, 2021, 15-Day, Japan, Hospitalization
PT: *Pneumonia aspiration*

A 73-year-old female with Alzheimer's disease and hypertension began brexpiprazole at 0.5 mg/day through a clinical study (NCT03724942). Her dose was increased to 1 mg/day after 7 days and increased again to 2 mg/day 14 days after initiation. Other medications included memantine, galantamine, valproic acid, and alacepril. Seventeen days later, the patient was noted to have "convulsion like tremulousness." Patient was diagnosed with aspiration pneumonia 34 days after drug initiation and brexpiprazole was discontinued. Patient was hospitalized for treatment of aspiration pneumonia.

FAERS Case #16688823, Version 8, MCN JP-OTSUKA-2019_028588, Initial FDA received date August 9, 2019, 15-Day, Japan, Hospitalization, Other
PTs: *Pneumonia aspiration, Hepatic mass*

A 75-year-old male with Alzheimer's type dementia participated in clinical trial 331-102-00088 (NCT0362098) and started on study drug brexpiprazole. The dosage of brexpiprazole was not reported. His past medical history was significant for gastric ulcer, iron deficiency anemia, and syncope. Other medications included memantine, ramelteon, and ferrous citrate. He became febrile and was diagnosed with aspiration pneumonia 12 days after starting brexpiprazole. Brexpiprazole was discontinued at that time. Pneumonia was reported as resolved, but without a specific date. The patient was later noted to have multiple hepatic masses approximately 2.5 months after brexpiprazole initiation.

Reviewer Comments: We assessed causality as possible in these three cases given the temporal relationship between brexpiprazole use and pneumonia or events that increased the risk for an aspiration event. In the two non-fatal cases, the onset of pneumonia was within 20 days of brexpiprazole initiation. In the fatal case ***(FAERS Case #18618418****), the increase in brexpiprazole to 2 mg/day was associated with oversedation and eating difficulties, which could have increased the risk for an aspiration event. However, the significant time between initial brexpiprazole exposure and the dose increase to 2 mg in relation to the aspiration pneumonia event (134 days and 43 days, respectively) make an association less likely. This was also the one fatal case out of the three patients with Alzheimer's disease in our case series, but the cause of death was not specifically attributed to pneumonia given the transient improvement in symptoms and laboratory values after antibiotic treatment. Also, without detailed medical data and knowledge of the treatment strategy based on the patient's or family's wishes, it is difficult to ascertain what intermediary medical events occurred between the pneumonia and death.*

Other concurrent medications could have contributed to the risk for aspiration pneumonia in these patients. Medications associated with somnolence or dysphagia have the potential to increase the risk for aspiration pneumonia.[22,23] *In* ***FAERS Case #19367465****, the patient was taking valproic acid which has been associated with sedation and dysphagia,*[23] *and in* ***FAERS Case #16688823,*** *the patient was taking ramelteon, which can cause somnolence.*[24] *All three patients were taking cognitive enhancing medications: two patients taking memantine, and two patients taking acetylcholinesterase inhibitors. Some observational studies have noted higher frequency of pneumonia in patients taking cognitive agents, but the overall relationship is unclear.*[25, 26]

The brexpiprazole labeling mentions pneumonia parenthetically under Section 5.1 as one of the potential causes of increased mortality in elderly patients treated with antipsychotics for dementia-related psychosis. The labeling also notes the potential for esophageal dysmotility and aspiration with antipsychotic drug use and to use cautiously in patients at risk for aspiration in Section 5.13.[13] However, as already noted, the brexpiprazole labeling omits specific reference to Alzheimer's dementia and pneumonia in contrast to some of the atypical antipsychotics. Antipsychotics are speculated to increase pneumonia risk through a number of mechanisms. Dysphagia and increased aspiration risk may be the result of drug related extrapyramidal symptoms, dyskinesias, changes in salivation, and other effects on oropharyngeal and esophageal function.[22, 23] Patients with Alzheimer's disease are already at increased risk for dysphagia and have increased mean latency in swallowing reflex which can be exacerbated by antipsychotics.[27] Antipsychotics can also potentially cause sedation and decreased alertness, leading to delays in swallowing and compromising airway protection. Aside from increasing the risk of an aspiration event, there is speculation that antipsychotics could impact immune function and therefore affect the ability to stave off worsening infection.[28]

Our ability to determine a specific causal role for brexpiprazole in these cases was limited due to the presence of elevated baseline risks for pneumonia from increased age and Alzheimer's disease, though it is possible brexpiprazole played a contributory role in conjunction with other risk factors. Independent of antipsychotic medications, patients with dementia have higher rates of pneumonia associated mortality compared to patients without dementia.[29] There are a number of factors that might be related to this increased risk. Dysphagia is particularly noticeable in later stages of dementia, although the specific onset is not well known and there can be deficits earlier in the course of illness.[30] Patients with dementia can suffer from anosmia and xerostomia and usually need assisted feeding due to amnesia and apraxia, all of which can increase the risk for aspiration.[31] Patients with dementia may also have difficulty effectively managing and clearing airway secretions. Finally, diagnosis of pneumonia may also be delayed by a patient's inability to communicate, failure to mount a robust immune response, and lack of caregiver awareness or monitoring.

The following two cases reported brexpiprazole use for schizophrenia, although one patient was also noted to have a prior brain contusion and unspecified type dementia. There was one death out of these two cases.

FAERS Case #16965973, Version # 4, MCN JP-OTSUKA-2019_036417, Initial FDA received date October 28, 2019, 15-Day, Japan, Death, Hospitalization, Other
PTs: *Interstitial lung disease, Pneumonia bacteria, Electrolyte imbalance, Liver disorder*

A 74-year-old male with schizophrenia received brexpiprazole starting at 1 mg/day. Thirty-five days later, his brexpiprazole dose was increased to 2 mg/day, his olanzapine dose was reduced to 2.5 mg/day, suvorexant 15mg/day was continued, and ramelteon 8 mg/day was also added. Eighteen days after the brexpiprazole was increased to 2 mg/day, the patient was hospitalized for aspiration pneumonia. Brexpiprazole and olanzapine were discontinued at that time. His pneumonia worsened over the following week, and he experienced worsening hypernatremia. There is no mention of antibiotic or other treatment. The patient died 17 days after admission. His death was attributed to aspiration pneumonia, although no autopsy was performed.

FAERS Case #15614118, Version #, MCN JP-OTSUKA-2018_035758, Initial FDA received date November 13, 2018, 15-Day, Japan, Hospitalization
PT: *Pneumonia aspiration*

A 74-year-old male with schizophrenia, dementia of unspecified type with previously noted brain contusion, and diabetes mellitus was started on brexpiprazole 1 mg/day. His other medications included memantine, flunitrazepam, nitrazepam, and linaclotide. He became hypoxic and febrile and was diagnosed with aspiration pneumonia 18 days after brexpiprazole initiation. The patient was hospitalized for treatment of aspiration pneumonia, which ultimately resolved 102 days after brexpiprazole initiation.

Reviewer Comments: We assessed causality in these two cases as possible given the temporal relationship between brexpiprazole use and the onset of pneumonia event. The patient who died ***(FAERS Case #16965973)*** *had a 69-day interval from brexpiprazole initiation to the pneumonia event, which makes an association less likely. However, a dose increase to 2 mg/day 18 days prior to the pneumonia diagnosis may have been a factor, although there was also a simultaneous addition of ramelteon to the regimen. In this case, pneumonia led to hospitalization and was considered the likely cause of death, but it was unclear the level of treatment aggressiveness and no autopsy was performed. In* ***FAERS Case #15614118****, the pneumonia event occurred 18 days after brexpiprazole initiation and led to hospitalization.*

Both cases had other factors that were potentially contributory. Both patients were treated with multiple other sedating medications, including one patient on a second antipsychotic and the other on two benzodiazepines, that could have caused sedation, dysphagia, and increased pneumonia risk.[18, 22, 23] *Aside from patients with Alzheimer's disease, antipsychotics have been associated with an increased risk of pneumonia in non-Alzheimer's disease cohorts.*[32] *Abnormal eating and swallowing have also been reported in patients with schizophrenia independent of antipsychotic medications, although systematic studies are lacking.*[33]

Both patients were at increased risk for pneumonia due to increased age, and one patient had comorbid dementia and diabetes mellitus which could additionally increase risk for pneumonia-related hospitalization.[34] *In this context, it is difficult to assess the specific contribution to aspiration pneumonia from brexpiprazole, but given the timing, we could not exclude the possibility that brexpiprazole may have played a role in these patients with elevated risk due to primary medical conditions and concomitant medications.*

3.1.1 Neuroleptic Malignant Syndrome and Extrapyramidal Adverse Events

We identified four cases of EPS and two cases of neuroleptic malignant syndrome (NMS) possibly associated with brexpiprazole use. There were no fatal cases and no cases that used brexpiprazole specifically for a dementia indication.

Neuroleptic Malignant Syndrome

The two cases of NMS either leading to hospitalization or prolonging a hospitalization are summarized below:

FAERS Case #14949105, Version #3, MCN JP-OTSUKA-2018_013646, Initial FDA received date May 29, 2018, 15-Day, Japan, Hospitalization, Other
PTs: *Neuroleptic malignant syndrome*

A 69-year-old female began brexpiprazole 1 mg/day for schizophrenia. The patient was in the middle of a medication switch and at times was receiving three additional antipsychotics: olanzapine, quetiapine, and zotepine. Other medications included mirtazapine and valproic acid. Indication, dosage, and therapy dates were not reported for the other antipsychotics and medications. On day 3 of brexpiprazole, the patient began experiencing restlessness and her laboratory values demonstrated elevated creatinine kinase (CK) of 1380 (unit unspecified). On the same day, the patient developed fever and muscle rigidity and was diagnosed with NMS. Brexpiprazole was discontinued and the patient received dantrolene. Her CK and blood urea nitrogen improved; however, the patient subsequently experienced a seizure (history of epilepsy) and was transferred to receive treatment. The patient's symptoms "relatively improved" for NMS and her symptoms related to seizures "were ameliorated".

FAERS Case #19984997, Version #4, MCN JP-OTSUKA-2021_032240, Initial FDA received date October 22, 2021, 15-Day, Japan, Hospitalization, Other
PTs: *Neuroleptic malignant syndrome, Fluid intake reduced, Dehydration, Off label use, Drug level increased*

A 77-year-old female was initially receiving brexpiprazole 1 mg/day for unspecified psychotic symptoms. Brexpiprazole was increased to 2 mg/day a week later. The patient began experiencing generalized muscle rigidity, tremor, salivation, and incontinence 33 days after dose increase. At the time of starting to experience these symptoms, the patient was also receiving candesartan 8 mg, tandospirone 20 mg, and quetiapine 25 mg (frequencies and indication not reported). Brexpiprazole was interrupted 10 days after symptom development; however, the patient continued quetiapine 25 mg/day. Four days after discontinuing brexpiprazole the patient developed fever, generalized muscle rigidity, leukocytosis, and had an elevated CK. Fluid replacement and dantrolene 150 mg/day was started. Six days after starting treatment with dantrolene, the patient's symptoms (e.g., fever, muscle rigidity) and CK elevation improved.

Reviewer Comments: We assessed causality as possible in these two cases given the temporal relationship between brexpiprazole use and NMS, but each case was complicated by antipsychotic polypharmacy which precluded exclusive linkage to brexpiprazole. ***FAERS Case #14949105*** *involved the use of multiple antipsychotics (i.e., brexpiprazole, olanzapine, quetiapine, zotepine), and in* ***FAERS Case #19984997****, the patient was concurrently treated with quetiapine. Therefore, it is challenging to identify one antipsychotic as the primary cause of NMS, and the concomitant use of multiple antipsychotics is a risk factor for the development of NMS.*[35]

In ***FAERS Case #19984997,*** *there were also conflicting details in time to onset of NMS from the brexpiprazole dose increase that limited the certainty of a causal association with brexpiprazole.*

Dates provided in the case indicated a 33-day time lapse between occurrence of NMS and brexpiprazole increase; however, the Applicant reviewers' comments indicate NMS occurred approximately 1 week after the dose increase, which would provide a stronger causal link with NMS. This differential in time to onset is significant, as NMS typically develops within 1 week and it would be uncommon for NMS to develop after 1 month of treatment.[36]

NMS is a known adverse event associated with all antipsychotics and is listed in the WARNINGS AND PRECAUTIONS section of the brexpiprazole labeling.[13]

Extrapyramidal Adverse Events

We summarized three of the four cases of EPS with possible causality associated with brexpiprazole use below. The fourth case **(FAERS Case #15331081)** is reviewed under section ***3.13 Cognitive Events of Interest***. Two of the cases reported the EPS resulted in hospitalization. The reason for hospitalization was unclear in the remaining two EPS cases.

FAERS Case #19627704, Version #2, Manufacturer Control # (MCN) JP-OTSUKA-2021_025686, Initial FDA received date July 28, 2021, 15-Day, Japan, Hospitalization
PTs: *Reduced facial expression, Parkinsonism, Gait disturbance, Parkinsonian gait, Salivary hypersecretion, Akathisia, Drug effective for unapproved indication*

Hirata et al.[37] reported a female in her late 60s received brexpiprazole 2 mg/day during a hospitalization for delusional disorder. After noted improvement on brexpiprazole, the patient was discharged from the hospital. The patient subsequently returned to the hospital, approximately 1 month later, presenting with akathisia, salivation, reduced facial expression, and gait disturbance. Drug-induced parkinsonism was suspected, leading to discontinuation of brexpiprazole. Improvement in motor function was minimal after discontinuation of brexpiprazole, guiding the clinicians to assume the clinical presentation could be caused by either Parkinson's disease or Lewy body dementia.

FAERS Case #16621825, Version #1, MCN US-OTSUKA-2018_039342, Initial FDA received date July 23, 2019, 15-Day, USA, Hospitalization
PTs: *Akathisia, Motor dysfunction, Heart rate increased, Blood pressure increased, Incorrect dosage administered*

A 72-year-old female with schizophrenia was admitted to the hospital for presumed drug-induced akathisia and diminished motor function about 1 month after starting brexpiprazole 3 mg/day. The patient previously visited the emergency room 1 week earlier with an elevated blood pressure of 200/80 mmHg and a heart rate of 108 beats per minute. The patient's concurrent medical conditions included depression, bipolar disorder, schizophrenia, and hypertension. The patient was also receiving losartan (unspecified dosage and indication). Brexpiprazole was withdrawn the day prior to the patient's arrival at the emergency room. The outcome of the events were not reported.

FAERS Case #15155181, Version #1, MCN US-OTSUKA-2018_013646, Initial FDA received date: May 29, 2018, 15-Day, USA, Hospitalization

PTs: *Dyskinesia, Tardive dyskinesia, Akathisia*

A 72-year-old female developed akathisia and involuntary mouth movements approximately 1.5 weeks after starting brexpiprazole 1 mg (unspecified frequency) for MDD. Brexpiprazole was stopped and the patient received benztropine. The involuntary mouth movements and akathisia were still ongoing.

Reviewer Comments: We assessed causality as possible for these three cases given the temporal relationship between brexpiprazole use and EPS. Akathisia and pseudoparkinsonism are known adverse events with antipsychotics, including brexpiprazole. In the pooled 6-week placebo-controlled, fixed-dose MDD trials in adults, akathisia rates were 4%, 7%, and 14% with the 1 mg, 2 mg, and 3 mg doses of brexpiprazole, respectively.[13] Drug-induced parkinsonism typically occurs between 2 to 4 weeks for longer half-life antipsychotics [38,39] and antipsychotic-induced akathisia occurs in approximately 50% of cases after 25 days of treatment and 90% of cases within 73 days of treatment.[40] Thus, the time frame for symptom development in these cases was congruent with the typical onset with a longer half-life antipsychotic, such as brexpiprazole which has a plasma half-life of 91 hours.[13] Accordingly, a negative dechallenge (i.e., continued presence of an adverse event after withdrawal of the suspected medication)[41] does not rule out a contributing role of brexpiprazole in these cases because symptom resolution could take longer to see improvement, and it is unclear if the duration of monitoring for symptom resolution after brexpiprazole discontinuation was sufficient. However, in ***FAERS Case #15155181,*** *we felt it unlikely that brexpiprazole was related to onset of tardive dyskinesia after 1.5 weeks of treatment since the majority of tardive movements occur after 1 to 6 months of treatment.[40, 42]*

In both cases, the certainty of causal relationship was limited by a lack of pertinent medical history and our inability to rule-out other causes of motor symptoms, such as underlying neurological disease or traumatic brain injury. Additionally, other medication interventions to help resolve acute drug-induced EPS were either not reported, or would likely be ineffective, such as the use of benztropine in ***FAERS Case #15155181*** *for the treatment of akathisia.[43]*

3.1.2 Cognitive Events of Interest

We identified one case of cognitive abnormality and EPS possibly associated with brexpiprazole use; it is detailed below:

FAERS Case #15331081, Version #3, MCN JP-OTSUKA-2018_029476, Initial FDA received date August 29, 2018, 15-Day, Japan, Hospitalization, Other
PTs: *Restlessness; Anxiety; Hallucination, auditory; Rhabdomyolysis; Soliloquy; Thinking abnormal; Muscle rigidity; Bradykinesia*

A 66-year-old female began brexpiprazole 1 mg/day for schizophrenia and increased to 2 mg/day 1 week later. The patient was also receiving perospirone at the time, an antipsychotic marketed in Japan. Reportedly, the patient used quetiapine, biperiden, and flunitrazepam; however, it is uncertain when the patient received these treatments. Eleven days after starting brexpiprazole, she experienced restlessness and auditory hallucinations. On day 14 of brexpiprazole, she was noted to have muscle rigidity and bradykinesia. On day 16, incoherent speech and disorganized

behavior were reported. Nineteen days after starting brexpiprazole, the patient received intravenous haloperidol (unclear dosage) for 3 days. On the second day of receiving haloperidol, the patient developed diaphoresis and brexpiprazole was discontinued (day 20). The patient subsequently developed fever and muscle tightness on the second day of receiving haloperidol. Two days after discontinuing brexpiprazole the patient had significant muscle tightness and creatine kinase was elevated. The patient received intravenous fluids, ceftriaxone, and nifedipine. Eight days after discontinuing brexpiprazole, CK was reduced, and the patient's fever resolved. Forty days after discontinuing brexpiprazole the patient's condition had fully remitted.

Reviewer Comments: We considered these adverse events as possibly related to brexpiprazole, as we could not entirely exclude a potential role. However, this case was complicated by the use of multiple antipsychotics which precluded causal attribution to a single agent. For the EPS, the patient experienced bradykinesia 2 weeks after initiation of brexpiprazole, so it is possible this was a drug-induced effect given the temporal relationship. However, the presence of at least one, and potentially two other, antipsychotics makes it difficult to draw specific conclusions about brexpiprazole's role. It was not reported when and at what dosage biperiden was used. Biperiden may have been used for treatment of new and emerging symptoms, but it is also feasible it was already being used for treatment of pre-existing EPS related to perospirone prior to initiation of brexpiprazole.

The later onset of muscle rigidity, increased CK, and fever could have been manifestations of NMS. Although these signs and symptoms developed after discontinuing brexpiprazole, we could not rule out an association given its long plasma half-life. However, the other major complicating factor is that these issues occurred after the addition of intravenous haloperidol to an existing regimen of antipsychotics. The patient's age, sex, and potency of dopamine receptor blocking agents used (i.e., haloperidol) are all risk factors for developing EPS,[42] and antipsychotic polypharmacy is a risk factor for the development of NMS.[35] Finally, the later use of antibiotics implies that an infectious cause was also in the differential.

Regarding the cognitive abnormalities reported, the constellation of symptoms seems more consistent with patient's primary psychiatric illness. The lack of detail on initial psychiatric presentation and interval mental status examinations makes it difficult to gauge changes over time. However, the patient could have developed a superimposed delirium, either within the context of developing NMS or simply from elevated risk because of age and presence of multiple psychoactive drugs.[44] In either case, brexpiprazole's role might have been an additional risk in aggregate with other potential contributing medications, including multiple antipsychotics and a benzodiazepine. Antipsychotics have the potential to induce delirium in older adults, which in turn is associated with negative effects on health outcomes, increased institutionalization, and overall mortality.[45] The other consideration that could diminish the likelihood of brexpriprazole causality is the possibility of latent infection as noted above.

Brexpiprazole's binding profile suggests limited anticholinergic and antihistaminergic properties and potentially lower risk of cognitive side effects and sedation.[46] However, effects on cognition and memory are still potential safety concerns due to the limited experience with brexpiprazole in older adults and the potential use in a high-risk population. Aside from the recent studies examining brexpiprazole for agitation in Alzheimer's disease, there have been

only small numbers of patients over the age of 65 in adjunctive depression treatment trials. Section 5.14 of the brexpiprazole labeling warns of the potential for cognitive and motor impairment,[13] (b) (4)

Antipsychotics have been associated with negative acute and chronic cognitive effects, although the relationship between antipsychotics and cognitive functioning is complex and may vary by drug, duration of treatment, patient population, and specific context studied. There are multiple potential cognitive impacts from antipsychotics in patients with Alzheimer's disease. Acutely, antipsychotics could cause somnolence and inattention, impairing daily function. Antipsychotics also have the potential to induce delirium, and adults with Alzheimer's dementia are at increased risk due to their baseline impairments and the frequent presence of polypharmacy. Delirium could exacerbate problems with agitation and aggression, leading to a vicious cycle of antipsychotic dose escalation and exacerbation of cognitive and behavioral problems. Delirium is also associated with negative effects on health outcomes, increased institutionalization, and overall mortality.[47,48] *However, the long-term impact of antipsychotics on cognition in Alzheimer's disease is unclear. There is concern that antipsychotic use may speed the rate of cognitive decline in patients with Alzheimer's disease,*[49] *but data is limited in this regard.*

3.1.3 Cardiovascular Events of Interest

We identified one case reporting a cardiovascular adverse event leading to hospitalization that was possibly associated with brexpiprazole use. This case is described below:

FAERS Case #15136340, Version # 1, MCN US-OTSUKA-2018_011296, Initial FDA received date July 12, 2018, 15-Day, USA, Hospitalization, Other
PTs: *Sinus tachycardia, Transient ischemic attack*

A 68-year-old female with a history of hypertension, hyperlipidemia, and hypothyroidism started brexpiprazole 1 mg/day for MDD. She was also taking duloxetine 90 mg/day and alprazolam 0.5 mg as needed for an unspecified indication. Thirty-four days after starting brexpiprazole, she was hospitalized for 24 hours for evaluation of a possible cerebrovascular event. However, brain magnetic resonance imaging and angiography did not find evidence for a new cerebrovascular event or other acute pathology. Antiplatelet treatment, if any, was not reported. The patient was given a discharge diagnosis of transient ischemic attack (TIA). Brexpipraozle was discontinued.

Reviewer Comments: We assessed causality in this case as possible given the temporal association between the initiation of brexpiprazole and the TIA event, and we could not entirely exclude the possibility of a relationship with brexpiprazole. However, there were no specific neurological findings or history reported to help support the diagnosis of TIA, and a TIA diagnosis can be difficult to interpret given the temporal nature of symptoms and varying definitions that have been used over time.[50] *Diagnostic testing did not reveal any evidence of a new cerebrovascular event. This patient had existing risk factors for a cerebrovascular event, including age, hypertension, and hyperlipidemia. There were no new acute findings on neuroimaging, so it is unclear if this was reference to existing small vessel cerebrovascular*

disease or a past lacunar infarct. The patient was also taking duloxetine, which has the potential to increase blood pressure.

Antipsychotics have been associated with increased risk for cerebrovascular adverse events in older adults with dementia-related psychosis as noted previously. However, it is not known whether this risk is unique to older adults with dementia. There has been concern for increased risk for cardiovascular events with antipsychotic use in general community-dwelling elderly populations (including patients without dementia) within the first weeks of treatment, although this risk may decrease over time with treatment.[51] Aside from the acute risk, atypical antipsychotics have also been associated with metabolic changes that may increase longer term cerebrovascular risk, including hyperglycemia, dyslipidemia, and body weight gain.

Brexpiprazole labeling refers to an associated increase in cerebrovascular events, specifically citing placebo-controlled trials in elderly patients with dementia who were randomized to risperidone, aripiprazole, and olanzapine that had a higher incidence of stroke and TIA, including fatal stroke.[13] A number of mechanisms have been postulated for increased risk for cerebrovascular events in patients with dementia treated with antipsychotics, but clear data to support these various hypotheses is lacking.[52,53] Absent clarification on specific pathophysiology or additional data, one cannot say brexpiprazole would have any particular advantage compared to other antipsychotics in this regard.

In terms of other cardiac events, there were no cases of sudden cardiac death, arrhythmia, congestive heart failure, or myocardial infarction caused by brexpiprazole in our case series. Brexpiprazole does not appear to significantly increase the corrected QT interval based on the data available, but other antipsychotics have been associated with QT interval prolongation and sudden cardiac death. Section 5.9 of the brexpiprazole labeling also includes the warnings on the risks for orthostatic hypotension and syncope similar to other atypical antipsychotics, and the admonition to monitor patients who are vulnerable to hypotension, including the elderly.[13]

3.1.4 Gastrointestinal and Hepatobiliary Events of Interest

We identified three cases of gastrointestinal and hepatobiliary events possibly associated with brexpiprazole use either leading to hospitalization or death. A case of drug-induced liver injury (DILI) is presented first, followed by two cases of ileus.

FAERS Case #17528871, Version #3, MCN JP-OTSUKA-2020_006912, Initial FDA received date March 11, 2020, 15-Day, Japan, Death, Life-threatening, Other
PTs: *Drug-induced liver injury, Hepatic failure, Sepsis*

A 75-year-old-male was admitted to a hospital for an unspecified cause. During the hospitalization the patient was started on valproate and received treatment with cefcapene for unknown reasons. Thirty-six days after starting valproate, the patient was started on brexpiprazole 1 mg/day for schizophrenia. Previous laboratory work-up a month prior revealed aspartate aminotransferase (AST) 50 u/L, alanine transaminase (ALT) 78 u/L, alkaline phosphatase (ALP) 321 u/L, and gamma-glutamyl transpeptidase (GGT) 30 u/L. Two days after starting brexpiprazole, his laboratory worked revealed AST 538 u/L, ALT 552 u/L, ALP 615

u/L, GGT 71 u/L, and total bilirubin 0.6 mg/dL. All medications were subsequently discontinued. Two days after discontinuing brexpiprazole, the patient's mental status worsened and the patient was started on zotepine and suvorexant. The patient was eventually transferred to another hospital and the patient's hepatic function never stabilized. Ten days after brexpiprazole was discontinued, the patient's ALT and AST increased to 4283 u/L and 7846 u/L, respectively. The patient's GGT increased to 196 u/L. ALP and total bilirubin were not reported. The patient received prednisolone for hepatic failure prophylaxis with some improvements (unspecified laboratory values). Thirty-four days after discontinuing brexpiprazole the patient was diagnosed with sepsis. The patient's condition deteriorated, and the patient died 40 days after stopping brexpiprazole.

Reviewer Comments: We assessed causality in this case as possible given the temporal association between the initiation of brexpiprazole and DILI. Although causality is plausible with brexpiprazole, several other factors likely contributed and the differential diagnosis for liver injury is broad. The patient was receiving valproate, a known hepatotoxic medication,[54] *and the time course for DILI was more congruent with the timing of receiving valproate (i.e., 38 days) versus brexpiprazole (i.e., 2 days).*[55] *The patient also had an elevated ALP prior to starting treatment with brexpiprazole, indicating possible liver pathology prior to starting therapy. The case does not mention ruling out cholestatic causes or extrahepatic causes of liver disease, which would be in the differential given subsequent elevations in ALP and GGT. The elevations in AST, ALT, and ALP might imply a severe impact on hepatocellular processes. Additionally, an infection and use of beta-lactam antibiotics can contribute to underlying mechanisms of liver injury.*[56] *Details regarding the reasoning for the patient's initial hospitalization and reasons for receiving cefacapene are missing from the case, implying other disease states could have played a contributing role in the patient's death. The patient's death appears to be secondary to sepsis, which occurred 40 days after brexpiprazole discontinuation; therefore, limiting a distinct causal role with brexpiprazole only.*

DILI has been reported with other atypical antipsychotics. The underlying mechanisms are poorly understood and many have been idiosyncratic in nature.[57] *Although the time course for developing DILI is plausible with brexpiprazole, the use of multiple medications concomitantly in the patient and unknown details regarding the patient's underlying infection makes it challenging to determine the true cause of DILI. The development of liver injury in this patient is likely multifactorial.*

FAERS Case #18580278, Version #4, MCN JP-OTSUKA-2021_032240, Initial FDA received date December 4, 2020, 15-Day, Japan, Hospitalization, Other
PT: *Ileus paralytic*

A 75-year-old male was switched to brexpiprazole 1 mg/day for schizophrenia after developing paralytic ileus previously on treatment with blonanserin. His past medical history (PMH) is significant for carcinoma of the large intestine resulting in a previous intestinal surgery. Other medications were reported including: dutasteride, silodosin, sennosides, neostigmine, magnesium oxide, panax ginseng root, zanthoxylum piperitum pericarp, zingiber officinale processed rhizome, pantethine, bacillus mesentericus, clostridium buytricum, and enterococcus faecalis. It is unclear if the patient was concomitantly taking these medications, and the dosage and

indication were not reported. The patient was also reported to be receiving 3 packs/day of ninjin yoeito, a traditional Japanese medicine, but it was unclear if he was taking it at the time of the event. Six days after starting brexpiprazole, the dose was increased to 2 mg/day. Fifty-four days after starting brexpiprazole, the patient developed paralytic ileus. Brexpiprazole was continued, and the patient received intravenous fluids with improvement of symptoms. Nineteen days after symptom resolution, the patient developed a recurrence of paralytic ileus. Brexpiprazole was discontinued and the patient was treated with blonanserin. The symptoms of paralytic ileus started to resolve 1 day after discontinuing brexpiprazole. The patient subsequently developed sigmoid colon volvulus approximately 9 months after brexpiprazole was discontinued and required emergency surgery. Outcome of the surgery was not reported.

FAERS Case #16979432, Version #3, MCN JP-OTSUKA-2019_036627, Initial FDA Received Date October 31, 2019, 15-Day, Japan, Hospitalization
PT: *Ileus*

A 70-year-old female began brexpiprazole 1 mg/day for schizophrenia. Eighty-six days after starting brexpiprazole, the patient developed ileus and was subsequently hospitalized on an unspecified date. Brexpiprazole was discontinued the day prior to her diagnosis of ileus and the patient received laxative treatment. Symptoms resolved 45 days after discontinuation of brexpiprazole.

Reviewer Comments: We assessed causality in these cases as possible given the development of ileus while receiving treatment with brexpiprazole and improvement with discontinuation of brexpiprazole. However, there are other contributing factors that limit the certainty of a causal association with brexpiprazole. In ***FAERS Case #*****18580278**, *the patient had a history of ileus, a history of intestinal carcinoma with unspecified status, and prior intestinal surgery. Functional obstruction of the gastrointestinal tract can be secondary to multiple causes including previous surgical procedures, abdominal inflammation, electrolyte abnormalities, hyperparathyroidism, and neuropathies.*[58] *Additionally, this patient was receiving several concomitant therapies, including herbal medications with unknown potential effects on gastrointestinal motility, so a contributing role cannot be ruled out. In* ***FAERS Case #*****16979432**, *missing details about medical workup, differential diagnosis, the patient's surgical history, concurrent medical conditions, and concomitant medications limit the certainty of a drug-induced cause. Immobility, inactivity, and low fiber intake can also play a role in the development of ileus, which are factors often found in patients with untreated psychiatric illness.*[59]

Many medications, including antipsychotics, have been associated with ileus. Mechanisms underlying the cause of ileus have primarily been attributed to anticholinergic activity; however, brexpiprazole does not possess anticholinergic activity and other antipsychotics without significant binding affinity to cholinergic receptors have caused ileus.[58, 60] *The mechanisms mediating gastrointestinal hypomotility outside of cholinergic interventions is not well understood. The serotonin system is involved in gastrointestinal motility, which enhances afferent pathways to promote peristalsis and contraction of intestinal smooth muscle. Serotonin-2A (5-HT$_{2A}$) receptors are present within intestinal smooth muscle and activation can lead to intestinal contraction.*[46] *Brexpiprazole exerts antagonistic action at 5-HT$_{2A}$ receptors and inhibitory action at 5-HT$_{2A}$ receptors might theoretically contribute to the development of*

constipation based on biological mechanisms. Additionally, constipation is labeled as an adverse reaction in the brexpiprazole labeling and occurred in 2% of patients treated with brexpiprazole compared to 1% treated with placebo in the short-term, major depressive disorder trials in adults.[13] Thus it is plausible that complications such as ileus could result from untreated constipation.[58, 61]

3.1.5 Non-Respiratory Infectious Events of Interest

We identified two cases of UTIs possibly associated with brexpiprazole use either leading to hospitalization or death. We summarized these cases below:

FAERS Case #15827543, Version #1, MCN US-OTSUKA-2019_000966, Initial FDA received date January 15, 2019, 15-Day, USA, Hospitalization, Life-threatening, Other
PTs: *Cardiac arrest, Hypoxia, Confusional state, Cognitive Disorder, Hypercapnia, Dyspnea, Hypokinesia, Gait disturbance, Dizziness, Urinary tract infection, Incorrect dose administered*

A 70-year-old male began brexpiprazole 3 mg/day for depression. Medical history included asthma and anxiety including panic attacks. The patient was overweight and had an enlarged prostate. Concomitant medications included alprazolam, clonazepam, and salbutamol at unknown doses. The patient was hospitalized within 1 year of starting brexpiprazole because of confusion, dyspnea, dizziness, hypoxia, cognitive impairment, and shuffling gait. During the hospitalization a computed tomography (CT) scan conducted showed no positive findings. During the CT scan the patient subsequently went into cardiac arrest and was resuscitated. The patient was then diagnosed with a UTI and received “antibiotic” treatment with “fluxinase”. The UTI resolved; however, the patient continued to be hospitalized and remained confused and cognitively impaired.

FAERS Case #15236766, Version #4, MCN JP-OTSUKA-2018_027540, Initial FDA received date August 3, 2018, 15-Day, Japan, Death, Life-threatening, Disability
PTs: *Sepsis, Hypoglycemia, Urinary tract infection, Arrhythmia*

An 85-year-old female treated with brexpiprazole for schizophrenia died from sepsis secondary to a UTI. The patient’s medical history included multiple episodes of pneumonia over the past 2 years, ileus, and was malnourished for “a few years” until her death. The patient’s concurrent medical conditions included schizophrenia, malnutrition, anemia, and cardiac valve disease. The patient was receiving concomitant treatment with asenapine, suvorexant, clocapramine, and lubiprostone at unspecified dosages and for unspecified indications. Ninety-five days prior to her death, the patient was started on brexpiprazole 1 mg/day and titrated to 2 mg/day 8 days later. Nineteen days prior to her death, brexpiprazole was discontinued due to depressed level of consciousness. One day after brexpiprazole discontinuation, the patient developed a fever, hypotension, proteinuria, and had a positive unspecified bacterial test. The patient died from sepsis secondary to a UTI, 19 days after the discontinuation of brexpiprazole.

Reviewer Comments: We assessed both cases as having a possible causal association with brexpiprazole based on the temporal relationship between the drug and event. However, the high

*background rate of UTI development in older adults and the variable latency in developing a UTI makes it difficult to fully attribute the event to a drug-related cause.[43] Antipsychotics have been associated with an increased risk of UTI development in older adults in observational studies, even though mechanisms are not well understood [62], but both cases had underlying medical conditions that also increased risk. In **FAERS Case #15827543**, the presence of an enlarged prostate increases the risk for urinary retention and subsequent UTI.[63] Additional risk for urinary retention may have been conferred by concurrent treatment with benzodiazepines.[63] In **FAERS Case #15236766**, malnutrition and multiple recent pneumonias likely left the patient with a compromised immune system and limited ability to stave off infection. She was also treated with other antipsychotics (e.g., asenapine, clocapramine) and a sedative (e.g., suvorexant), which likely contributed to oversedation and downstream effects on feeding and immunity.*

3.1.6 Other Events of Interest

We identified five cases of interest that did not align with the previous SAE categories with the outcome of hospitalization or death possibly associated with brexpiprazole use. We summarized these cases below:

FAERS Case #21486653, Version #1, MCN US-OTSUKA-2022_048782, Initial FDA received date October 20, 2022, 15-Day, USA, Death, Other
PTs: *Toxicity to various agents, Suspected suicide*

A 78-year-old female died by suspected suicide secondary to acute-on-chronic exposure to multiple medications, including brexpiprazole. Other medications the patient was exposed to include amlodipine, carvedilol, lamotrigine, and trazodone. The patient's autopsy report revealed the following blood concentrations: lamotrigine 23 mcg/mL, metachlorophenylpiperazine 0.057 mcg/mL, and trazodone 1.8 mcg/mL. Blood concentrations were unknown for other medications.

Reviewer Comments: The lack of blood concentrations for brexpiprazole in the autopsy report does not rule out causal association with brexpiprazole; thus, we assessed the causality in this case as possible. Although a causal role for brexpiprazole cannot be ruled out, the presence of multiple medications likely contributed to the patient's death.

FAERS Case #14091827, Version #1, MCN FDA-CDER-CTU-2017-65488, Initial FDA received date October 13, 2017, Direct, USA, Hospitalization, Other
PTs: *Gambling disorder, Tobacco user, Depressed mood*

A 66-year-old male started brexpiprazole (unspecified dosage) as an augmenting agent for major depression. After taking brexpiprazole for 2 days, the patient began having strong compulsions to gamble and smoke cigarettes. These were vices the patient admitted to have problems with previously; however, he had been abstinent for approximately 1 year. The patient subsequently "lost all [of his] money" at a casino in the 2 following months after starting treatment. The patient became depressed and was admitted to a hospital for 9 days. The patient discontinued brexpiprazole prior to his hospital admission.

Reviewer Comments: The close temporal relationship in developing compulsive behaviors after starting brexpiprazole supports a possible causal role. Pathological Gambling and Other Compulsive Behaviors is listed in Section 5.7 of the brexpiprazole labeling.[13] Patients with gambling disorder can have spontaneous relapses, especially in times of heightened stress or depression, making it challenging to differentiate from drug-induced causes.[64] The absolute certainty of a causal relationship with brexpiprazole use and gambling disorder is limited by the inability to discriminate between a drug-induced cause and a spontaneous relapse in the natural course of illness.

FAERS Case #15676519, Version #2, MCN JP-OTSUKA-2018_037441AA, Initial FDA received date November 30, 2018, 15-Day, Japan, Hospitalization
PTs: *Neutropenia, Gastroenteritis, Product use in unapproved indication*

A 76-year-old female received treatment for senile depression with brexpiprazole 1 mg/day that was increased to 2 mg/day 11 days later. The patient was treated with mirtazapine concomitantly and it was started and increased at overlapping time intervals during brexpiprazole administration. Twelve days after the dose increase, the patient had a reduction in WBC count from 13,000 (unit unspecified, blood drawn the day before starting brexpiprazole) to 3000 (unit unspecified). The patient then began to experience fever and received a transfusion due to poor appetite. The patient was suspected to have gastroenteritis because of symptoms of vomiting and diarrhea. Brexpiprazole was discontinued. One day after brexpiprazole was discontinued and 29 days after the dose of brexpiprazole was increased, the patient's WBC count reduced further to 1000 (unit unspecified) and neutrophils were reported as "40". The patient was transferred to the hematology unit of the hospital. Five days after discontinuing brexpiprazole, the patient's WBC count improved to 8600 (unspecified units) and neutrophils improved to "6160". Of note, the patient's PMH included malignant lung cancer and uterine leiomyoma.

Reviewer Comments: We assessed this case of leukopenia as having a possible causal association with brexpiprazole based on the temporal relationship (i.e., time to onset 1.5 weeks) and positive dechallenge (i.e., leukopenia resolved after discontinuing brexpiprazole). Atypical antipsychotics, including brexpiprazole, have leukopenia and neutropenia listed in the WARNINGS AND PRECAUTIONS section of their labeling.[13] There are several contributing factors likely impacting the development of leukopenia. Agranulocytosis is listed in Section 5.2 of mirtazapine's labeling, thus a contributing role in the patient's leukopenia cannot be ruled out.[65] Additionally, the patient's PMH could have contributed to leukopenia development. The patient's poor appetite and nutritional status also likely played an influential role in WBC changes. It is unclear based on the narrative whether the reported value of 40 for neutrophils represented a percentage or unit, making it challenging to fully assess neutropenia in the case. Lack of details regarding the clinical status and treatment of the patient's malignant lung cancer further limits the overall assessment of the case.

FAERS Case #20987316, Version #4, MCN JP-OTSUKA-2022_032738, Initial FDA received date June 21, 2022, 15-Day, Japan, Hospitalization
PT: *Platelet count decreased*

A 94-year-old female was started on brexpiprazole 0.5 mg/day for delusion of poverty. Concurrent medical condition was gastroduodenal ulcer. Other medications included amlodipine, duloxetine, amoxicillin/clavulanate potassium, lemborexant, imidapril, alfaclcidol, pitavastatin, prednisolone, lansoprazole, alendronate, minodronic acid, and rosuvastatin. Ten days later, brexpiprazole was increased to 1 mg/day. On the day of initiating brexpiprazole the patient's platelet count was 173,000/mcL. Thirteen days after starting brexpiprazole the patient's platelet count dropped to 45,000/mcL and brexpiprazole was discontinued the day before. The platelet count had fully renormalized, nine days after stopping brexpiprazole.

Reviewer Comments: We assessed causality in this case as possible because the patient developed thrombocytopenia approximately 2 weeks after starting brexpiprazole, and her platelet count returned to a normal level after discontinuing brexpiprazole (i.e., positive dechallenge). However, certainty of a causal association with brexpiprazole is limited because of several unknown and additional contributing factors in the case. It is unclear if the patient was receiving each concomitant medication or if medications within the same class were substituted during transitions of care, making it difficult to determine whether concomitant medications played a contributing role. The patient was receiving amlodipine, which has been associated with thrombocytopenia.[58] *The reasoning for the patient's hospitalization is unclear and the concurrent gastroduodenal ulcer could be a cause of the patient's low platelets. Additionally, it is difficult to fully attribute thrombocytopenia to brexpiprazole because there are multiple etiologies for thrombocytopenia. Without information regarding the patient's current clinical status of the patient's medical conditions and information to rule out other medical causes, the certainty of a drug-induced cause is not absolute.*

FAERS Case #16918790, Version #4, MCN JP-OTSUKA-2019_034994, Initial FDA received date October 15, 2019, 15-Day, Japan, Hospitalization, Other
PTs: *Status epilepticus, Rhabdomyolysis*

A 72-year-old male started brexpiprazole 1 mg/day for schizophrenia. The patient's concomitant medications (dosage and indication not reported) included: olanzapine, tamsulosin, levetiracetam, and brotiozolam. Thirty-seven days after starting brexpiprazole, the patient developed status epilepticus and received an infusion of phenytoin. The next day the patient developed continuous and rapidly repeating seizures, fever, and discolored urine. Brexpiprazole was withdrawn. Laboratory measurements were obtained revealing an elevated creatine phosphokinase, AST, and ALT. The patient was diagnosed with rhabdomyolysis. The patient received fluid administration and an infusion of levetiracetam. The patient's seizures resolved (unclear timeframe). The patient's creatine phosphokinase, AST, and ALT values declined and the patient's fever improved. Rhabdomyolysis resolved 8 days after presenting with status epilepticus, and 45 days after brexpiprazole initiation. Brexpiprazole was not restarted.

Reviewer Comments: We assessed causality in this case as possible because the patient developed status epilepticus while receiving brexpiprazole and developed signs and symptoms of rhabdomyolysis. Although a causal role cannot be excluded with brexpiprazole, there are several contributing factors that limit the certainty of a causal association. Seizures is in Section 5.11 of the brexpiprazole labeling and antipsychotics, including olanzapine, are known to decrease seizure threshold.[13, 66] *Thus, olanzapine cannot be ruled out as a possible contributor to the*

development of the patient's seizure. It is unclear if the patient had a prior history of a seizure disorder and the indications for brotiozolam and levetiracetam were not specified. Information regarding indications for treatment and events leading up to the seizure are needed to help clarify and differentiate between other etiologies for seizure development. Although rhabdomyolysis can occur in the setting of NMS, the recurrent seizures the patient experienced likely resulted in muscle breakdown and contributed to the patient developing rhabdomyolysis.

3.2 LITERATURE SEARCH

DPV identified 14 publications using the search criteria outlined in **Table 4**. We excluded seven publications because they either did not involve brexpiprazole or the patient was less than 65 years of age. Three of the remaining seven publications reported adverse events associated with brexpiprazole use, including dyskinesia, tardive dystonia, and possible drug-induced parkinsonism. Pseudoparkinsonism and tardive dyskinesia are known adverse events with antipsychotics, including brexpiprazole. In the brexpiprazole labeling, tardive dyskinesia is in Section 5.5, and dystonia is in Section 6.1.[13] None of these patients were hospitalized or died and were not included in our case series. We summarized three literature case reports in **Appendix F**.

3.3 PERIODIC SAFETY REPORTS

DPV screened the Periodic Benefit-Risk Evaluation Reports (PBRERs) from July 10, 2018 through July 9, 2022, to identify safety concerns for brexpiprazole use in the older adult population not captured in our FAERS search and literature review.[67-73]

Each PBRER comments that the core safety profile is missing information about use of brexpiprazole in the elderly. Clinical trials investigating the use of brexpiprazole in elderly patients include one MDD trial and two phase 3 trials for the treatment of agitation associated with Alzheimer's disease. The Applicant commented that elderly patients treated with brexpiprazole had similar safety outcomes compared to the adult population in the MDD trial. Based on the data from the two phase 3 trials for the treatment of agitation associated with Alzheimer's disease, the Applicant commented that brexpiprazole was safe and well-tolerated in elderly patients.

We did not find any new safety concerns in the PBRERs regarding the use of brexpiprazole that were not captured in our FAERS search or literature review.

3.4 DRUG UTILIZATION

3.4.1 Setting of care

In 2022, U.S. manufacturer sales distribution data showed that (b) (4)% of total brexpiprazole tablets were primarily sold to outpatient retail pharmacies[b,c]. Approximately (b) (4)% of the total sales were to non-retail settings[d] and mail-order/specialty pharmacies, respectively. Based on this

[b] Outpatient retail pharmacies include chain stores, independent pharmacies, food stores.
[c] IQVIA National Sales Perspective™, NSP. Data year 2022. Extracted January 2023.
[d] Non-retail settings include clinics, non-federal hospitals, federal facilities, long-term care facilities, home health care, and other miscellaneous settings.

sales pattern, we assessed the utilization of brexpiprazole from U.S. outpatient retail pharmacies. Data from non-retail settings or mail-order/specialty pharmacies were not included in these analyses.

3.4.2 Patient utilization data

Table 7 in **Appendix G** shows the annual estimated number of patients who received a dispensed prescription for brexpiprazole from U.S. outpatient retail pharmacies, stratified by patient age, from 2017 through 2022. In 2022, an estimated total of (b) (4) patients aged 65 years or older were dispensed a prescription for brexpiprazole: representing approximately (b) (4)% of the total patients. Similar patterns were observed from 2017-2021. As illustrated in **Figure 2** below, brexpiprazole use among patients aged 65 years or older more than doubled from approximately (b) (4) patients in 2017 to (b) (4) patients in 2022. During the study period, among patients aged 65 years or older, the majority of brexpiprazole use was observed among patients aged 65 – 74 years, accounting for approximately (b) (4)% of total use in this population annually (data not shown).[e]

Figure 2. Annual estimated number of patients aged 65 years or older who received a dispensed prescription for brexpiprazole from U.S. outpatient retail pharmacies, from 2017 through 2022

Source: IQVIA Total Patient Tracker, TPT. Data years 2017 – 2022. Data extracted January 2023. File: 2022-3081 TPT Brexpiprazole patients 2017-2022_01-10-2023.xlsx. K represents thousands
Patient estimates are nationally projected based on a sample of prescriptions claims. Summing these projected patient counts across time periods may lead to differences due to rounding attributable to IQVIA's proprietary projection methodology utilized.

[e] IQVIA Total Patient Tracker, TPT. Data years 2017 – 2022. Extracted January 2023.

3.4.3 Office-based healthcare provider survey data

Table 8 shows the diagnoses (ICD-10-CM) associated with the use of brexpiprazole, stratified by patient age, as reported by U.S. office-based healthcare providers, from January 2017 through December 2022. Cumulatively from 2017 through 2022, brexpiprazole use mentions during office visits for patients aged 65 years or older were relatively low and accounted for approximately (b) (4)% of the total use mentions compared to patients aged 64 years or younger. Among patients aged 65 years or older, Major Depressive Disorder (MDD) single or recurrent episode (F32 – 33) was the top diagnosis, (b) (4)% of the use mentions, reported for brexpiprazole use during the study period. This was followed by bipolar disorder (F31) at approximately (b) (4)%, and schizophrenia (F20) at approximately (b) (4)% of brexpiprazole use mentions in this patient population. Of note, the use mentions reported for the diagnosis of bipolar disorder and schizophrenia were too low (b) (4). Therefore, given the small sample size and low precision associated with the estimates, these data may not be representative of national use. No use mentions for brexpiprazole was reported for Alzheimer's dementia diagnosis in this patient population during the study period. It is worth mentioning that the lack of data could possibly be related to less common use of brexpiprazole for this unlabeled indication or an inherent limitation of these survey data— not robust enough to capture less common use of drugs.

Table 8. Diagnoses† associated with the use of brexpiprazole, stratified by patient age, as reported by office-based healthcare providers, from January 2017 to December 2022, cumulative.

Source: Syneos Health Research & Insights LLC., Treatment Answers™. Data years 2017 – 2022. Data extracted January 2023. File: 2022-3081 PDDA_Brexpiprazole_diagnoses_02-07-2023.xlsx
MDD represents Major Depressive Disorder. Use refers to the mentions of a drug in association with a diagnosis during a patient's visit to an office-based healthcare provider's practice.
†Diagnoses information in terms of 'use mentions" were obtained from a survey database from a sample of office-based healthcare providers reporting on patient activity during one typical workday per month. These "use mentions" are not linked to and may not result in dispensed prescriptions.
††The projected use mentions below 100,000 estimates may not be representative of providers' prescribing habits at the national level.

4 LIMITATIONS

When considering databases to assess postmarketing safety, it is prudent to consider the strengths and limitations of the respective database used. The main utilities of the FAERS database include assessing the reports for any new safety signals associated with the marketed products, including rare adverse events. The FAERS database is particularly useful for detecting rare and serious adverse events with drugs. However, FAERS data have limitations. FAERS data cannot be used to quantify risks and events with high background rates are difficult to assess, as in the case of pneumonia, cardiovascular disease, or urinary tract infections in the older adult population. Underreporting, a limitation of FAERS, exists due to the fact that reporting of adverse events by health care professionals and consumers is voluntary. For any given report, there is no certainty that the reported suspect product(s) led to the reported adverse event(s). Individual causality assessments in our review cannot be made in many circumstances, due to the confounding factors and limited details in many reports.

Drug utilization analyses should be interpreted within the context of the limitations of the databases used. The patient exposure estimates are generalizable to utilization in outpatient retail pharmacies and may not be applicable to non-retail institutions (such as clinics, hospitals, long-term care facilities, mail-order/specialty pharmacies) where this product may be used. The patient estimates are not intended to be representations of exact enumerations but are nationally projected based on a sample of prescriptions claims. Summing projected patient estimates across age groups or time periods may lead to differences due to rounding attributable to IQVIA's proprietary projection methodology utilized. In addition, patient demographic information such as patient age could not be verified due to lack of access to medical charts or records in the database used. The survey data were used to provide insight into prescriber intent for the typical uses for a drug in office-based healthcare prescriber's clinical practice and may not necessarily result in a prescription being generated. Moreover, survey data with use mentions (b) (4) are too low to provide a reliable estimate of national use due to small sample size captured and low precision associated with these estimates. Finally, no statistical tests of significance were performed on the estimates; therefore, all changes over time should be considered approximate.

The BOXED WARNING for Increased Mortality in Elderly Patients with Dementia-Related Psychosis may also deter use of brexpiprazole for dementia indications, although non-specific psychiatric symptoms such as delusions, hallucinations, and neuropsychiatric symptoms may lead to off-label use in patients with underlying dementia.

5 CONCLUSION

DPV identified 22 cases of SAEs with brexpiprazole leading to hospitalization or death in patients aged 65 years and older in the FAERS database. Although a causal relationship was possible for all 22 cases, the presence of contributors or confounders in each case decreased the exclusivity of the adverse event or death being solely related to brexpiprazole use. Additionally, the high background rate of several SAEs of interest in the older adult population (e.g., UTIs, cardiovascular disease) makes it difficult to discern the role of brexpiprazole use from typical disease development in older adults.

(b) (5)

(b) (5)

Other SAEs identified are consistent with the known safety profile of brexpiprazole and other atypical antipsychotics. We did not identify any particular trends in frequency of events or severity; with the exception of each case using brexpiprazole specifically for Alzheimer's dementia developed aspiration pneumonia with one of the cases resulting in death. A limitation of our evaluation is the limited number of assessable reports, making it difficult to generalize our findings. Additionally, the number of cases using brexpiprazole for Alzheimer's dementia was small (n=3), which is congruent with the relative low use of brexpiprazole in the older adult population. (b) (4) and the labeling also notes the association of esophageal dysmotility and aspiration with antipsychotic drug use and recommends caution in using brexpiprazole in patients at risk for aspiration in Section 5.13.[13] (b) (4)

Although there is a relatively small number of patients currently using brexpiprazole for Alzheimer's disease, the trend in the cases of aspiration pneumonia in the Alzheimer's disease population warrants continued monitoring and continued, unedited use of the Boxed Warning language in Section 5.1 of the brexpiprazole labeling.

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7 APPENDICES

7.1 APPENDIX A. RISPERIDONE CEREBROVASCULAR ADVERSE EVENTS, INCLUDING STROKE, IN ELDERLY PATIENTS WITH DEMENTIA WARNING (2003)

Cerebrovascular Adverse Events, Including Stroke, in Elderly Patients With Dementia

Cerebrovascular adverse events (e.g., stroke, transient ischemic attack), including fatalities, were reported in patients (mean age 85 years; range 73-97) in trials of risperidone in elderly patients with dementia-related psychosis. In placebo-controlled trials, there was a significantly higher incidence of cerebrovascular adverse events in patients treated with risperidone compared to patients treated with placebo. RISPERDAL® is not approved for the treatment of patients with dementia-related psychosis.

7.2 APPENDIX B. ARIPIPRAZOLE CEREBROVASCULAR ADVERSE EVENTS, INCLUDING STROKE, IN ELDERLY PATIENTS WITH DEMENTIA WARNING (2005)

Cerebrovascular Adverse Events, Including Stroke, in Elderly Patients with Dementia

In placebo-controlled clinical studies (two flexible dose and one fixed dose study) of dementia-related psychosis, there was an increased incidence of cerebrovascular adverse events (e.g., stroke, transient ischemic attack), including fatalities, in aripiprazole-treated patients (mean age: 84 years; range: 78-88 years). In the fixed-dose study, there was a statistically significant dose response relationship for cerebrovascular adverse events in patients treated with aripiprazole. Aripiprazole is not approved for the treatment of patients with dementia-related psychosis. (See also PRECAUTIONS: Use in Patients with Concomitant Illness: Safety Experience in Elderly Patients with Psychosis Associated with Alzheimer's Disease.)

7.3 APPENDIX C. OLANZAPINE CEREBROVASCULAR ADVERSE EVENTS, INCLUDING STROKE, IN ELDERLY PATIENTS WITH DEMENTIA WARNING (2004)

Cerebrovascular Adverse Events, Including Stroke, in Elderly Patients with Dementia

Cerebrovascular adverse events (e.g., stroke, transient ischemic attack), including fatalities, were reported in patients in trials of olanzapine in elderly patients with dementia-related psychosis. In placebo-controlled trials, there was a significantly higher incidence of cerebrovascular adverse events in patients treated with olanzapine compared to patients treated with placebo. Olanzapine is not approved for the treatment of patients with dementia-related psychosis.

7.4 APPENDIX D. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FAERS is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support FDA's postmarketing safety surveillance program for drug and therapeutic biological products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Council on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

7.5 APPENDIX E. DRUG UTILIZATION DATABASE DESCRIPTIONS

IQVIA National Sales Perspectives (NSP)

The IQVIA National Sales Perspectives™ measures the volume of prescription drug products moving from distributors and manufacturers into various outlets within the retail and non-retail markets. It is the industry standard for measuring pharmaceutical spending because it captures ~89% of the total pharmaceutical market. Any capture of non-pharmaceutical product sales is a collection of convenience and not by database design. As such, NSP's coverage on over-the-counter (OTC) products is generally less than 50%, though it may be higher for OTC products with an NDC number.

Sales volume is expressed in terms of sales dollars, eaches, extended units, and share of market. Outlets within the retail channel include chain drug stores, independent drug stores, mass merchandisers, and food stores. Outlets within the non-retail channel include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings. Outlets within the mail channel are mail service pharmacies. NSP is used to monitor the actual volume amount of a product that is being distributed in any channel of the pharmaceutical marketplace. Except for the mail channel, these data are estimated based on national projections. Data are available in IQVIA's business intelligence tool SMART for 72-rolling months and are updated monthly.

IQVIA Total Patient Tracker™

IQVIA Total Patient Tracker (TPT) is a national-level projected service designed to estimate the total number of unique (non-duplicated) patients across all drugs and therapeutic classes dispensed in U.S. retail pharmacies. Data are available back to January 2002 and are available approximately 20 days after the close of the month. TPT uses prescription activity as part of its projection and integrates anonymized patient information from pharmacies to eliminate duplicate patients and multiple prescription fills, producing quick and reliable estimated unique patient counts. IQVIA has 93% coverage and a sample of 48,900 retail pharmacies. IQVIA captures about 3.7 billion retail transactions annually. TPT is projected to the known universe of retail pharmacies.

Patient estimates are nationally projected based on a sample of prescriptions claims. Summarization of projected patient estimates across age groups or time periods may lead to differences in patient count due to rounding attributable to the projection methodology utilized. Of note, the estimated patient counts provided are based on projections of sample prescription claims data and therefore have some degree of inherent sampling error. These estimates are not intended to be representations of exact enumerations and should be interpreted with caution particularly if they are based on a small sample size. In addition, the data cannot be validated due to lack of access to medical records in the data sources.

Syneos Health Research & Insights LLC., TreatmentAnswers™

Syneos Health Research & Insights, LLC., TreatmentAnswers™ and TreatmentAnswers™ with Pain Panel is a monthly survey designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based physician practices in the U.S. The survey consists of data collected from over 3,500 office-based physicians, physician assistants and nurse practitioners representing 32 specialties across the United States that report on all patient activity during one typical workday per month. These data may include profiles and trends of diagnoses, patients, drug products mentioned during the office visit and treatment patterns. The Pain Panel supplement surveys over 115 pain specialists' physicians each month. With the inclusion of visits to pain specialists, this will allow additional insight into the pain market. In August 2019, the nurse practitioner and physician assistant specialties were added to the panel. This enhancement provides a more precise view of prescribing habits since nurse practitioners and physician assistants are increasingly playing an important role in patient care. All data collected, is projected nationally by physician specialty and region to reflect national prescribing patterns.

7.6 APPENDIX F. LITERATURE CASE SUMMARIES (N=3)

Nagai Y, Yamazaki T, Sugita T, et al. Brexpiprazole-Associated Pisa Syndrome (Pleurothotonus) in a Patient With Dementia. Clin Neuropharmacol. 2022;45(3):72-73.

Nagai et al. described a 71-year-old female with suspected Pisa syndrome after treatment with brexpiprazole. The patient was diagnosed with Alzheimer's type dementia characterized by an 11-year functional and cognitive decline. She had notable behavioral problems due to her dementia, including physical aggression and psychomotor agitation. She was treated sequentially with donepezil, memantine, and quetiapine, which were all eventually stopped due to lack of benefit. Due to her ongoing behaviors, she was started on brexpiprazole 1 mg/day and trazodone 75 mg/day. After 1 month of treatment, she was noted to have gradual worsening of posture, characterized by 30-degree tonic flexion and forward rotation to the left side with no acute changes on neuroimaging. Brexpiprazole was stopped and quetiapine was restarted. Within 2 weeks, the postural symptoms had improved and resolved.

Reviewer Comments:
Pleurothonus, otherwise known as Pisa syndrome, is considered a rare form of acute or tardive dystonia with lateral deviation of the trunk. We assessed causality in this case as probable because the onset of dystonia after starting brexpiprazole and the resolution of symptoms after dechallenge with brexpiprazole suggests a causative role for brexpiprazole in this case. No other medications appear to be likely causes, and the patient did not have a history of long-term antipsychotic exposure prior to taking quetiapine or brexpiprazole. There were no new neuroimaging findings to suggest a new neurological event. The onset of dystonia appears gradual over 1-2 months, which is consistent with tardive rather than acute dystonia.[40] The patient did have risk factors for an antipsychotic-induced tardive movement disorder including age, female sex, and neurodegenerative disorder.[40, 42] Tardive dystonia is a less common presentation of tardive movement disorders from antipsychotic class medications. The brexpiprazole labeling includes Section 5.5 for tardive dyskinesia, though it is speculated that new antipsychotic agents with partial dopamine agonism may have lower rates of movement disorders.

Sharma VD, Gupta HV, Espay AJ. Copulatory Dyskinesia: Pathognomonic Manifestation of Tardive Dyskinesia. Tremor Other Hyperkinet Mov (NY). 2020;10:56.

Sharma et al. described a 71-year-old male with a history of depression who was treated with aripiprazole for 9 months and experienced slowing of movements and hypophonia. He was switched to brexpiprazole with improvement of parkinsonism, but within "a few months" he developed subsequent problems with rhythmic involuntary pelvic movements that were only transiently suppressible. Brexpiprazole was discontinued after 3-4 months, but the abnormal movements persisted for at least 2 more years without resolution. Treatment with clonazepam and propranolol were ineffective, and valbenzaine aggravated his parkinsonism.

Reviewer Comments: Copulatory dyskinesia is an involuntary pelvic movement thought to be a subtype of tardive dyskinesia. At the time of publication, the authors felt this to be the first case of tardive dyskinesia associated with brexpiprazole. We assessed causality in this case as possible because the onset of dyskinesia a few months after brexpiprazole initiation suggests brexpiprazole as a causative agent rather than the unmasking of dyskinesia from stopping aripiprazole, as this likely would present earlier after discontinuation. However, other factors may have increased this patient's risk for tardive dyskinesia, including his age, prior antipsychotic exposure, and the history of drug induced parkinsonism.[40] It is also noted that while the patient's parkinsonism almost completed resolved, there may have been residual symptoms suggesting this may be an early presentation of a primary neurodegenerative disorder like Parkinson's disease.

Jackowiak EM, Chou KL. Severe parkinsonism caused by brexpiprazole: A case report. Parkinsonism Relat Disord. 2019;69:138-139.

Jackowiak and Chou described a 71-year-old female with a history of depression presented for neurological evaluation of worsening tremor. She had been seen by a neurologist 3 years before, who had documented action tremor of hands with mild resting persistence, but no bradykinesia or rigidity. She had also been treated with aripiprazole over the last 2 years, but therapy dates and dosages were not reported. Concomitant medications included unspecified treatments for gastroesophageal reflux disease, alprazolam, and duloxetine. Initial neurological examination revealed mild parkinsonism with asymmetric bradykinesia and rigidity, bilateral resting and postural upper extremity tremor, and bilateral lower extremity tremor. She was started on low dose carbidopa/levodopa but continued to have worsening tremor and marked decline in mobility over the following 2 months. Dopamine transporter scan was normal at that time. Additional history from the patient's psychiatrist revealed that the patient had been started on brexpiprazole around the time of her initial neurological evaluation with titration to 2 mg over 2 months coinciding with worsening parkinsonism. She was tapered off brexpiprazole. Seven months later, she was noted to have significant improvement in posture, gait, and mobility, though continued to have mild residual resting tremor. Dopamine transporter scan was repeated at that time and was once again normal.

Reviewer Comments: Brexpiprazole does appear to play a contributory role in worsening parkinsonism in this patient. We assessed causality in this case as possible because her symptoms worsened with starting and increasing her dose of brexpiprazole and there was improvement in symptoms with discontinuation of brexpiprazole. However, she did continue to have persistent resting tremor after stopping brexpiprazole, which may suggest underlying Parkinson's disease. She did have two negative dopamine transporter scans which would argue against primary Parkinson's disease, but it is possible that brexpiprazole revealed an underlying physiologic vulnerability with onset of disease in the future. Duloxetine may have contributed to tremor, though does not likely explain the other symptoms of parkinsonism correlated with brexpiprazole use. There is also no specific mention of the action taken with carbidopa/levodopa after stopping brexpiprazole which could have impacted the clinical reassessment at the 6-month follow-up after stopping brexpiprazole.

7.7 APPENDIX G. DRUG UTILIZATION TABLE.

Table 7. Annual estimated number of patients who received a dispensed prescription for brexpiprazole from U.S. outpatient retail pharmacies, stratified by patient age, from 2017 through 2022

	2017		2018		2019		2020		2021		2022	
	Patients (N)	Share %	Patients (N)	Share %	Patients (N)	Share %	Patients (N)	Share %	Patients (N)	Share %	Patients (N)	Share %
Total patients	(b) (4)											
0-64 years												
65+ years												
Unknown age												

Source: IQVIA Total Patient Tracker. Data years 2017 - 2022. Data extracted January 2023. File: 2022-3081 TPT Brexpiprazole patients 2017-2022_01-10-2023.xlsx

Patient estimates are nationally projected based on a sample of prescriptions claims. Summing these projected patient counts across time periods and/or age-groups may lead to differences due to rounding attributable to IQVIA's proprietary projection methodology utilized

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