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Brexpiprazole (NDA 205422-S012)

Psychopharmacologic Drugs Advisory Committee
July 18, 2025

Tiffany R. Farchione, MD
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Posttraumatic Stress Disorder (PTSD)

- Follows exposure to actual or threatened death, serious injury, or sexual violence
- Intrusive memories, hyperarousal, and avoidant behavior
- Comorbid mood and substance use disorders common
- High risk for suicidal ideation and behavior
- Limited medication options
  - Two FDA-approved medications: sertraline and paroxetine
  - Response rates rarely exceed 60%
  - Less than 20 to 30% of patients achieve full remission
- Unmet need

Standard of Care

- For pharmacotherapy, current treatment guidelines recommend monotherapy
- Per Veteran's Administration Clinician's Guide to Medications for PTSD (2023):
  - "… no data support the use of any other medication combination with any other medication for the treatment of PTSD, including the use of adjunctive atypical antipsychotic medication with recommended pharmacotherapy for PTSD."
- Proposed co-initiation of brexpiprazole and sertraline is a novel treatment paradigm

End of Phase 2 Advice

- “You may also wish to consider elimination of the placebo arm from your phase 3 study protocols, considering that the pertinent question is whether brexpiprazole + sertraline is superior to sertraline monotherapy”
- “You should demonstrate that the combination therapy is superior to the approved sertraline monotherapy. Such demonstration must meet the statutory standard for substantial evidence of effectiveness”

Clinical Trial Data

- Two phase 3 studies
  - One robustly positive
  - One clearly negative
  - Unable to identify a reason for these discordant results despite extensive exploratory analyses
- One phase 2 study
  - Similar in design to phase 3 studies
  - Initially designed as exploratory study, to generate hypotheses for the design of phase 3 studies
  - Statistical significance cannot be claimed because of retrospective selection of hypothesis and use of post hoc multiple testing procedures

Safety

- Reported adverse events consistent with known effects
- Although no new safety signals were identified in the development program, the risks of brexpiprazole in combination with sertraline align with the known risks of each drug
- We need to consider the evidence of benefit in the context of the known risks of these two drugs

Discussion Question 1

- Discuss the strength of evidence provided by the two phase 3 studies 00071 and 00072, in particular discuss the impact of the discordant results on your overall assessment of efficacy.

Discussion Question 2

- Discuss your view on the contribution of Study 00061 on the overall evidence of effectiveness.

Discussion Question 3

- Based on available data, and with consideration of the known risks of brexpiprazole and sertraline individually, discuss the acceptability of the proposed concurrent initiation treatment paradigm.

Voting Question

- Based on the available data presented, has the efficacy of brexpiprazole, when initiated concurrently with sertraline, been established for the treatment of PTSD?

  Please provide your rationale and indicate the specific information (e.g., statistical analyses, other data) on which you base your vote.

Brexpiprazole for the Treatment of Post-Traumatic Stress Disorder (PTSD) in Adults, in Combination With Sertraline

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Statistical Reviewer, Division of Biometrics I

Agenda

I. Introduction: Disease Background and Product Description
II. Relevant Regulatory History
III. Efficacy
IV. Safety

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I. Introduction: Disease Background and Product Description

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Disease Background

- PTSD: disabling condition characterized by intrusive memories, nightmares, hyperarousal, and avoidant behavior following exposure to actual or threatened death, serious injury, or violence (including sexual violence)
- Seriousness:
  - High risk for suicidal ideation and behavior
  - High risk of mood and substance use disorders
- Prevalence:
  - US prevalence of PTSD estimated to be 13 million
  - 3.6% of US population estimated to have PTSD in the past year

Current Treatment Options

- Current treatment options include psychotherapy and pharmacotherapy
- Sertraline was approved for PTSD in 1999, paroxetine in 2001. No new medications have been approved for PTSD since then
- Limitations:
  - Response rates range from 37% to 62%
  - Off-label treatment common (atypical antipsychotics, clonidine, prazosin, bupropion, buspirone, monoamine oxidase (MAO) inhibitors, mirtazapine, gabapentin, lamotrigine, trazodone, and propranolol)

Product Description

- Generic name: Brexpiprazole
- Chemical structure: Atypical antipsychotic
- Pharmacological mechanism: Partial agonist activity at serotonin 5-HT1A and dopamine D2 receptors, and antagonist activity at serotonin 5-HT2A receptors
- Approved for: treatment of schizophrenia in adults and adolescents, adjunctive treatment of major depressive disorder (MDD) in adults, and agitation associated with dementia due to Alzheimer's disease
- Proposed indication: Treatment of PTSD in adults, in combination with sertraline
- Treatment regimen:
  - Days 1 to 7: 0.5 mg once daily in combination with sertraline 50 mg
  - Days 8 to 14: titrate brexpiprazole to 1 mg once daily in combination with sertraline 100 mg once daily
  - On Day 15: titrate to the target dosage of brexpiprazole 2 mg once daily in combination with sertraline 150 mg once daily based on the patient's clinical response and tolerability
  - Increase brexpiprazole dosage at weekly intervals (maximum recommended daily dosage is 3 mg)

Agenda

I. Introduction: Disease Background and Product Description

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Relevant Regulatory History

- **Initial Development**
  - Originally intended as adjunctive therapy to sertraline or paroxetine
  - Early-stage trial (Study 14865A) terminated due to insufficient enrollment
- **Indication Change**
  - Shifted to combination therapy – brexpiprazole and sertraline initiated concurrently
- **Phase 2 Study 00061 Protocol submitted**
  - No prior requirement of inadequate response to sertraline or SSRIs
  - Objectives: Generate hypotheses for future phase 3 studies
    - to investigate the contribution of the single components (brexpiprazole monotherapy or sertraline monotherapy) to the treatment effect of the brexpiprazole plus sertraline combination therapy compared to placebo

Relevant Regulatory History – End of Phase 2 Meeting May 2019

- **Development plan**
  - Confirmed shift from "adjunctive" to "combination" therapy
- **Agreement on future phase 3 study designs**
  - One flexible dose and one fixed dose study
  - Both trials would compare the combination therapy to fixed-dose sertraline
  - Brexpiprazole monotherapy arm not required
  - Placebo arm can be omitted
    - combination treatment would need to consistently outperform sertraline monotherapy to show convincing evidence of efficacy

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I. Introduction: Disease Background and Product Description

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Efficacy Studies

	Study 00061 (Phase 2)	Study 00071 (Phase 3)	Study 00072 (Phase 3)
Description	Multicenter (all US), randomized, DB. One-week double-blinded placebo run-in followed by 11-week double-blinded randomization treatment		
Study Population	Adults aged 18-65 years with PTSD		
Dose/Schedule **No. of Subjects Randomized**	Flexible dose (N=321) • Brex (1-3 mg/day) + Sert (100-200 mg/day) (n=82) • Brex (1-3 mg/day) + Placebo (n=75) • Sert (100-200 mg/day) + Placebo (n=81) • Placebo + Placebo (n=83)	Flexible dose (N=416) • Brex (2-3 mg/day) + Sert (150 mg/day) (n=214) • Sert (150 mg/day) + Placebo (n=202)	Fixed dose (N=553) • Brex (2 mg/day) + Sert (150 mg/day) (n=191) • Brex (3 mg/day) + Sert (150 mg/day) (n=185) • Sert (150 mg/day) + Placebo (n=177)
Primary Endpoint	Change from baseline (Week 1) to Week 10 in CAPS-5 total score		
Efficacy Analysis Population	ITT population	**Enriched population** • CAPS-5 total score at least 27 at the randomization visit (Week 1) • reduction in CAPS-5 total score less than 50% at end of the placebo run-in phase (from Day 0 to Week 1)	

Key Inclusion/Exclusion Criteria

Most inclusion/exclusion criteria were similar among the three studies, including the following:

- Moderate PTSD (CAPS-5 total score ≥33 at screening and baseline)
- The studies enrolled only participants willing to discontinue antidepressants and excluded those receiving adequate doses of sertraline at the time of screening
- Participants with a current major depressive episode were excluded from the studies to prevent confounding the treatment effect with improvements in depressive symptoms

One notable difference was the time since the index traumatic event:

  - Studies 71 and 72: ≤ 9 years
  - Study 61: ≤ 15 years

Primary Outcome: CAPS-5

CAPS-5 is an acceptable primary endpoint, typical for PTSD studies.

Overview

- 30-item clinician-reported outcome measure
- Aligns with DSM-5 clinical criteria for PTSD
- Administered by blinded, centralized independent clinician raters
- Semi-structured interviews assess key PTSD symptoms over the last month/week

Scoring System

- Each item rated on two dimensions:
  - Intensity: minimal, clearly present, pronounced, extreme
  - Frequency: number of times or percentage of time (symptom-dependent)
- Intensity and frequency are both considered when assigning a rating on this scale (single 5-point (0-4) severity scale)
- Higher scores indicating more severe symptoms
- Total severity score: sum of first 20 items (range: 0-80)

Study 61: Efficacy Analysis

- The study objective was to **evaluate the efficacy of brexpiprazole as monotherapy or as combination treatment with sertraline** in adult subjects with PTSD
- The SAP was submitted after data unblinding (at EOP2 meeting)
- No control for Type I error or multiple comparisons due to the exploratory nature of the study
- Primary analysis: MMRM with change from baseline in CAPS-5 total score as the dependent variable; all scheduled post-baseline CAPS-5 visits (Week 3, 6, 10, 12) were included in the analysis, but the primary endpoint was at Week 10
- Primary efficacy population was the ITT population (i.e., including placebo responders from the placebo run-in phase)

ITT: all subjects in the randomized sample who took at least one dose of double-blind IMP and have a baseline and at least one postbaseline evaluation for the CAPS-5 total score.

Study 61: Efficacy Results

CAPS-5 Total Score	Brex+Sert (N=79)	Brex+Plcb (N=72)	Sert+Plcb (N=77)	Plcb+Plcb (N=80)
n	77	69	75	78
Mean at baseline (SD)	35.7 (11.50)	33.9 (13.31)	36.5 (10.19)	35.1 (10.68)
LS Mean Change at Week 10 (SE)	-16.4 (1.43)	-12.2 (1.57)	-11.4 (1.46)	-10.5 (1.40)
Treatment Difference (95% CI) (vs **Plcb+Plcb**)	-6.0 (-9.79, -2.19)	-1.7 (-5.70, 2.22)	-0.9 (-4.74, 2.92)	
Nominal p-value	0.0021	0.3868	0.6399	
Treatment Difference (95% CI) (**Brex**+**Sert** vs **Sert**+**Plcb**)	-5.1 (-8.96, -1.20)			
Nominal p-value	0.0106			
Treatment Difference (95% CI) (**Brex**+**Sert** vs **Brex**+**Plcb**)	-4.2 (-8.26, -0.23)			
Nominal p-value	0.0384			

Source: statistical reviewer

Studies 71 and 72: Efficacy Analyses

- The objective of phase 3 studies 71 and 72 was to **assess the efficacy of the combination of brexpiprazole plus sertraline** compared with sertraline plus placebo in in adult subjects with PTSD
- Primary efficacy analysis for both studies used a MMRM model similar to Study 61
- Primary efficacy analysis population for both studies was the **FAS for the enriched population** (i.e., excluding placebo responders from placebo run-in phase)
- In Study 72, to control the overall Type I error for multiple doses compared with the control, a global test was first conducted by comparing the **average effect** of (a) *brexpiprazole 2mg plus sertraline* and (b) *brexpiprazole 3mg plus sertraline* with the *sertraline plus placebo group*. If the global test was statistically significant, each combination group was then compared with the sertraline plus placebo group

FAS: all subjects who received at least one dose of double-blind IMP, have a baseline value (Week 1) and at least one postbaseline CAPS-5 total score.

Studies 71 and 72: Efficacy Results

71

CAPS-5 Total Score	Brex Plus Sert (N=149)	Sert Plus Plcb (N=137)
n	148	134
Mean at baseline (SD)	38.4 (7.18)	38.7 (7.75)
LS Mean change from baseline at Week 10 (SE)	−19.2 (1.17)	−13.6 (1.24)
Treatment difference (95% CI)	−5.6 (−8.79, −2.38)	
P-value	0.0007	

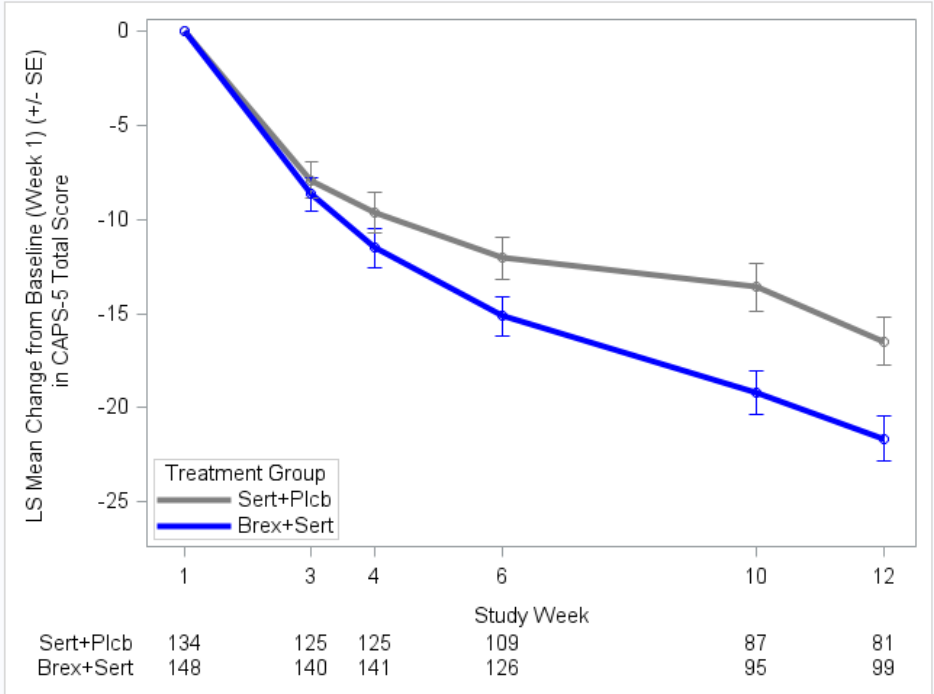
72

CAPS-5 Total Score	Brex 2 mg Plus Sert (N=132)	Brex 3 mg Plus Sert (N=126)	Average	Sert Plus Plcb (N=130)
n	132	124		130
Mean at baseline (SD)	38.8 (8.26)	37.9 (7.38)		39.3 (7.75)
LS mean change from baseline at Week 10 (SE)	−16.5 (1.19)	−18.3 (1.23)		−17.6 (1.19)
Treatment difference vs sert plus plcb (95% CI)	1.0 (−2.09, 4.16)	−0.7 (−3.88, 2.46)	0.2 (−2.56, 2.88)	
P-value	0.5165	0.6593	0.9073	

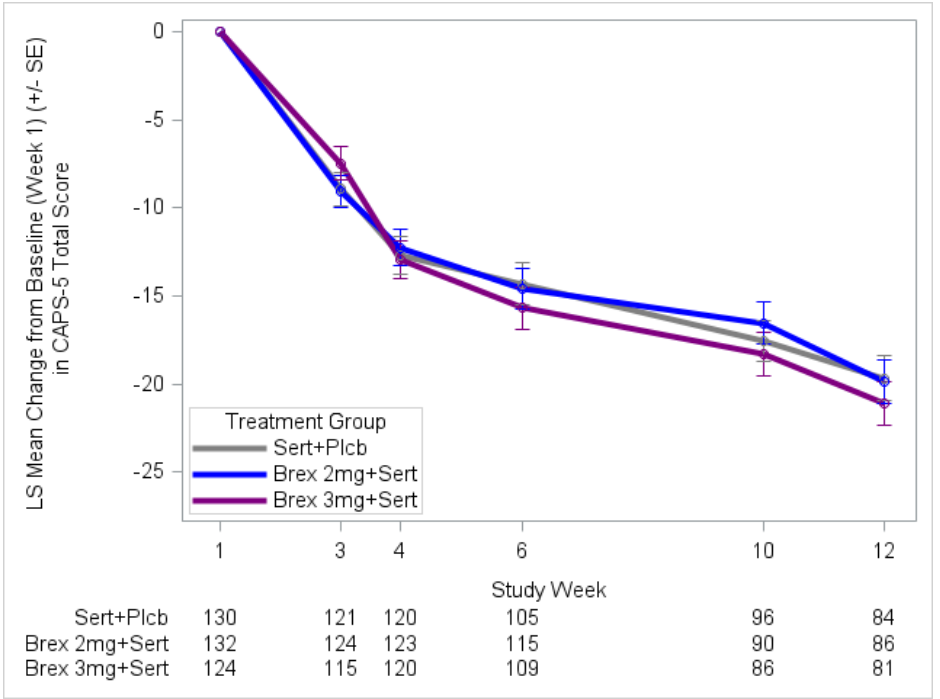
Source: statistical reviewer

Studies 71 and 72: Efficacy Results

71



72



Source: statistical reviewer

Assessments Conducted to Understand Negative Results of Study 72

- Demographic and clinical characteristics were comparable with small differences
  - Study 72 enrolled more Hispanic subjects compared to Study 71 (24% vs 13%)
  - Study 72 geographic distribution differed from Study 00071, but similar to Study 00061
- Post hoc subgroup analyses by sex, ethnicity, prior PTSD treatment, and baseline severity did not detect any signals in the primary efficacy population
- Different dosing schema (fixed vs flexible)
- Plasma concentration ranges for brexpiprazole and sertraline were comparable between Studies 71 and 72

Revisiting Study 61

- Given only one positive phase 3 study, the Applicant sought additional evidence from the phase 2 exploratory Study 61 to support approval
- **Study 61:** The SAP listed five comparisons, but did not pre-specify a method to control the overall Type I error
  - Hence, the Applicant retrospectively proposed three post-hoc multiple testing procedures which weigh three selected comparisons equally

Study 61: Post-hoc Analyses Results

Conclusions from Hypothesis Testing: Pass vs Fail (Statistically Significant vs Not)

Variable	Brex+Sert vs Sert+Plcb	Brex+Sert vs Plcb+Plcb	Brex+Plcb vs Plcb+Plcb
ITT population, N=308			
Nominal p-value	0.0106	0.0021	0.3868
Pre-specified in protocol addendum, but abandoned in SAP			
Hierarchical testing procedure	**Fail**	**Pass**	**Fail**
Post-hoc multiple testing procedures considered by Applicant in sNDA package			
Bonferroni procedure	**Pass**	**Pass**	**Fail**
Holm step-down procedure	**Pass**	**Pass**	**Fail**
Hochberg step-up procedure	**Pass**	**Pass**	**Fail**

Source: statistical reviewer

- Study 61 protocol addendum pre-specified a hierarchical testing procedure to control for multiplicity; however, the SAP stated that the hierarchical testing procedure would not be performed due to the exploratory nature of this study.
- The hierarchical testing procedure pre-specified in the protocol addendum used the following order: 1) brexpiprazole plus sertraline vs. placebo; 2) brexpiprazole vs. placebo; 3) brexpiprazole plus sertraline vs. sertraline.

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Source: statistical reviewer

Study 61: Efficacy Results

Based on Prespecified Multiplicity Control Method in Protocol Addendum

CAPS-5 Total Score	Brex+Sert (N=79)	Brex+Plcb (N=72)	Sert+Plcb (N=77)	Plcb+Plcb (N=80)
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Nominal p-value	**0.0021**	**0.3868**		
Treatment Difference (95% CI) (**Brex+Sert** vs **Sert+Plcb**)	**-5.1** **(-8.96, -1.20)**			
Nominal p-value	**0.0106**			

1 → 2

X

3

The bold numbers 1, 2, and 3 and arrows denote the hierarchical testing order pre-specified in the protocol addendum but abandoned in the SAP.

Source: statistical reviewer

Remarks on Post-Hoc Analyses of Study 61

- Study 61 protocol addendum pre-specified a multiplicity control method (hierarchical testing procedure), which was consistent with the study primary objective (**to assess the efficacy of brexpiprazole as monotherapy or as combination therapy with sertraline**). In the subsequent SAP, the Applicant decided to abort the multiplicity control and instead listed all five comparisons before data unblinding
- After unblinding of all three studies, the Applicant attempts to extract information from Study 61 to support the objective of phase 3 studies (**to assess the efficacy of the combination of brexpiprazole plus sertraline compared with sertraline plus placebo**)

Remarks: The post-hoc analyses of Study 61 raise concerns about lack of overall Type I error control, which is crucial for demonstrating efficacy.

Overall Summary of Efficacy

- Studies 71 and 72 were two adequate and well-controlled phase 3 trials
  - Study 71 was a robustly positive study
  - Study 72 was a clearly and convincingly negative study with an essentially zero-point treatment effect estimate on its primary endpoint
- Study 61 was a phase 2 exploratory hypothesis-generating study
  - Although nominally significant for the comparison of brexpiprazole plus sertraline with sertraline plus placebo, it was analyzed retrospectively to provide additional efficacy evidence, following the completion and read out of phase 3 results
    - Methods to control for multiplicity were selected post-hoc
      - Testing results depend on methods to control for multiplicity
    - The failure of sertraline to demonstrate superiority over placebo raises concerns about the interpretability of Study 61

Agenda

I. Introduction: Disease Background and Product Description

II. Regulatory History and Key Issues

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Safety

Sertraline

---------- **WARNINGS AND PRECAUTIONS** ----------

- Serotonin Syndrome: Increased risk when co-administered with other serotonergic agents, but also when taken alone. If it occurs, discontinue ZOLOFT and serotonergic agents and initiate supportive treatment. (5.2)
- Increased Risk of Bleeding: Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), other antiplatelet drugs, warfarin, and other anticoagulants may increase this risk. (5.3)
- Activation of Mania/Hypomania: Screen patients for bipolar disorder. (5.4)
- Seizures: Use with caution in patients with seizure disorders. (5.6)
- Angle Closure Glaucoma: Avoid use of antidepressants, including ZOLOFT, in patients with untreated anatomically narrow angles. (5.7)
- QTc Prolongation: ZOLOFT should be used with caution in patients with risk factors for QTc prolongation. (5.10)
- Sexual Dysfunction: ZOLOFT may cause symptoms of sexual dysfunction. (5.11)

---------- **ADVERSE REACTIONS** ----------

Most common adverse reactions (≥5% and twice placebo) in pooled placebo-controlled MDD, OCD, PD, PTSD, SAD and PMDD clinical trials were nausea, diarrhea/loose stool, tremor, dyspepsia, decreased appetite, hyperhidrosis, ejaculation failure, and decreased libido. (6.1)

Brexpiprazole

---------- **WARNINGS AND PRECAUTIONS** ----------

- *Cerebrovascular Adverse Reactions in Elderly Patients with Dementia-Related Psychosis:* Increased incidence of cerebrovascular adverse reactions (e.g., stroke, transient ischemic attack) (5.3)
- *Neuroleptic Malignant Syndrome:* Manage with immediate discontinuation and close monitoring. (5.4)
- *Tardive Dyskinesia:* Discontinue if clinically appropriate. (5.5)
- *Metabolic Changes:* Monitor for hyperglycemia/diabetes mellitus, dyslipidemia, and weight gain. (5.6)
- *Pathological Gambling and Other Compulsive Behaviors:* Consider dose reduction or discontinuation. (5.7)
- *Leukopenia, Neutropenia, and Agranulocytosis:* Perform complete blood counts (CBC) in patients with pre-existing low white blood cell count (WBC) or history of leukopenia or neutropenia. Consider discontinuing REXULTI if a clinically significant decline in WBC occurs in absence of other causative factors. (5.8)
- *Orthostatic Hypotension and Syncope:* Monitor heart rate and blood pressure and warn patients with known cardiovascular or cerebrovascular disease, and risk of dehydration or syncope. (5.9)
- *Seizures:* Use cautiously in patients with a history of seizures or with conditions that lower the seizure threshold. (5.11)
- *Potential for Cognitive and Motor Impairment:* Use caution when operating machinery. (5.14)

---------- **ADVERSE REACTIONS** ----------

- Most common adverse reactions in adults were (6.1):
- *Adult patients with major depressive disorder (adjunctive treatment to antidepressant therapy):* Weight increased, somnolence, and akathisia (≥5% and at least twice the rate for placebo)
- *Adult Patients with schizophrenia*: Weight increased (≥4% and at least twice the rate for placebo)
- *Pediatric patients (13 to 17 years) with schizophrenia*: Extrapyramidal symptoms, excluding akathisia (≥5% and at least twice the rate for placebo)
- *Adult patients with agitation associated with dementia due to Alzheimer's disease:* Nasopharyngitis, dizziness (≥4% and at least twice the rate for placebo)

Safety Summary

- The safety results across all three studies demonstrate consistency with the established safety profiles of both brexpiprazole and sertraline as reported in their product information
- Although no new safety signals were identified in the development program, the evidence of benefit of co-initiation of brexpiprazole and sertraline for the treatment of PTSD should also be considered in the context of the known risks of these two drugs


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