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Drug Class Update with New Drug Evaluation: Antidepressants

Date of Review: June 2024

Date of Last Review: December 2023
Dates of Literature Search: 10/01/2023 - 02/16/2024
Brand Name (Manufacturer): Exxua (Mission Pharmacal Company)
Dossier Received: no

Generic Name: gepirone extended release

Current Status of PDL Class:
See **Appendix 1**.

Purpose for Class Update:
The purpose of this class update is to evaluate evidence for gepirone and any new evidence for antidepressants.

Plain Language Summary:
- Medicines used to treat depression are called antidepressants. Some antidepressants are also used to help people stop smoking, to reduce pain, and to treat anxiety disorders.
- The Food and Drug Administration recently approved a new medicine for people with depression. This medicine is called gepirone. Gepirone improved symptoms of depression more than placebo in people who had moderate to severe depression.
- Based on this information, we do not recommend any changes to the antidepressant preferred drug list for the Oregon Health Plan fee-for-service program.

Research Questions:
1. Is there new comparative evidence related to efficacy of antidepressants for important outcomes (e.g., symptom reduction and remission)?
2. Is there new comparative evidence for harms for antidepressants?
3. Are there specific populations based on demographic characteristics, such as age, race, ethnicity, pregnancy status, or people with certain comorbidities, for which certain antidepressants are better tolerated or more effective than other antidepressants in improving symptoms and remission of depression?
4. What is the comparative evidence for efficacy and harms for gepirone?

Conclusions:
- There were no new high-quality systematic reviews or guidelines that met inclusion criteria to be added to the class update. One randomized controlled trial, 2 Food and Drug Administration (FDA) safety updates and one new drug review are included in this update.

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- There is moderate quality evidence that, in adult patients with treatment-resistant depression (on background therapy with selective serotonin reuptake inhibitors [SSRIs] or serotonin norepinephrine reuptake inhibitors [SNRIs]), esketamine improved remission rates compared to quetiapine extended release (ER) at 8 weeks with an absolute risk reduction (ARR) of 9.5% and number needed to treat (NNT) of 11.[1]
- Two, 8-week studies provide low-quality evidence that gepirone is superior to placebo for improving depression symptoms in patients with major depressive disorder (MDD).[2,3] Low-quality evidence demonstrates that gepirone reduces Hamilton Rating Scale for Depression (HAM-D 17) total scores by 2.29 to 2.34 points more than placebo ($p<0.05$ for both studies). The number of responders at 8-weeks was higher for gepirone compared to placebo with a number needed to treat (NNT) of 7-8.
- There are no high-quality studies comparing gepirone to other antidepressants to compare efficacy and safety.
- There is insufficient evidence to determine the most effective therapies for depression in any identified populations based on age, race ethnicity, or people with certain co-morbidities.

Recommendations:
- No changes to the Oregon Health Plan (OHA) fee-for-service (FFS) preferred drug list (PDL) are recommended.
- Maintain gepirone as a voluntary medication on the PDL.
- Update Tricyclic Antidepressant prior authorization (PA) based on OHA Mental Health Clinical Advisory Group (MHCAG) recommendations.
- After evaluation of costs in executive session, trazodone, ZULRESSO, and SYMBYAX were assigned voluntary non-preferred on PDL.

Summary of Prior Reviews and Current Policy
- Antidepressants are designated as preferred or part of the voluntary PDL. Specific antidepressants have criteria to promote safe and medically appropriate use. Because there is limited data to demonstrate clinically significant differences in efficacy and safety between specific antidepressants or classes of antidepressants, previous recommendations from the Pharmacy and Therapeutics (P&T) Committee are to base antidepressant treatment selection on patient characteristics, adverse effects and cost.
- The OHA Mental Health Clinical Advisory Group support SSRIs, SNRIs, mirtazapine, or bupropion as reasonable first-line treatment options. Additional treatment options are available at: https://www.oregon.gov/oha/HPA/DSI-Pharmacy/Pages/MHCAG-Recommendations.aspx.
- The antidepressant class was last reviewed in December of 2023. A safety edit was added for zuranolone to ensure appropriate use when prescribed for moderate-to-severe post-partum depression. In February 2024, a safety edit for esketamine was updated to include outpatient initiation of esketamine for people with suicidal ideation who have optimized alternative treatments for depression.

Background:
Antidepressant medications are categorized based on mechanism of action and chemical structure. They are classified as first-generation (tricyclic antidepressants [TCAs] and monoamine oxidase inhibitors [MAOIs]) and second-generation antidepressants (SSRIs and SNRIs, and newer antidepressants). They are used for a wide variety of psychiatric conditions including depression, post-traumatic stress disorder (PTSD), bipolar disorder, obsessive compulsive disorder, anxiety disorders and bulimia. Specific antidepressants have Food and Drug Administration (FDA) labeled indications for other conditions including fibromyalgia (which is not a funded diagnosis by the Health Evidence Review Commission), diabetic peripheral neuropathy, post-partum depression (PPD), premenstrual dysphoric disorder, and smoking cessation.[4]

The choice of antidepressant is typically dependent on patient preference and adverse effect profile, as current evidence demonstrates little difference in efficacy between agents. Second-generation antidepressants are recommended as first-line agents due to improved tolerability, decreased risk of adverse events, and less risk for overdose, compared to first-generation antidepressants. For the treatment of moderate to severe depression in adults, guidelines from both the National Institute for Health and Care Excellence (NICE) and the American College of Physicians (ACP) recommend both antidepressant and psychotherapy.[5,6] SSRIs are recommended by NICE as a first-line option, though individual drug choice can vary depending on adverse effects. ACP guidelines and the OHA MHCAG support SSRIs, SNRIs, mirtazapine, or bupropion as reasonable first-line treatment options.[5,7] Two antidepressants are specifically approved to manage PPD, oral zuranolone and brexanolone (given as a continuous intravenous [IV] infusion over 60 hours).

It is not uncommon for first-line treatments to fail to manage depressive symptoms. In major depressive disorder, about two-thirds of patients have an inadequate response to initial therapy and about one-third of patients have treatment-resistant depression.[1] There is no consistent definition in the literature for treatment-resistant depression; however, it is often described as failure of 2 or more antidepressants given at therapeutic doses.[8] There is little evidence to guide next steps in therapy after an initial treatment failure.[1] Common treatment options used in clinical practice include trial of a different first-line antidepressant, use of an antidepressant from a different class, and augmentation of current therapy with a second agent. All antidepressants for major depressive disorder (MDD) have an FDA black box warning for suicide risk in young adults and can be associated with a discontinuation syndrome when agents are abruptly stopped. Other notable adverse events include risk for serotonin syndrome, which increases when used in combination with other serotonergic medications, and anticholinergic adverse events.

Goals of treatment for depression typically include symptom and function improvement, remission, and relapse prevention. A wide variety of rating scales are used to evaluate symptom improvement, quality of life, and function in patients living with depression. Scales vary depending on the condition. There is some evidence that measurement-based care (MBC), via depression rating scale improves outcomes. However, the recommendation from the Veterans Administration (VA)/Department of Defense (DoD) for use of these scales was weak due to lack of high-quality supporting evidence.[4] Some of the most commonly used rating scales include the Montgomery-Asberg Depression Rating Scale (MADRS) and Hamilton Depression Rating Scale (HAM-D). The MADRS is a 10-item scale which assesses depression symptoms (range 0 to 60) with higher scores indicating more severe depression.[4] The HAM-D is a clinician-rated, 17-item scale to assess symptoms (range 0 to 52) with scores of 10-13 indicating mild depression, 14-17 indicating mild to moderate depression and 17 and greater indicating moderate to severe depression.[4] The FDA has stated that this tool is valuable in the study of depressive symptoms but may be associated with a higher representation of evaluation of somatic symptoms (e.g., insomnia and somatic anxiety) compared to other tools.[9] Remission is defined as the person being free from depressive symptoms for several months after two or more depressive episodes, and response to therapy is typically defined as a 50% improvement in symptom score from baseline.[4] A 2-point improvement on the MADRS may be associated with a minimum clinically important improvement and HAM-D scores of 3 to 7 points may be clinically significant.[4]

In Oregon, mental health drug classes, including antidepressants, are carved out from the coordinated care organizations (CCOs) and paid for by FFS. Non-preferred products do not automatically require prior authorization, but safety criteria are in place for esketamine, brexanolone, and TCAs in children. In 2023, the demographics of FFS members with a diagnosis of depression were 67% White and 68% female. In the fourth quarter of 2023, there were over 376,000 antidepressant medication claims for OHP FFS members.

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits

used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, the Canadian Agency for Drugs and Technologies in Health (CADTH), the Oregon Mental Health Clinical Advisory Group (MHCAG), and the Scottish Intercollegiate Guidelines Network (SIGN) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:
No new high quality systematic reviews were identified.

After review, 8 systematic reviews were excluded due to poor quality (e.g., indirect network-meta analyses), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).[10–17]

New Guidelines:
No new high-quality guidelines were identified.

After review, 1 guideline was excluded due to poor quality.[18]

New Formulations or Indications:
None identified.

New FDA Safety Alerts:

Table 1. Description of New FDA Safety Alerts

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Esketamine[19]	SPRAVATO	October 2023	Boxed Warning	The risk for respiratory depression after administration was added to the boxed warning based on observations during post marketing use. In rare cases, this caused respiratory arrest. Monitor patients for at least 2 hours post administration.
Desvenlafaxine[20] Duloxetine[21] Escitalopram[22]	PRISTIQ CYMBALTA LEXAPRO	August 2023	Precautions	SSRIs/SNRIs may be associated with increased risk for postpartum hemorrhage and anosmia/hyposmia. Combination use of SNRIs and opioids may be

Fluvoxamine[23] Sertraline[24] Venlafaxine[25] Citalopram[26] Levomilnacipran[27]6/20/2024 11:18:00 AM[28]6/20/2024 11:18:00 AM6/20/2024 11:18:00 AM	LUVOX ZOLOFT EFFEXOR XR CELEXA FETZIMA PAXIL VIIBRYD			associated with increased risk for serotonin syndrome.

Randomized Controlled Trials:

A total of 181 citations were manually reviewed from the initial literature search. After further review, 180 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). The remaining trial is summarized in the table below. The full abstract is included in **Appendix 2**.

Table 2. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results	Notes/Limitations
Reif, et al[1] ESCAPE-TRD OL, SB, Phase 3b RCT	Esketamine Nasal spray* Vs. Quetiapine ER* * Flexible dosing was used for both medications and given in conjunction with a SSRI or SNRI 8-week treatment phase Maintenance phase 24 weeks	Adult patients with treatment resistant depression (n=676)	Remission (defined as a MADRS score of 10 or less at week 8)	1. Esketamine: 91 (27.1%) 2. Quetiapine ER: 60 (17.6%) TD 9.5% (95% CI, 3.3 to 15.8) P=0.003 ARR 9.5%/NNT 11	♦ Baseline MADRS score: 31 ♦ Mean age: 45 years ♦ 2 Past failed treatments: 61.4% ♦ Discontinuation rates were high in both groups: esketamine 40.3% and quetiapine ER 23.2%. Discontinuations in the quetiapine ER group was due to adverse events or lack of efficacy. ♦ Study was divided into 4 phases: screening phase (up to 14 days), initial treatment phase (8 weeks) and maintenance phase (24 weeks) and safety follow-up phase (through 2 weeks

					after last dose of trial treatment) ♦ Remission rates at week 32 were 49.1% for esketamine and 32.9% for quetiapine ER.
Abbreviations: ARR = absolute risk reduction; ER = extended release; MADRS = Montgomery-Asberg Depression Rating Scale; NNT = number needed to treat; OL = open-label; RCT = randomized controlled trial; SB = single-blind; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TD = treatment difference.					

NEW DRUG EVALUATION:

Clinical Efficacy:

In September 2023, gepirone (EXUAA) was approved by the FDA for the treatment of MDD in adult patients.[29] Gepirone is an azapirone class of compounds which is an analog of buspirone.[9] Gepirone modulates serotonin activity by antagonism of the 5HT1A receptors. The acute mechanism of action of gepirone is to decrease firing rate of serotonergic neurons and release of 5-HT. Prolonged treatment cases desensitization of the 5HT1A autoreceptors and the firing rate of the serotonergic receptors returns resulting in an increase in postsynaptic 5HT neurotransmission.

Gepirone should be taken with food and started at 18.2 mg daily and increased to 36.3 mg daily on day 4. On day 7 the dose of gepirone may be increased to 54.5 mg daily and increased again after 7 more days to 72.6 mg, if needed. The recommended dose in geriatric patients is a starting dose of 18.2 mg once daily and increased to a maximum dose of 36.3 mg once daily after day 7 if needed. Doses should be reduced in patients with renal or hepatic impairment. A dose reduction of 50% is required when gepirone is given in combination with moderate CYP3A4 inhibitors and contraindicated in patients receiving strong CYP3A4 inhibitors. Patients should have electrolyte abnormalities corrected, if needed, before starting therapy and an ECG should be done prior to initiation. If QTc is > 450 msec, then gepirone should not be used.

A new drug application for gepirone was originally submitted for FDA approval in 1999 and again in 2002 and 2004 but gepirone was not approved till 2023.[9] The FDA identified 25 clinical studies for gepirone ER; however, only 2 were positive, well-controlled efficacy studies and used as evidence for approval (**Table 5**). In Phase II/III studies, the demographics of patients treated with gepirone consists of approximately 63% females and 37% males, 95% <65 years of age, and 5% ≥65 years of age, and approximately 83% Caucasians, 8% Black, and 8% Other race.[9] All studies of gepirone extended release formulation, with the exception of two, were conducted in patients with MDD. A meta-analysis of 12 gepirone double-blind, placebo-controlled studies was not positive for gepirone and additional supportive studies were determined to not support effectiveness of gepirone over placebo in the treatment of MDD.[9] In the clinical evaluation of gepirone, the FDA states, "The efficacy of gepirone has not been established with confidence and this drug would seem to be an unlikely choice over other approved antidepressants."[9] Gepirone has also been studied as an immediate release (IR) formulation which was discontinued. Buspirone is also a 5HT1A receptor agonist approved by the FDA in 1986 for the treatment of generalized anxiety disorder. Gepirone ER has also been studied for mood-panic disorder and generalized anxiety disorder but lacked evidence of efficacy for these indications.

In a study by Bielski, et al patients were randomized to gepirone 40-80 mg daily (most patients on 60-80 mg daily by week 3) compared to placebo (n=238)(Table 5).[3] Doses were initiated at 20 mg daily and increased to 40 mg on day 4 and increased again to 60 mg daily on day 8. A final dose increase to 80 mg daily after day 15 was permitted based on response and tolerability. Patients had to have a HAM-D score of 20 or greater at the time of screening. Patients were excluded if they had treatment-refractory depression (e.g., trial of 2 or more antidepressants utilizing adequate dose and duration) with an incomplete or no response). The average age was 38 years, 68% females and 65% White. The baseline HAM-D score was 24, indicating moderate to severe depression. The primary endpoint was change in HAM-D 17 total score from baseline at 8 weeks. Gepirone was more effective than placebo at reducing HAM-D scores (least square mean [LSM] 2.29; confidence interval [CI] not provided; p=0.032).[3] There were more responders (e.g., patients who experienced at least a 50% reduction in HAM-D score from baseline) in patients treated with gepirone compared to placebo with an ARR of 16% and NNT of 7.[3]

In a placebo-controlled, published study by Feiger, et al, gepirone was studied at doses of 40 mg to 80 mg daily in patients with moderate to severe depression.[2] Doses were initiated at 20 mg daily and increased to 40 mg on day 4 and increased again to 60 mg daily on day 7. A final dose increase to 80 mg daily after day 14 was permitted based on response and tolerability. The average age was 40 years, 61% female, 76% White and 41.5% had received prior antidepressant therapy. The study enrolled 204 patients and they were followed for 8 weeks[2]. The primary endpoint was change in HAM-D 17 total score from baseline. Gepirone was found to be more effective than placebo at reducing the HAM-D total score (-9.77 vs. -7.43 points with placebo; LSM 2.29; P=0.18 [CI not provided]).[2] Differences between gepirone and placebo were statistically significant but not clinically significant. A higher number of patients who received gepirone were responders (defined as at least 50% reduction from baseline in HAMD-17 total scores) compared to placebo (43.6% vs. 30.7%). The difference in clinical global impression (CGI) score between groups was not significantly different at 8 weeks.

Limitations to the evidence include that lack of confidence intervals for the results in both studies. Additionally, high levels of attrition in both groups increase risk for bias, reducing confidence in the findings. In both studies, the methods used in the trials were not reported leading to unclear risk of selection, performance, and detection bias. Many studies evaluated in the FDA clinical review failed to demonstrate superior efficacy of gepirone compared to placebo, suggesting a weak treatment effect. All studies were funded by the manufacturer with unclear descriptions of result analysis, which could lead to bias. There was insufficient evidence to determine treatment differences for amongst subgroup populations.

Clinical Safety:
The most common adverse reactions associated with gepirone were dizziness, nausea, insomnia, abdominal pain and dyspepsia, which occurred at 2% or more with gepirone than placebo (**Table 3**).[29] Like other antidepressants, gepirone has a boxed warning for the increased risk of suicidal thinking and behavior in pediatric and young adult patients. Gepirone is not approved in pediatric patients. Gepirone should not be used in patients with a prolonged QTc interval (450 msec or more), congenital long QT syndrome, in combination with medications that are strong CYP3A4 inhibitors, severe hepatic impairment or in combination with monoamine oxidase inhibitors (MAOIs).[29] There is evidence that gepirone does not cause sexual dysfunction, which is a common adverse effect of other antidepressants.[9]

There was a high rate of attrition in both studies, exceeding 10%, over an 8-week period. Discontinuations due to adverse events ranged from 6.5% to 9.8% in the gepirone group compared to 2.4% to 2.8% with placebo.[2,3] There is a lack of long-term data on the use of gepirone for MDD.

Table 3. Adverse Reactions Occurring in >2% or more patients treated with Gepirone (pooled MDD Studies) versus Placebo*[29]

Adverse Reaction	Placebo (n=230)	Gepirone (n=226)
Dizziness	10%	49%
Nausea	13%	35%
Headache	20%	31%
Feeling sleepy or tired	14%	15%
Insomnia	5%	14%

Key: * Doses ranged from 18.2 mg to 76.2 mg

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Remission of depression
2) Reduction of depressive symptoms (e.g., HAM-D or MADRS score changes)
3) Serious adverse events
4) Study withdrawal due to an adverse event

Primary Study Endpoint:

1) Change from baseline in HAM-D scores

Table 4. Pharmacology and Pharmacokinetic Properties.

Parameter	
Mechanism of Action	5HT1A receptor agonist
Oral Bioavailability	14% to 17%
Distribution and Protein Binding	94.5 liters Protein binding *in vitro* 72%
Elimination	81% urine and 13% feces
Half-Life	5 hours
Metabolism	CYP3A4

Table 5. Comparative Evidence Table.

Ref./ Study Design	**Drug Regimens/ Duration**	**Patient Population**	**N**	**Efficacy Endpoints**	**ARR/NNT**	**Safety Outcomes**	**ARR/NNH**	**Risk of Bias/ Applicability**
1. Bielski, et al[3]	1. Gepirone ER 20-80 mg orally once daily	Demographics: Age: 38 years Female: 68.1% White: 64.9%	ITT: 1. 116 2. 122 PP:	Primary Endpoint: Change in HAM-D 17 total score from baseline at week 8:		Discontinuations due to AE: 1. 8 (6.5%) 2. 3 (2.4%)	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: (unclear) No details provided. Baseline characteristics were well matched. Performance Bias: (unclear) Stated double-blind design but no details.

DB, PC, PG, RCT	2. Placebo once daily 8-week	Baseline HAM-D 17: 24 points <u>Key Inclusion Criteria</u>: - moderate to severe depression based on DSM-IV - Daily dysphoria for the past 4 weeks or more - Baseline HAM-D 17 score of 20 or greater - 18-64 years old <u>Key Exclusion Criteria</u>: - 20% or more decrease in HAM-D 17 total score between baseline and screening - Primary DSM-IV Axis I disorder other than depression - Axis II disorders (e.g., personality disorders) - Seizures, bipolar, refractory depression - substance abuse - alcohol abuse	1. 97 2. 102 <u>Attrition</u>: 1. 19 (16%) 2. 20 (16%)	1. -10.2 2. -8.0 LSM difference 2.29 (CI not provided) P=0.032 <u>Secondary Endpoints</u>: <u>HAM-D 17 Responders at week 8:</u> 1. 53 (46%) 2. 37 (30%) P=0.014 <u>Change in MADRS at week 8:</u> 1. -13.7 2. -9.9 P=0.008 <u>Change in CGI-S at week 8:</u> 1. -1.3 2. -0.9 P=0.015	NA ARR 16% /NNT 7 NA NA	<u>Dizziness</u>: 1. 56 (45.2%) 2. 12 (9.7%) <u>Nausea:</u> 1. 45 (36.3%) 2. 16 (12.9%) <u>Insomnia:</u> 1. 7 (5.6%) 2. 3 (2.4%) 95% CI and p-value not provided for all		<u>Detection Bias</u>: (unclear) Not described. <u>Attrition Bias</u>: (high) More than 10% attrition in both groups. Analysis was on ITT population with LOCF dataset. <u>Reporting Bias</u>: (low) Results reported as described. <u>Other Bias:</u> (unclear) Funded by manufacturer. **Applicability**: <u>Patient</u>: Patients are similar to OHP patients with the majority being female and White with moderate to severe depression. Patients with treatment-resistant depression and other common comorbid conditions were excluded. <u>Intervention</u>: Gepirone had been studied across multiple doses with efficacy demonstrated for 40-80 mg. <u>Comparator</u>: Placebo appropriate to determine efficacy. Active treatment comparison would be more informative to determine role of gepirone compared to current standard of care. <u>Outcomes</u>: HAMD-17 score is an accepted measurement of depression severity. HAM-D scores of 3 to 7 points may be clinically significant Setting: Not described.
2. Feiger, et al[2] DB, PC, RCT	1. Gepirone ER 20-80 mg orally once daily 2. Placebo orally once daily 8-week	<u>Demographics</u>: Age: 40 years Female: 61% White: 76% Prior AD therapy: 41.5% <u>Key Inclusion Criteria</u>:	<u>ITT</u>: 1. 103 2. 101 <u>PP</u>: 1. 74 2. 81 <u>Attrition</u>:	<u>Primary Endpoint</u>: Mean change in HAM-D 17 total score from baseline at week 8: 1. -9.77 2. -7.43 LSM 2.34 (CI not provided) P=0.018	NA	<u>Discontinuations due to AE:</u> 1. 10 (9.8%) 2. 3 (2.8%) p-value not provided <u>Dizziness</u>: 1. 54 (52.0%) 2. 11 (11.3%)	NA ARR 40.7%/	**Risk of Bias (low/high/unclear)**: <u>Selection Bias</u>: (unclear) See above. <u>Performance Bias</u>: (unclear) Matching placebo. No details were provided on blinding. <u>Detection Bias</u>: (unclear) Not described. <u>Attrition Bias</u>: (high) More than 10% attrition in both groups and higher in gepirone patients. Analysis was on ITT population with LOCF dataset.

		- moderate to severe depression based on DSM-IV - Daily dysphoria for the past 4 weeks - Baseline HAM-D 17 score of 20 or greater - 18-70 years old Key Exclusion Criteria: - See above	1. 29 (28%) 2. 20 (20%)	Secondary Endpoints: HAM-D 17 Responders at week 8: 1. 44 (43.6%) 2. 31 (30.7%) P=0.059 Change in MADRS at week 8: 1. -12.28 2. -9.22 P=0.024 CGI Responders at week 8: 1. -44 (43.6%) 2. -36 (35.6%) P=0.251	ARR 13% / NNT 8 NA NS	P<0.001 Nausea: 1. 36 (35.3%) 2. 14 (14.2%) P<0.001 Insomnia: 1. 20 (19.6%) 2. 7 (6.6%) P=0.007	NNH 3 ARR 21.1%/ NNH 5 ARR 13%/ NNH 8	Reporting Bias: (low) See above. Other Bias: (unclear) See above. **Applicability**: Patient: Patients are similar to OHP patients with the majority being female and White with moderate to severe depression It is unclear if patients with treatment resistant depression could be included. Intervention: Same as above. Comparator: Same as above. Outcomes: Same as above. Setting: Six US study sites and one site in the Netherlands.

Abbreviations AD = antidepressant; AE = adverse effects; ARR = absolute risk reduction; CI = confidence interval; CGI= Clinical Global Impression; CGI-S = Clinical Global Impression Severity; DSM = Diagnostic and Statistical Manual of Mental Disorders HAM-D = Hamilton Rating Scale for Depression; ITT = intention to treat; LOCF = last observation carried forward; mITT = modified intention to treat; LOCF = last observation carried forward; LSM = least-square means; MADRS = Montgomery-Asberg Depression Rating Scale; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; PC = placebo controlled; PG = parallel-group; PP = per protocol

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19. SPRAVATO (esketamine) [prescribing information]. Titusville, NJ; Janssen Pharmaceuticals. October 2023.

20. Viibryd (vilazodone) [prescribing information]. Madison, NJ; Allergan. September 2021.

21. CYMBALTA (duloxetine) [prescribing information]. Indianapolis, IN; Lilly USA. October 2023.

22. LEXAPRO (escitalopram) [prescribing information]. North Chicago, IL; Abbvie, Inc. October 2023.

23. LUVOX (fluvoxamine) [prescribing information]. Baudette, MN; ANI Pharmaceuticals, Inc. August 2023.

24. ZOLOFT (sertraline) [prescribing informatiom]. Morgantown, WV; Viatris Specialty LLC. August 2023.

25. Effexor XR (venlafaxine extended-release capsules) [prescribing information]. Philadelphia, PA; Pfizer, Inc., November 2021.

26. CELEXA (citalopram) [prescribing information]. Madison, NJ; Allergan USA, Inc. August 2023.

27. FETZIMA (levominacipran) [prescribing information]. North Chicago, IL; AbbVie, Inc. August 2023.

28. PAXIL (paroxetine) [prescribing information]. Weston, FL; Apotex Corp. August 2023.

29. EXXUA (gepirone extended release) [prescribing information]. San Antonio, TX; Mission Pharmacal Company. September 2023.

Appendix 1: Current Preferred Drug List

Generic	Brand	Form	PDL
amitriptyline HCl	AMITRIPTYLINE HCL	TABLET	Y
amitriptyline HCl	ELAVIL	TABLET	Y
bupropion HCl	BUPROPION XL	TAB ER 24H	Y
bupropion HCl	WELLBUTRIN XL	TAB ER 24H	Y
bupropion HCl	BUPROPION HCL SR	TAB SR 12H	Y
bupropion HCl	WELLBUTRIN SR	TAB SR 12H	Y
bupropion HCl	BUPROPION HCL	TABLET	Y
citalopram hydrobromide	CITALOPRAM HBR	SOLUTION	Y
citalopram hydrobromide	CELEXA	TABLET	Y
citalopram hydrobromide	CITALOPRAM HBR	TABLET	Y
desipramine HCl	DESIPRAMINE HCL	TABLET	Y

desipramine HCl	NORPRAMIN	TABLET	Y
desvenlafaxine succinate	DESVENLAFAXINE SUCCINATE ER	TAB ER 24H	Y
desvenlafaxine succinate	PRISTIQ	TAB ER 24H	Y
doxepin HCl	DOXEPIN HCL	CAPSULE	Y
doxepin HCl	DOXEPIN HCL	ORAL CONC	Y
duloxetine HCl	CYMBALTA	CAPSULE DR	Y
duloxetine HCl	DULOXETINE HCL	CAPSULE DR	Y
escitalopram oxalate	ESCITALOPRAM OXALATE	TABLET	Y
escitalopram oxalate	LEXAPRO	TABLET	Y
fluoxetine HCl	FLUOXETINE HCL	CAPSULE	Y
fluoxetine HCl	PROZAC	CAPSULE	Y
fluoxetine HCl	FLUOXETINE HCL	SOLUTION	Y
fluoxetine HCl	FLUOXETINE HCL	TABLET	Y
fluvoxamine maleate	FLUVOXAMINE MALEATE	TABLET	Y
imipramine HCl	IMIPRAMINE HCL	TABLET	Y
mirtazapine	MIRTAZAPINE	TAB RAPDIS	Y
mirtazapine	REMERON	TAB RAPDIS	Y
mirtazapine	MIRTAZAPINE	TABLET	Y
mirtazapine	REMERON	TABLET	Y
nefazodone HCl	NEFAZODONE HCL	TABLET	Y
nortriptyline HCl	NORTRIPTYLINE HCL	CAPSULE	Y
nortriptyline HCl	PAMELOR	CAPSULE	Y
nortriptyline HCl	NORTRIPTYLINE HCL	SOLUTION	Y
paroxetine HCl	PAROXETINE HCL	TABLET	Y
paroxetine HCl	PAXIL	TABLET	Y
sertraline HCl	SERTRALINE HCL	ORAL CONC	Y
sertraline HCl	ZOLOFT	ORAL CONC	Y
sertraline HCl	SERTRALINE HCL	TABLET	Y
sertraline HCl	ZOLOFT	TABLET	Y
venlafaxine HCl	EFFEXOR XR	CAP ER 24H	Y
venlafaxine HCl	VENLAFAXINE HCL ER	CAP ER 24H	Y
venlafaxine HCl	VENLAFAXINE HCL	TABLET	Y
amoxapine	AMOXAPINE	TABLET	V
bupropion HBr	APLENZIN	TAB ER 24H	V
bupropion HCl	BUPROPION XL	TAB ER 24H	V
bupropion HCl	FORFIVO XL	TAB ER 24H	V
citalopram hydrobromide	CITALOPRAM HBR	CAPSULE	V
clomipramine HCl	ANAFRANIL	CAPSULE	V
clomipramine HCl	CLOMIPRAMINE HCL	CAPSULE	V
desvenlafaxine	DESVENLAFAXINE ER	TAB ER 24H	V

dextromethorphan HBr/bupropion	AUVELITY	TAB IR ER	V
duloxetine HCl	DRIZALMA SPRINKLE	CAP DR SPR	V
escitalopram oxalate	ESCITALOPRAM OXALATE	SOLUTION	V
esketamine HCl	SPRAVATO	SPRAY	V
fluoxetine HCl	FLUOXETINE DR	CAPSULE DR	V
fluvoxamine maleate	FLUVOXAMINE MALEATE ER	CAP ER 24H	V
imipramine pamoate	IMIPRAMINE PAMOATE	CAPSULE	V
isocarboxazid	MARPLAN	TABLET	V
levomilnacipran HCl	FETZIMA	CAP SA 24H	V
levomilnacipran HCl	FETZIMA	CAP24HDSPK	V
paroxetine HCl	PAROXETINE HCL	ORAL SUSP	V
paroxetine HCl	PAXIL	ORAL SUSP	V
paroxetine HCl	PAROXETINE CR	TAB ER 24H	V
paroxetine HCl	PAROXETINE ER	TAB ER 24H	V
paroxetine HCl	PAXIL CR	TAB ER 24H	V
paroxetine mesylate	PEXEVA	TABLET	V
phenelzine sulfate	NARDIL	TABLET	V
phenelzine sulfate	PHENELZINE SULFATE	TABLET	V
protriptyline HCl	PROTRIPTYLINE HCL	TABLET	V
selegiline	EMSAM	PATCH TD24	V
sertraline HCl	SERTRALINE HCL	CAPSULE	V
tranylcypromine sulfate	TRANYLCYPROMINE SULFATE	TABLET	V
trimipramine maleate	TRIMIPRAMINE MALEATE	CAPSULE	V
venlafaxine besylate	VENLAFAXINE BESYLATE ER	TAB ER 24	V
venlafaxine HCl	VENLAFAXINE HCL ER	TAB ER 24	V
vilazodone HCl	VIIBRYD	TAB DS PK	V
vilazodone HCl	VIIBRYD	TABLET	V
vilazodone HCl	VILAZODONE HCL	TABLET	V
vortioxetine hydrobromide	TRINTELLIX	TABLET	V
zuranolone	ZURZUVAE	CAPSULE	V
brexanolone	ZULRESSO	VIAL	
olanzapine/fluoxetine HCl	OLANZAPINE-FLUOXETINE HCL	CAPSULE	
olanzapine/fluoxetine HCl	SYMBYAX	CAPSULE	
trazodone HCl	TRAZODONE HCL	TABLET	

Appendix 2: Abstracts of Comparative Clinical Trials

Esketamine Nasal Spray versus Quetiapine for Treatment-Resistant Depression

Andreas Reif, Istvan Bitter, Jozefien Buyze, Kerstin Cebulla, Richard Frey, Dong-Jing Fu, Tetsuro Ito, Yerkebulan Kambarov, Pierre-Michel Llorca, Albino J Oliveira-Maia, Thomas Messer, Siobhán Mulhern-Haughey, Benoît Rive, Christian von Holt, Allan H Young, Yordan Godinov; ESCAPE-TRD Investigators

Abstract

Background: In treatment-resistant depression, commonly defined as a lack of response to two or more consecutive treatments during the current depressive episode, the percentage of patients with remission is low and the percentage with relapse is high. The efficacy and safety of esketamine nasal spray as compared with extended-release quetiapine augmentation therapy, both in combination with ongoing treatment with a selective serotonin reuptake inhibitor (SSRI) or a serotonin-norepinephrine reuptake inhibitor (SNRI), in patients with treatment-resistant depression are unknown.

Methods: In an open-label, single-blind (with raters unaware of group assignments), multicenter, phase 3b, randomized, active-controlled trial, we assigned patients, in a 1:1 ratio, to receive flexible doses (according to the summary of product characteristics) of esketamine nasal spray (esketamine group) or extended-release quetiapine (quetiapine group), both in combination with an SSRI or SNRI. The primary end point was remission, defined as a score of 10 or less on the Montgomery-Åsberg Depression Rating Scale (MADRS), at week 8 (scores range from 0 to 60, with higher scores indicating more severe depression). The key secondary end point was no relapse through week 32 after remission at week 8. All patients were included in the analysis; patients who discontinued the trial treatment were considered as having had an unfavorable outcome (i.e., they were grouped with patients who did not have remission or who had a relapse). Analyses of the primary and key secondary end points were adjusted for age and number of treatment failures.

Results: Overall, 336 patients were assigned to the esketamine group and 340 to the quetiapine group. More patients in the esketamine group than in the quetiapine group had remission at week 8 (91 of 336 patients [27.1%] vs. 60 of 340 patients [17.6%]; P = 0.003) and had no relapse through week 32 after remission at week 8 (73 of 336 patients [21.7%] vs. 48 of 340 patients [14.1%]). Over 32 weeks of follow-up, the percentage of patients with remission, the percentage of patients with a treatment response, and the change in the MADRS score from baseline favored esketamine nasal spray. The adverse events were consistent with the established safety profiles of the trial treatments.

Conclusions: In patients with treatment-resistant depression, esketamine nasal spray plus an SSRI or SNRI was superior to extended-release quetiapine plus an SSRI or SNRI with respect to remission at week 8. (Funded by Janssen EMEA; ESCAPE-TRD ClinicalTrials.gov number, NCT04338321.).

Appendix 3: Medline Search Strategy

Database(s): **Ovid MEDLINE(R) ALL** 1946 to February 12, 2024
Search Strategy:

#	Searches	Results
1	gepirone.mp.	299
2	limit 1 to (english language and humans and clinical trial, all)	34

Database(s): **Ovid MEDLINE(R) ALL** 1946 to February 16, 2024
Search Strategy:

#	Searches	Results
1	Amitriptyline/ or amitriptyline.mp.	10006
2	bupropion.mp. or Bupropion/	5724
3	citalopram.mp. or Citalopram/	7813
4	desipramine.mp. or Desipramine/	7999
5	desvenlafaxine.mp. or Desvenlafaxine Succinate/	558
6	duloxetine.mp. or Duloxetine Hydrochloride/	3371
7	doxepin.mp. or Doxepin/	1548
8	escitalopram.mp. or Escitalopram/	3377
9	fluoxetine.mp. or Fluoxetine/	15888
10	Fluvoxamine.mp. or Fluvoxamine/	3358

11	imipramine.mp. or Imipramine/	13601
12	mirtazapine.mp. or Mirtazapine/	2792
13	nefazodone.mp.	810
14	nortriptyline.mp. or Nortriptyline/	3300
15	paroxetine.mp. or Paroxetine/	6916
16	sertraline.mp. or Sertraline/	6182
17	venlafaxine.mp. or Venlafaxine Hydrochloride/	5092
18	amoxapine.mp. or Amoxapine/	492
19	clomipramine.mp. or Clomipramine/	4154
20	dextromethorphan.mp. or Dextromethorphan/	3235
21	esketamine.mp.	952
22	isocarboxazid.mp. or Isocarboxazid/	419
23	levomilnacipran.mp. or Levomilnacipran/	103
24	phenelzine.mp.	1695
25	protriptyline.mp. or Protriptyline/	417
26	selegiline.mp. or Selegiline/	3032
27	tranylcypromine.mp. or Tranylcypromine/	2322
28	trimipramine.mp. or Trimipramine/	549
29	vilazodone.mp. or Vilazodone Hydrochloride/	279
30	vortioxetine.mp. or Vortioxetine/	723
31	brexanolone.mp.	151
32	trazodone.mp. or Trazodone/	2387
33	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32	85733
34	limit 33 to (english language and humans)	48261

35	limit 34 to yr="2022 -Current"	2608
36	limit 35 to (clinical trial, phase iii or guideline or meta analysis or practice guideline or "systematic review")	287
37	limit 36 to yr="2023 -Current"	147

Appendix 4: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use EXXUA safely and effectively. See full prescribing information for EXXUA.

EXXUA (gepirone) extended-release tablets, for oral use
Initial U.S. Approval: 2023

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS
See full prescribing information for complete boxed warning.

Increased risk of suicidal thinking and behavior in pediatric and young adult patients taking antidepressants. Closely monitor for worsening and emergence of suicidal thoughts and behaviors (5.1). EXXUA is not approved for use in pediatric patients (8.4).

----------INDICATIONS AND USAGE----------
EXXUA is indicated for the treatment of major depressive disorder (MDD) in adults (1).

----------DOSAGE AND ADMINISTRATION----------
- Correct electrolyte abnormalities and perform electrocardiogram (ECG) prior to initiating treatment with EXXUA. Do not initiate EXXUA if QTc is > 450 msec (2.1).
- Perform ECGs during dosage titration and periodically during treatment (2.1).
- The recommended starting dose is 18.2 mg administered orally once daily with food at approximately the same time each day (2.2, 2.3).
- Depending on clinical response and tolerability, the dosage may be increased to 36.3 mg once daily on Day 4. Dosage may be further titrated to 54.5 mg once daily after Day 7 and to 72.6 mg once daily after an additional week (2.3).
- Geriatric patients: Recommended starting dosage is 18.2 mg once daily. Dosage may be increased to 36.3 mg after 7 days (2.4).
- Renal Impairment (creatinine clearance < 50 mL/min): Recommended starting dosage is 18.2 mg once daily. Dosage may be increased to 36.3 mg once daily after 7 days (2.5, 8.6).
- Moderate Hepatic Impairment (Child Pugh B): Dosage may be increased to 36.3 mg once daily after 7 days (2.6, 8.7).
- Adjust EXXUA dose by 50% when a moderate CYP3A4 inhibitor is administered (2.7).

----------DOSAGE FORMS AND STRENGTHS----------
Extended-release tablets: 18.2 mg, 36.3 mg, 54.5 mg, and 72.6 mg (3).

----------CONTRAINDICATIONS----------
- Known hypersensitivity to gepirone or components of EXXUA (4).
- Prolonged QTc interval > 450 msec at baseline (4).
- Congenital long QT syndrome (4).
- Concomitant use of strong CYP3A4 inhibitors (4).
- Severe hepatic impairment (4).
- Use with an MAOI or within 14 days of stopping treatment with EXXUA. Do not use EXXUA within 14 days of discontinuing an MAOI (4).

----------WARNINGS AND PRECAUTIONS----------
- QT Interval Prolongation: EXXUA prolongs the QTc. Correct electrolyte abnormalities. Perform ECGs prior to initiation, during dose titration, and periodically during treatment with EXXUA. Monitor ECGs more frequently when EXXUA is used concomitantly with drugs known to prolong the QT interval, in patients who develop QTc ≥ 450 msec during treatment or are at significant risk of developing torsade de pointes. Do not escalate dosage if QTc > 450 msec (2.1, 5.2, 7).
- Serotonin Syndrome: Increased risk when co-administered with other serotonergic agents. If serotonin syndrome occurs, discontinue EXXUA and initiate supportive measures (5.3).
- Activation of Mania/Hypomania: Screen patients for bipolar disorder (5.4).

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence of ≥5% and at least twice incidence of placebo) were dizziness, nausea, insomnia, abdominal pain, and dyspepsia (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Fabre-Kramer at 713-975-6900 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
Strong CYP3A4 inducers: Reduces EXXUA exposure. Avoid concomitant use (7).

----------USE IN SPECIFIC POPULATIONS----------
Pregnancy: Third trimester use may increase the risk for persistent pulmonary hypertension and symptoms of poor adaptation (respiratory distress, temperature instability, feeding difficulty, hypotonia, irritability) in the neonate (8.1).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 09/2023

Appendix 5: Key Inclusion Criteria

Population	Patients with an indication for antidepressant use (e.g., depression, anxiety, pain)
Intervention	Antidepressant treatment
Comparator	Placebo or active treatment comparison
Outcomes	Reduction in depressive symptoms and remission of symptoms
Setting	Outpatient

Appendix 6: Prior Authorization Criteria

Tricyclic Antidepressants

Goal(s):

- Ensure safe and appropriate use of tricyclic antidepressants in children less than 12 years of age
- Discourage off-label use not supported by compendia

Length of Authorization:

- Up to 12 months

Requires PA:

- Tricyclic antidepressants in children younger than the FDA-approved minimum age (new starts)
- Auto-PA approvals for:
  - Patients with a claim for an SSRI or TCA in the last 6 months
  - Prescriptions identified as being written by a mental health provider

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Table 1. FDA-Approved Indications of Tricyclic Antidepressants in Children

Drug	FDA-Approved Indications	Maximum Daily Dose	Minimum FDA-Approved Age
amitriptyline HCl	Depression	50 mg	12
amoxapine	Depression	400 mg	18
clomipramine HCl	Obsessive-compulsive disorder	200 mg	10

desipramine HCl	Depression	300 mg (150 mg for 10-19 years of age)	10
doxepin HCl	Depression Anxiety	150 mg	12
imipramine HCl	Depression Nocturnal enuresis	75 mg	6
imipramine pamoate	Depression	200 mg	18
maprotiline HCl	Depression Bipolar depression Dysthymia Mixed anxiety and depressive disorder	225 mg	18
nortriptyline HCl	Depression	50 mg	12
protriptyline HCl	Depression	60 mg	12
trimipramine maleate	Depression	100 mg	12

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Does the dose exceed the maximum FDA-approved dose (**Table 1**)?	**Yes:** Go to #3	**No:** Go to #4
3. Is there documentation that the prescriber is monitoring blood levels to support use of the prescribed dose?	**Yes:** Go to #4	**No:** Go to #6
4. Is the request for an FDA-approved indication and age (**Table 1**)?	**Yes:** Approve for up to 6 months	**No:** Go to #5
5. Is the request for prophylactic treatment of headache or migraine and is the therapy prescribed in combination with cognitive behavioral therapy?	**Yes**: Approve for up to 6 months	**No:** Go to #6
6. Is the drug prescribed by or in consultation with an appropriate specialist for the condition (e.g., mental health specialist, neurologist, etc.)?	**Yes**: Approve for up to 6 months	**No:** Pass to RPh. Deny; medical appropriateness.

P&T/DUR Review: 6/24 (KS); 12/23 (KS), 2/23, 2/21(SS) 11/19
Implementation:7/1/24; 2/1/2020

Zuranolone (Zurzuvae)

Goal(s):
- To ensure appropriate use of zuranolone in patients with post-partum depression.

Length of Authorization:
- One time use only.

Requires PA:
- Zuranolone requires a prior authorization approval due to safety concerns.

Covered Alternatives:
- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this an FDA approved indication and age (e.g., ≥18 years)?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Does the patient have moderate to severe post-partum depression? Note: Zuranolone is not indicated for major depressive disorder but can be covered for depression meeting the clinical diagnosis of post-partum depression (e,g., moderate to severe depression with peripartum onset).	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
4. Has the patient been previously treated with zuranolone for severe post-partum depression related to their most recent pregnancy?	**Yes:** Pass to RPh. Deny; medical appropriateness. Multiple courses of zuranolone have not been studied.	**No:** Approve for a single 14-day treatment.

P&T/DUR Review: 6/24 (KS); 12/23 (KS)
Implementation: 1/1/24

Brexanolone (Zulresso)

Goal(s):
- To ensure appropriate use of brexanolone in patient with post-partum depression.

Length of Authorization:
- One time use only.

Requires PA:
- Brexanolone requires a prior authorization approval due to safety concerns (pharmacy and physician administered claims)

Covered Alternatives:
- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this an FDA approved indication and age (e.g., ≥15 years)?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
3. Is the patient with moderate to severe post-partum depression?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Has the patient been previously treated with brexanolone for severe post-partum depression related to their most recent pregnancy?	**Yes:** Pass to RPh. Deny; medical appropriateness. Multiple doses of brexanolone have not been studied.	**No:** Go to #5
5. Has the patient had an adequate trial (6-8 weeks) of an oral antidepressant?	**Yes:** Approve for a single, continuous, intravenous infusion over 60 hours (titrated per prescribing recommendations)	**No:** Pass to RPh. Deny; recommend trial of oral antidepressant

P&T/DUR Review: 6/24(KS); 12/23 (KS), 2/23, 2/21(SS) 7/19
Implementation: 4/1/23; 8/19/19

Esketamine (Spravato)

Goal(s):

- To ensure safe and appropriate use of esketamine in patients with treatment resistant depression or suicidal ideation.

Length of Authorization:

- Up to 6 months

Requires PA:

- Esketamine requires a prior authorization approval due to safety concerns (pharmacy and physician administered claims).

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this an FDA approved indication?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the request for maintenance dosing of esketamine (for determining response to therapy) OR for continuation after initiation during a recent hospitalization?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #4
4. Is the patient 65 years or older?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #5
5. Is the member currently engaged in or been referred for psychotherapy?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness.
6. Is the patient currently on a therapeutic dose of an oral antidepressant (Average minimum effective dose for antidepressants can be found at: https://www.oregon.gov/oha/HPA/DSI-Pharmacy/MHCAGDocs/Switching-Between-Anti-Depressant-Medications.pdf)	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness. Esketamine is indicated for use with an oral antidepressant.
7. Does the patient have treatment resistant depression (failure of two separate antidepressant trials which were each given for at least 6 weeks at therapeutic doses)?	**Yes:** Go to #10	**No:** Go to #8
8. Is the request for treatment of major depressive disorder in the setting of acute suicidal ideation or behavior?	**Yes:** Go to #9	**No:** Pass to RPh. Deny; medical appropriateness. Recommend an adequate trial (minimum of 6-8 weeks) of 2 or more antidepressants.

Approval Criteria		
9. Is there a documented plan to optimize oral antidepressant treatment in one of the following ways: a. Titrating the dose of the current antidepressant to a therapeutic level b. Switching to a different antidepressant OR c. Adding oral augmentation therapy (e.g., a second antidepressant, an atypical antipsychotic, or mood stabilizer)?	**Yes:** Go to #10	**No:** Pass to RPh. Deny; medical appropriateness.
10. Does the patient have documentation of any of the following: • Current Aneurysmal vascular disease or arterial venous malformation OR • History of Intracerebral hemorrhage OR • Current Pregnancy OR • Current Uncontrolled hypertension (e.g., >140/90 mmHg)	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Approve up to 28 days for induction (either 56 mg and/or 84 mg for titration) not to exceed 24 units total to be covered within the approved time window. The approved time window typically spans 60 days to accommodate scheduling visits.

Renewal Criteria		
1. Is there documentation that the patient demonstrated an adequate response during the 4-week induction phase (an improvement in depressive symptoms)?	**Yes:** Go to #2	**No**: Go to #4
2. Is the request for administration of esketamine once weekly or every 2 weeks?	**Yes:** Go to #3	**No**: Pass to RPh. Deny; medical appropriateness.
3. Has the patient been adherent to oral antidepressant therapy?	**Yes:** Approve for up to 6 months (maximum of 12 per 28 days)	**No:** Pass to RPh. Deny; medical appropriateness.

Renewal Criteria		
4. Has the patient been on therapy for at least 4 weeks?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Approve for completion of induction phase (total 28 days of treatment with a maximum of 24 nasal spray devices (each device contains 28 mg of esketamine)

P&T/DUR Review: 6/24(KS); 2/24; 12/23 (KS); 2/23, 10/21; 2/21; 7/19
Implementation:7/1/24; 1/1/22; 3/1/21; 8/19/19