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DEXTROMETHORPHAN AND BUPROPION EXTENDED-RELEASE TABLETS (AUVELITY 45 MG/105 MG)

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ABBREVIATIONS

AE	Adverse event
APA	American Psychological Association
CBT	Cognitive Behavioral Therapy
CI	Confidence interval
CNS	Central nervous system
CYP	Cytochrome P450
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
DEX	Dextromethorphan
DUR	Drug Utilization Review
ER	Extended release
FDA	U.S. Food and Drug Administration
IR	Immediate release
MADRS	Montgomery-Åsberg Depression Rating Scale
MAOI	Monoamine oxidase inhibitor
MDD	Major Depressive Disorder
MOA	Mechanism of action
NCT	National Clinical Trial
NICE	National Institute for Health and Care Excellence
NMDA	N-methyl-D-aspartate
ODT	Oral disintegrating tablet
OTC	Over the counter product
PA	Prior authorization
PDL	Utah Medicaid Preferred Drug List
PHQ-9	Patient Health Questionnaire-9 Item
RANZCP	The Royal Australian and New Zealand College of Psychiatrists
RCT	Randomized controlled trial
SAE	Serious adverse event
SC	Subcutaneous
SR	Sustained release
SNRI	Serotonin-norepinephrine reuptake inhibitor
SSRI	Selective-serotonin reuptake inhibitor
TCA	Tricyclic antidepressant
TRD	Treatment-resistant depression
US	United States
QIDS-SR	Quick Inventory of Depressive Symptomatology – Self Report

1.0 INTRODUCTION

Auvelity is a new drug combination of dextromethorphan (DEX; 45 mg) and bupropion (105 mg), approved in August 2022 for the treatment of major depressive disorder (MDD) in adults.[1] This product was designated as a breakthrough therapy for depression and granted a priority review by the US Food and Drug Administration (FDA). Auvelity (DEX/bupropion) is an extended-release (ER) oral tablet, administered on a daily basis. Co-formulation with bupropion, an inhibitor of cytochrome P450 (CYP) 2D6, serves to increase the plasma concentration of DEX that is otherwise rapidly metabolized by CYP 2D6 in extensive metabolizers (ie, normal metabolizers, the predominant phenotype). Bupropion also has antidepressant properties as a norepinephrine and dopamine reuptake inhibitor (NDRI). Dextromethorphan employs several mechanisms of action (MOA) implicated in alleviating depression, but its NMDA (N-methyl-D-aspartate) receptor antagonist and sigma-1 agonist actions are highlighted by investigators and the sponsor as the primary MOAs thought to yield anti-depressive effects. NMDA antagonism is unique from the MOAs of traditional antidepressants.[2,3]

Clinical trials that led to FDA approval compared DEX/bupropion ER to placebo (phase 3) or to bupropion sustained release (SR) monotherapy (phase 2) in adults with major depression who did not yet have a diagnosis of treatment-resistant depression (TRD). DEX/bupropion ER has not been studied in the pediatric population, nor in combination regimens with other antidepressant therapies (including other NMDA antagonists, esketamine or ketamine). Unpublished or in-progress phase 2 or 3 studies have been designed to assess DEX/bupropion ER (Auvelity) for TRD, smoking cessation, and agitation associated with Alzheimer's disease (for which there are no FDA-approved agents[4]).

This report reviews the place in therapy of this new combination medication for the treatment of depression in adults, outlines its safety profile, and provides potential prior authorization (PA) criteria for consideration. **Table 1** summarizes the labeled indication and dosing recommendations for Auvelity. As of November 1, 2022, the Utah Medicaid Preferred Drug List (PDL) does not yet include Auvelity. Nonetheless, there are a variety of PDL-preferred antidepressants among various drug-class designations (eg, SSRI/SNRIs, TCAs) on the Utah Medicaid PDL. The *Antidepressant, Miscellaneous* category includes several single-ingredient bupropion products as preferred, along with additional preferred agents as follows: bupropion, bupropion SR, bupropion XL 150 and 300 mg, Marplan, phenelzine, trazodone 50-150 mg, mirtazapine 15-45mg, and mirtazapine ODT.

Table 1. Auvelity (dextromethorphan/bupropion ER) Indication and Recommended Dosage

Dextromethorphan and bupropion (Auvelity) 45 mg/105 mg oral extended-release tablets

- **Approved for the treatment of adults** (≥18 years of age) with **major depressive disorder (MDD)**
  - Prior to initiation: assess blood pressure, screen for history of bipolar disorder, mania, or hypomania,[a] and ensure patients are not receiving any other bupropion- or dextromethorphan-containing agents
- **Maintenance dose:** 1 tablet twice daily
  - Initiate as 1 tablet once daily in the morning and increase to 1 tablet twice daily after 3 days on the starting dosage; administer with or without food
  - For moderate renal impairment or for known CYP2D6 poor metabolizers: max dose of 1 tablet daily

[a] *Antidepressants can precipitate a manic, mixed, or hypomanic manic episode. Patients should be screened for bipolar disorder and the presence of risk factors for bipolar disorder (eg, family history of bipolar disorder, suicide, or depression)*

2.0 METHODS

We searched literature databases and ClinicalTrials.gov for information about safety and efficacy of DEX/bupropion ER, primarily focusing on phase 2 or 3 trials. In particular, Ovid Medline, Embase, and Epistemonikos (a systematic review database) were searched using various combinations of keywords for the drugs and the indication of interest. For details regarding the literature search strategies, refer to **Appendix A**.

The following databases or medical association websites were searched for recent clinical guidelines (ie, published in the last 3 years) about pharmacotherapy for MDD in adults:

- The American Psychiatric Association: https://psychiatry.org/psychiatrists/practice/clinical-practice-guidelines
- The College of Psychiatric and Neurologic Pharmacists: https://aapp.org/guideline/external/depression
- Epistemonikos.org, using keywords (eg, guideline AND depress*)
- UpToDate.com

Reference lists of pertinent systematic reviews[5,6] of clinical guidelines that were identified among literature database search results were also reviewed for recent guidelines.

The current professional prescribing information (ie, package insert) for Auvelity was obtained from the drug sponsor's website dedicated to the product (https://www.auvelity.com).

3.0 DISEASE OVERVIEW

According to the National Health Interview Survey, during 2019, 1 in 5 US adults experienced depressive symptoms of any severity. Of the total US adult population, 11.5% experienced mild depressive symptoms, and 7.0% experienced moderate to severe symptoms as measured using the validated 8-item Patient Health Questionnaire (PHQ–8) for depressive symptom severity[*].[7] Women were more likely than men to experience depressive symptoms.[7]

Diagnosis criteria for adult MDD, according to the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5), includes the requirement for depressed mood or loss of pleasure or interest for most of the day and occurring nearly every day for at least 2 weeks. Additionally, at least 3 of the following symptoms must occur during the depressive episode, and should occur on most days with the exception of the last 2 bullet points marked with an asterisk (*)[8,9]:

- weight and/or appetite change
- insomnia or hypersomnia
- psychomotor retardation or restlessness,
- fatigue or loss of energy
- feeling guilty or worthless
- impaired decision-making or ability to concentrate
- recurrent thoughts of death or suicidal ideation*
- suicide plan or attempt*

[*] PHQ-8 score ranges of 0–4, 5–9, 10–14, and 15–24 correspond to no/minimal, mild, moderate, or severe symptoms of depression, respectively.

Symptoms must cause significant distress and/or impairment in functioning, and should not be attributable to a different medical condition or substance use disorder.[8,9]

3.1 Pharmacotherapy Management of MDD

Recent clinical guidelines for the management of MDD are published by the American Psychological Association (APA; 2019), the National Institute for Health and Care Excellence (NICE; 2022), the Royal Australian and New Zealand College of Psychiatrists (RANZCP; 2020), and the French Association for Biological Psychiatry and Neuropsychopharmacology (FABPN, 2019). Since Auvelity is the first combination product of DEX/bupropion and just recently approved, in August 2022, clinical guidelines do not yet incorporate this medication into their recommendations.

The APA recommends that either psychotherapy, pharmacotherapy with a second-generation antidepressant, or a combination of these can be used as first-line therapy for depressive disorders in the general adult population.[10] Second-generation antidepressants were specified to include either selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs).[10] Refer to **Table 2** for the various psychological interventions recommended. Similarly, the FABPN recommended SSRIs and SNRIs as first-line therapy for MDD of any severity, and specifies that for severe depression, psychotherapies should only be used in combination with pharmacotherapy (rather than as monotherapy). The 2022 NICE guideline recommends a similar first-line approach as to the APA (ie, psychological and/or pharmacologic treatment) for moderate to severe depression (ie, scoring 16 or more on the PHQ-9 scale).[11] However, the NICE's list of recommended first-line antidepressant options is broader than the APA recommendation. NICE states SSRIs, SNRIs, *or any other antidepressant if indicated* can be used.[11] While the RANZCP guideline does not provide a formal strength or graded recommendation regarding a preference of agents, it does include a set of 7 "Choice" agents described to be marginally preferable over other traditional antidepressants, based on head-to-head efficacy studies and clinical experience. These 7 agents are specified in 3 subgroups to infer tolerability/efficacy relative to one another[12]:

- *Group 1 (better tolerability)*: escitalopram, vortioxetine, and agomelatine
- *Group 2 (efficacy and tolerability descriptively in-between groups 1 and 3):* venlafaxine, mirtazapine, **bupropion**
- *Group 3 (better efficacy)*: amitriptyline

Ultimately the choice of therapy should be tailored to the patient's clinical profile. Authors highlight that bupropion can be particularly useful when fatigue is a major symptomatic complaint of depression, or for smokers with comorbid depression to help reduce nicotine cravings.[12,13] RANZCP recommends that at least one evidence-based psychological intervention should be offered to patients as foundational care, since a combined psychotherapy/antidepressant approach is more effective than either treatment alone. In order to sustain a positive clinical response to pharmacotherapy, RANZCP recommends continuing the beneficial antidepressant for at least 6 months, and that patients should be offered cognitive-behavioral therapy (CBT) to help prevent relapse of depressive episodes.[12]

Guideline authors describe that "…response rates to the first-line antidepressant (ADT) are moderate (40–60%), and remission is achieved in a minority of patients (from 30 to 45%)."[14] Even though

remission may be achieved after a number of weeks to months with antidepressant therapy, patients may not experience *sustained* remission in the longer term, as shown in the follow-up phase of the Star*D study.[15] This randomized controlled trial (RCT) followed the course of 3,671 patients with MDD along up to 4 successive trials of traditional antidepressants[†] +/- CBT in order to achieve remission (mimicking clinical practice). Notably, rates of remission tended to decline with successive treatment trials. The remission rates after the first, second, third, and fourth treatment trial were 36.8%, 30.6%, 13.7%, and 13.0%, respectively.[15] Of the 1,518 patients who entered the follow-up phase after having achieved remission on any step of therapy (and who had follow-up contact), approximately 34-50% of patients relapsed during follow-up with the mean time to relapse of 2.5 to 4.5 months, depending on which treatment step the patient reached.[15]

Among a variety of developing definitions for TRD, the threshold gaining traction is inadequate response to *2 or more* antidepressants in the current depressive episode (which will be used for the remainder of this report unless otherwise specified).[2,3,16,17] The 2019 FABPN guideline uses a similar definition for TRD: failure of 2 first-line antidepressant therapies of adequate dose and duration, with the optimal duration being 4-6 weeks at the target dose.[14] Other recent guidelines included in Table 2 do not specify a definition for TRD.

The approach after antidepressant treatment failure generally includes re-evaluation of the diagnosis, comorbidities, and engagement/adherence to therapy.[5] Treatment adjustments may include any of the following: antidepressant dose adjustment, switch to a different antidepressant, switch to or addition of an evidence-based psychotherapy if not already tried, augmentation with a second medication (eg, antidepressant[9], antipsychotic[‡], lithium, or triiodothyronine [T3]), or consideration of physical treatments (eg, electroconvulsive therapy or repetitive transcranial magnetic stimulation) for severe or treatment-resistant cases.[5,9,12,14] Additionally, intranasal esketamine, also an NMDA antagonist, is approved for patients with MDD with acute suicidal ideation or behavior, and for treatment-resistant depression.[§,18] The FDA-approved indication for acute suicidal ideation/behavior in MDD is unique to esketamine, as no other agent has an FDA-approved indication specifically for this purpose.[19]

Many patients are unable to achieve or maintain remission in spite of more aggressive steps of therapy. This may compel clinicians to prioritize improving function and quality-of-life as much as possible, while placing less emphasis on an elusive remission goal, which may or may not be attained/maintained via more aggressive pharmacotherapy regimens.[20-22]

[†] Citalopram was the first treatment level, followed by seven possible treatments in level 2 (either switches from citalopram to bupropion SR, cognitive therapy, sertraline, or extended-release venlafaxine, or augmentation of citalopram with bupropion, buspirone, or cognitive therapy). Level 3 included either switching to mirtazapine or nortriptyline, or augmenting with lithium or T3. Level 4 included tranylcypromine or venlafaxine ER plus mirtazapine.

‡ Antipsychotics with an FDA-approved indication for the treatment of depression as adjunctive treatment include aripiprazole, brexipiprazole, and quetiapine ER. The combination of olanzapine/fluoxetine is specifically indicated for treatment-resistant depression (ie, patients who failed at least 2 different antidepressants).

§ For the esketamine clinical trials in TRD, included patients were those who failed at least 2 different antidepressants of adequate dose and duration. Notably, this was not an inclusion criteria for the clinical trials in MDD that led to the approved indication of esketamine for MDD-associated acute suicidal/ideation.

Table 2 contains a synthesis of recent clinical guideline recommendations for pharmacotherapy management of MDD in adults.

Table 2. Clinical Guidelines Addressing Antidepressants for the Treatment of Depression in Adults

American Psychological Association (APA 2019)[9,10]

- The guideline is intended to be aspirational, and does not serve to limit the scope of practice or the limit coverage for therapy reimbursement by payers.
- **Initial therapy for depressive disorders[a] is psychotherapy, pharmacotherapy, or combined treatment** *[Recommendation for use][b]*
  - A shared decision-making process should take place to decide therapy. The following options can be considered as first-line:
    - **Second-generation antidepressants (defined as SSRIs or SNRIs)**
    - Psychotherapy including the following (which are all considered similarly effective):
      - Behavioral therapy
      - Cognitive, cognitive-behavioral, or mindfulness-based cognitive therapy
      - Interpersonal psychotherapy
      - Psychodynamic therapies
      - Supportive therapy
    - Combined therapy (ie, psychotherapy plus pharmacotherapy)
      - Either CBT or interpersonal psychotherapy are the preferable modalities to combine with a second-generation antidepressant. Cognitive therapy plus antidepressant appears most favorable to improve likelihood of full recovery.
      - While combined psychotherapy/pharmacotherapy may be more effective than either alone in *some subpopulations*, the choice is left to providers/patients because there are increased demands on patients, access issues, increased costs, risk of side effects; and some evidence suggesting combined treatment may impede with enduring effects of psychotherapy. For chronic and treatment-resistant depression, combined treatment is usually preferable.
- When selecting between treatments the panel suggests considering behavioral therapy rather than antidepressant medication alone *[conditionally recommended][b]*
  - Complementary and alternative treatments that may be considered when the psychotherapy or pharmacotherapy options are either ineffective or unacceptable included the following *[conditionally recommended][b]*: exercise monotherapy, St. John's Wort monotherapy; or secondary in preference, bright light therapy, yoga, or adjunctive acupuncture.

Partial or nonresponders to initial antidepressant therapy

- *Recommendation for use*[b]: either 1) switch from antidepressant monotherapy to cognitive monotherapy, or 2) switch from antidepressant monotherapy to a different antidepressant
- *Conditional recommendation for* use[b]: either 1) add interpersonal psychotherapy, cognitive-behavioral therapy, or psychodynamic psychotherapy to the antidepressant, or 2) augment with another antidepressant medication

Relapse prevention: offer cognitive-behavioral therapy, mindfulness-based cognitive therapy, or interpersonal psychotherapy, rather than antidepressant or treatment as usual *[conditionally recommended][b]*

Table 2. Clinical Guidelines Addressing Antidepressants for the Treatment of Depression in Adults

National Institute for Health and Care Excellence (NICE 2022)[11]

Pharmacotherapy Options
• *For a new episode of less severe depression*
  o The SSRI drug class is the only pharmacologic option specified, among other therapy interventions (eg, psychotherapy, behavioral therapy, cognitive behavioral therapy, counseling, etc.)
• *For a new episode of moderate and severe depression (defined as scoring 16 or more on the PHQ-9 scale):*
  o **First line treatment is any of the following:**
  ▪ Combination of individual cognitive-behavioral therapy and an antidepressant
  ▪ Individual CBT
  ▪ Individual behavioral activation
  ▪ **Antidepressant medication including SSRI, SNRI, or other antidepressant if indicated per clinical/treatment history**
  ▪ Individual problem-solving
  ▪ Counseling
  ▪ Short-term psychodynamic psychotherapy
  ▪ Interpersonal psychotherapy
  ▪ Guided self-help
  ▪ Group exercise
• *For limited response to antidepressant therapy, and no obvious cause can be found and resolved, further options may include*
  o Adding a group exercise intervention
  o Switching to or adding psychological therapy (see previous list for suggested psychological options for more severe depression)
  o Increasing the dose of the current antidepressant or changing to another agent in the same class
  o Switching to an antidepressant of a different class
• *For limited response to combined antidepressant/psychological therapy, and no obvious cause can be found and resolved, further options may include*
  o Switching to another psychological therapy
  o Increasing the dose or switching to another antidepressant
  o Adding another antidepressant from a different drug class; adding a second-generation antipsychotic (eg, aripiprazole, olanzapine, quetiapine or risperidone); or adding lithium
  ▪ Consider referral to or consulting a specialist for combination medication management
  o Augmentation with electroconvulsive, lamotrigine, or triiodothyronine (liothyronine).
• Note that the guideline advises for vortioxetine to be reserved for after the patient has had no or limited response to at least 2 previous antidepressants
• *For chronic depressive symptoms* that significantly impair personal and social functioning and who have not yet received treatment; may consider CBT, SSRIs, SNRIs, TCAs, or combination of CBT and SSRI or TCA.

Table 2. Clinical Guidelines Addressing Antidepressants for the Treatment of Depression in Adults

The Royal Australian and New Zealand College of Psychiatrists (2020)[12]
Advice regarding the choice of antidepressant • While authors do not provide a formal recommendation regarding the preference of agents, they classify certain agents as "Choice" antidepressants which is inferred as the preferred first-line agents. This set of 7 "Choice" agents is described to be slightly more effective than other agents, as found by cited network meta-analyses. This includes the following, also specified in groups based on tolerability/efficacy: o Group 1: Escitalopram, vortioxetine, and agomelatine (best tolerability) o Group 2: Venlafaxine, mirtazapine, bupropion (efficacy and tolerability descriptively in between groups 1 and 3) o Group 3: Amitriptyline (best efficacy) • Ultimately the choice of therapy should be tailored to the patient's clinical profile • Authors highlight that bupropion can be particularly useful, and is the preferred "choice" antidepressant when a patient suffers from fatigue as a symptom of their depression. **Graded Recommendations[c]** • Acute MDD o Assist patients to overcome barriers to psychological intervention (CBR) o Psychological interventions should be delivered by trained clinicians on the evidence-based approach (EBR I) o At least one evidence-based psychological intervention should be offered to all patients. Interventions with the most supportive evidence are CBT and IPT, but there are also others with some support. (EBR I) o **Combined psychological intervention and antidepressant medication are more effective than either alone. (EBR I)** • Long-term treatment of MDD o Patients should receive psychoeducation regarding lifetime risk of relapse and should be regularly monitored beyond the acute phase for continued remission and functional recovery (CBR) o Offer CBT to prevent relapse or MBCT for those with recurrent depressive episodes (EBR I) o The dose of antidepressant at which a satisfactory response was achieved should be continued during the continuation and preventative phases of treatment. (EBR I) o Maintenance antidepressant phase should last for at least 6 months and review of ongoing pharmacotherapy should occur at 1 year (CBR)
The French Association for Biological Psychiatry and Neuropsychopharmacology and FondaMental (2019)[14]
• Treatment-resistant depression was defined as the failure of two adequate courses (optimal duration is 4-6 weeks and at target dose) of different antidepressants. • See guideline for indications for hospitalization **Recommendations for mild, moderate, and severe depression** • SSRIs and SNRIs are first-line treatment for any clinical severity • For *severe depression*, psychotherapies should only be used in combination with an antidepressant, whereas psychotherapies can be tried as monotherapy in mild to moderate major depressive episodes**.** Refer to the full guideline regarding specific psychotherapies recommended. • For second-line therapy: o Tricyclic antidepressants, α2-antagonists, or agomelatine can be considered for severe depression.

Table 2. Clinical Guidelines Addressing Antidepressants for the Treatment of Depression in Adults

- For **partial response or non-response** to antidepressant treatment, ensure the dose has been optimized (as tolerated)
- For **partial response** to first-line antidepressant therapy, consider adding an α2-antagonist (eg, mirtazapine)

- For **non-response** to the initially tried antidepressant, switching antidepressants is recommended first rather than adding a second agent
- After the 3rd depressive episode, preventive strategies can be considered.
  - Strategies considered to be effective for preventing recurrences include electroconvulsive therapy and lithium; or, secondarily, lamotrigine or quetiapine.

Switching antidepressants

- Switching antidepressants is recommended for consideration when the patient experiences no response or poor tolerance to the initial treatment; or when the patient has had a positive prior response to an antidepressant to be re-introduced
- The first switch is recommended to be an inter-class switch (ie, switch to agent of a different class). Refer to the guideline Table 1 for the 2nd switch in therapy where suggested antidepressants are specified according to the 2 prior antidepressants tried.

Combination antidepressant strategies: such strategies are recommended only in cases of partial response (ie, after 4-6 weeks of treatment)

- First-line combination strategies: (SSRI or SNRI or tricyclic antidepressant) + α2 antagonist (eg, mirtazapine, mianserine)

Add-on strategies to ongoing antidepressant

- Add-on strategies are recommended for consideration in cases of partial response to antidepressant therapy of adequate duration (ie, after 4 to 6 weeks). Recommended options include the following:
  - First-line add-on options: lithium or quetiapine
  - Second-line add-on options: thyroid hormones (tri-iodothyronine), aripiprazole, or lamotrigine
    - Other second-generation antipsychotics such as risperidone, olanzapine, clozapine, amisulpride, or anticonvulsants are not recommended.

Recommended prescreening/examinations for patients with TRD

- Complete blood count, blood electrolytes, liver and renal functions
- Lipids and glucose levels
- Thyroid-stimulating hormone levels
- Plasma levels of the trialed antidepressant
- Electrocardiogram
- Brain MRI

Recommended monitoring while on antidepressants

- Blood pressure, abdominal circumference, weight
- Suicide risk, mood-switching,
- Lipid profile and glucose levels

Adjuvant treatments

- Recommendation to consider benzodiazepines or hydroxyzine for patients with anxious features
  - Possible to consider adding buspirone, pregabalin, or an antidepressant belonging to a different class
- Recommendation to consider hypnotics (zolpidem or zopiclone) for co-occurring sleep disorders
  - Possible to consider using hydroxyzine, benzodiazepines or an different antidepressant belonging to a different class

Table 2. Clinical Guidelines Addressing Antidepressants for the Treatment of Depression in Adults

• For patients with a high risk of self-harm injury, limited evidence-based therapies exist but based on expert opinion the following are possible options: hydroxyzine, benzodiazepines, second-generation antipsychotics, or lithium. • The following augmentation agents are recognized as having antidepressant properties: lithium, lamotrigine, and second-generation antipsychotics

[a] *The recommendations apply to MDD, along with subsyndromal depression, and persistent depressive disorder; however, do not extend to psychotic depression*

[b] *Recommendation for use: treatment was consistently superior to inactive control or equivalent, or superior to other treatments. Conditionally recommended: treatment was consistently superior to inactive control but was either not superior to the recommended treatment, had insufficient evidence of comparable efficacy to other treatments, or the greater harm or burden profile of the treatment appeared less favorable.*

[c] *Refer to the full guideline (Box 1) regarding physical treatments such as electroconvulsive therapy (ECT) and repetitive transcranial magnetic stimulation (rTMS)*

Abbreviations: CBR: consensus-based recommendation; EBR I: evidence-based recommendation based on systematic review of randomized controlled trial(s); CBT: cognitive behavioral therapy; IPT: interpersonal therapy; MBCT, mindfulness-based cognitive therapy; MDD: major depressive disorder; SNRIs, serotonin-norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors; TRD, treatment-resistant depression

4.0 DEX/BUPROPION ER FOR MDD

While the pharmacologic actions of bupropion and DEX (an NMDA receptor antagonist[23] similar to [es]ketamine[1,18]) are known, the exact downstream pathways that modify depression are not entirely clear, and have been debated for other NMDA antagonists.[1,24,25] Several neurologic pathways including the NMDA receptor are affected by DEX and implicated in improving depression.[25,26] In addition to NMDA modulation, the antidepressant effects of DEX could also be partly mediated by 1) its agonist action at the sigma-1 receptor, which may play a role in modulating glutamate and monoamine neurotransmitters, and upregulating NMDA receptor expression;[26,27] and 2) its inhibitory action at serotonin and norepinephrine transporters.[1]

In order to achieve therapeutic plasma levels required for treating depression, DEX is co-formulated with bupropion in Auvelity to increase DEX bioavailability. Bupropion competitively slows the rapid breakdown of DEX via CYP **2D6**.[1,2] The DEX metabolite via CYP2D6, dextrophan, is thought to cause dissociative effects when DEX is taken at very high doses (as in recreational misuse/abuse of cough suppressant DEX dosage forms).[24] Not only does bupropion enhance DEX effects indirectly, it also has antidepressant properties as a norepinephrine and dopamine reuptake inhibitor (NDRI). Both DEX and bupropion are also nicotinic acetylcholine receptor antagonists (which may also play a role in alleviating depression) and have anti-inflammatory properties.[1,26]

Plasma steady concentrations of the parent molecules, DEX/bupropion, are typically achieved after 8 days.[1] The extended elimination half-life of DEX when paired with bupropion in this formulation (Auvelity) is 22 hours, which is about 3-fold longer than that of DEX unaccompanied by bupropion. The

mean elimination half-life of bupropion is about 15 hours. Elimination half-lives of active bupropion metabolites (hydroxybupropion [HB], erythrohydroxybupropion and threohydroxybupropion) are longer than bupropion (33-44 hours). Animal models suggest these active metabolites are less potent than bupropion. CYP **2B6** is the primary enzyme responsible for HB production, whereas other bupropion metabolites do not seem to form through CYP enzymes.[1]

4.1 Efficacy of DEX/bupropion ER for MDD in Pivotal Clinical Trials

The clinical development program leading to FDA approval of DEX/bupropion ER included a phase 3 placebo-controlled RCT and a phase 2 active-comparator RCT with bupropion SR. Both trials were double-blind studies in adults (18 to 65 years of age) who met DSM-5 diagnostic criteria for MDD and who had a Montgomery-Asberg Depression Rating Scale (MADRS) score of at least 25 (ie, moderate or greater depression severity) at study entry.[2,3] The trials excluded patients with TRD (defined as having failed 2 or more antidepressants), patients with psychotic features, certain anxiety disorders, and patients with clinically significant risk of suicide.[2,3] **Appendix B** provides additional details about the inclusion and exclusion criteria for these clinical trials.

The primary efficacy endpoints for these studies were based on the change from baseline in MADRS total score. MADRS is a clinician-rated, 10-item questionnaire with the total possible score ranging from 0 to 60 and higher scores indicating more severe depression. In the 2 trials, clinical response was defined as a reduction in MADRS score of 50% or more from baseline, and clinical remission was defined as having achieved a MADRS score of ≤10.[2,3] **Table 3** summarizes the primary outcomes and responder/remitter results from these two trials.

Table 3. Summary Results for Key Endpoints of DEX/bupropion ER (Auvelity) Pivotal Clinical Trials [2,3]

	Comparator Arm	DEX/bupropion
Phase 3 RCT: Dextromethorphan/bupropion 45 mg/105 mg **vs. Placebo** (GEMINI, NCT04019704)[2]		
MADRS change from baseline to week 6 (least squares mean) – *primary endpoint*	-12.0	-15.9
Difference from placebo: -3.9 (95% CI -6.4, -1.4); P=0.002		
% Responders at week 6 (ie, MADRS ≥50% reduction from baseline)	34%	54%
Difference from placebo: 20.0%, P<0.001		
% Remitters at week 6 (ie, MADRS score ≤10)	17.3%	39.5%
Difference from placebo: 22.2%, P<0.001		
Phase 2 RCT: Dextromethorphan/bupropion 45 mg/105 mg **vs Bupropion SR** (ASCEND, NCT03595579)[3]		
Average of the changes from baseline in MADRS scores taken at 5 time points from week 1 to 6 (least squares mean)—*primary outcome*	-8.8	-13.7
Difference from bupropion SR: -4.9 (95% CI -6.8, -3.1); P<0.001		
MADRS change from baseline, at week 6 (least squares mean)	-12.1	-17.3
Difference from bupropion SR: -5.2 (95% CI -9.3, -1.1); P=0.013		

Table 3. Summary Results for Key Endpoints of DEX/bupropion ER (Auvelity) Pivotal Clinical Trials [2,3]

	Comparator Arm	DEX/bupropion
% Responders at week 6 (ie, MADRS ≥50% reduction from baseline)	40.5%	60.5%
Difference from bupropion SR: 19.9%, Non-significant difference		
% Remitters at week 6 (ie, MADRS score ≤10)	16.2%	46.5%
Difference from bupropion SR: 30.3%, P=0.004		

Abbreviations: CI, confidence interval; DEX, dextromethorphan; ER, extended release; MADRS, Montgomery-Åsberg Depression Rating Scale; RCT, randomized controlled trial; SR, sustained release

The phase 3 study (GEMINI, Glutamatergic and Monoaminergic Modulation in Depression) compared DEX 45 mg/bupropion 105 mg ER twice daily (N=156) to placebo twice daily (N=162).[2] The mean baseline MADRS score was approximately 33-34 for each study arm. Compared to placebo, there were significantly larger MADRS reductions from baseline with DEX/bupropion at the primary endpoint (week 6) and at all other measured time points (week 1, 2, 3, and 4). MADRS scores declined progressively in the DEX/bupropion group between the start and end of the trial. By week 6, the experimental group had a 16-point reduction (per least-squares mean) in MADRS score from baseline, which was an additional 3.9 point reduction over the placebo arm. The between-group difference for the experimental arm versus placebo was significant by week 1 and maintained to week 6. Forty percent of the experimental arm achieved remission at week 6, a difference of 22% from the placebo arm. Compared to placebo, a significantly greater proportion (20% more) of DEX/bupropion-treated patients had a clinical response (54% vs. 34%, P<0.001). Significant improvements over placebo for patient-rated depression symptoms, based on the Quick Inventory of Depressive Symptomatology-Self Rated (QIDS-SR) tool, were demonstrated with active treatment at week 1 through 6. Treatment with DEX/bupropion also led to greater improvement in quality-of-life (per the Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form) and a greater reduction in functional disability, as assessed by the Sheehan Disability Scale (SDS), at week 6 compared to placebo.[2]

The phase 2 study (ASCEND) compared DEX/bupropion ER twice daily (N=43) to bupropion SR 105 mg twice daily (N=37).[3] The mean baseline MADRS score was approximately 32 for each study arm. Compared to bupropion alone, treatment with DEX/bupropion significantly improved the average change from baseline in MADRS score for week 1 through week 6 (average of 5 time points; primary outcome). The treatment effect on MADRS change from baseline significantly separated from the control group by week 2 and was maintained to week 6. By week 6, the DEX/bupropion treatment group had a 17-point reduction (per least squares mean) in MADRS score from baseline and an additional 5.2-point reduction over the control arm. Forty-seven percent of DEX/bupropion-treated patients achieved remission at week 6, a significant difference of 30% from the control arm. Regarding the proportion of patients experiencing a clinical response, DEX/bupropion significantly outperformed bupropion monotherapy at week 3 and 4. At week 6, the difference was not significant but the trend favored DEX/bupropion (60.5% vs. 40.5%, P=0.075). A significant improvement in patient-rated depression symptoms was also demonstrated, as assessed by the overall treatment effect on QIDS-SR over the 6 weeks of treatment. At week 6, a greater proportion of the DEX/bupropion arm had a QIDS-SR score of ≤5 (ie, remission on QIDS-SR) compared to treatment with bupropion alone.[3]

5.0 PLACE-IN-THERAPY CONSIDERATIONS

The published evidence from the pivotal studies, GEMINI and ASCEND, can be extrapolated most directly to use of DEX/bupropion ER (Auvelity) as the first- or second-line treatment for moderate to severe, non-psychotic, major depression. These studies, leading to the approval of DEX/bupropion ER for the treatment of MDD, were open to include a mix of patients in the following scenarios at study entry:

- having no prior antidepressant therapy in the current episode (ie, DEX/bupropion would be the *initial* therapy)
- undergoing a switch from a previously initiated antidepressant to DEX/bupropion (ie, tapered and discontinued prior therapy prior to starting DEX/bupropion)
- having failed 1 prior antidepressant therapy (DEX/bupropion would be a *next-in-line* treatment)

The above patient characteristics are inferred from study exclusion criteria (ie, MDD trials excluded those having failed 2 or more antidepressants in the current episode) and the explanation in at least one study (ASCEND) that patients were allowed to discontinue a previously initiated antidepressant prior to study entry.[2,3] Nonetheless, the authors do not detail the baseline proportions of included patients according to each of these possible inclusion scenarios. There are also DEX/bupropion ER studies in progress in populations with TRD, though not fully published in a peer reviewed journal. Top-line results from these studies are included in section 5.1.1.

Regarding the approved indication, the FDA accepted broad indication wording (eg, for the treatment of major depression in adults) without limiting use to a particular phase in therapy.

5.1 Difficult-to-treat MDD

The sponsor of Auvelity is also assessing the product for TRD. It is unclear whether the sponsor will seek a formal label extension. Nevertheless, it is possible for practitioners to turn to this medication for patients with MDD who have failed other antidepressants, as the usual course of therapy generally entails different antidepressant trials if initial attempts fail, regardless of whether the antidepressant next-in-line has been specifically indicated for TRD.[10,14]

Few pharmacologic options have a specific FDA-approved indication for difficult-to-treat MDD cases, or TRD. The only pharmacotherapies with a specific FDA approval for TRD include the oral combination product, olanzapine/fluoxetine (Symbyax), and the NMDA-antagonist, esketamine (Spravato, an intranasal formulation). Augmentation with certain antipsychotics (aripiprazole [Abilify], brexipiprazole [Rexulti], quetiapine extended release [Seroquel XR])** is also approved for patients with MDD having failed a prior antidepressant; the studied populations may overlap with TRD.[28-30]

** Antipsychotics with an FDA-approved indication for major depression, as an adjunct to antidepressant therapy (eg, SSRI or SNRI), include aripiprazole (studied in patients with inadequate response to at least 1 antidepressant), brexipiprazole (studied in patients with inadequate response to 1-3 courses of antidepressants), quetiapine ER (studied in patients with inadequate response to at least 1 antidepressant). The combination of olanzapine/fluoxetine is specifically indicated for TRD (ie, patients who failed at least 2 different antidepressants).

There are potential disadvantages with these options:

- Esketamine treatment is time and resource intensive, considering that doses must be administered in the clinic under direct supervision of a healthcare provider in order to minimize the misuse/abuse potential, and due to common transient dissociative effects of esketamine. Patients must be monitored in the clinic for at least 2 hours after its administration.[18] Doses occur twice weekly during the 4-week induction phase, and once every 1 to 2 weeks during the maintenance phase (for TRD). Common adverse events (AEs) in clinical trials, with an incidence of ≥7% and at least twice that of placebo plus oral antidepressant, included the following per study population:[18]
  - *TRD*: dissociation (41%), dizziness (29%), nausea (28%), sedation (23%), vertigo (23%), hypoesthesia (18%), anxiety (13%), lethargy (11%), blood pressure increase (10%), and vomiting (9%)
  - *Acute suicidal ideation/behavior in MDD:* dissociation (48%), dizziness (45%), sedation (29%), blood pressure increased (15%), hypoesthesia (13%), vomiting (11%), and euphoric mood (7%)

  There is also potential risk of long-term cognitive and memory impairment with repeated, ongoing use of this medication,[18] but this labeled potential risk seems to be based on weak evidence, from descriptive reports involving cases of ketamine misuse and abuse, which are subject to confounding factors. Physical dependence, tolerance, and urinary toxicity are also concerns with long-term use of esketamine, as these have been observed with ketamine, including psychological dependence.[18,31] Yet, DEX/bupropion is not devoid of some similar concerns; for example, the abuse potential and long-term safety implications are uncertain (refer to the Safety section 7.6 of this report).
- Antipsychotics have many AEs that providers and patients may wish to avoid if possible. Tardive dyskinesia and/or metabolic changes (eg, hyperglycemia, diabetes mellitus, dyslipidemia, and body weight gain) are AEs associated with long-term use of these agents.[29,30,32] Common AEs occurring in 7% or more of MDD patients in clinical trials, and at least twice that for placebo, are labeled as follows:
  - *Aripiprazole*: akathisia (25% of patients), restlessness (12%), insomnia (8%), and fatigue (8%)[30]
  - *Brexpiprazole*: weight gain (7%) and akathisia (9%)[29]
  - *Quetiapine ER 150-300 mg*: somnolence (37-43%), dry mouth (27-40%), fatigue (11-14%), and constipation (6-11%)[28]

Ultimately, when a course of traditional antidepressants fails, providers/patients may have various reasons to prefer trial of a different antidepressant or dual antidepressant therapy, and reserve esketamine or antipsychotic augmentation for later-in-line therapy.

5.1.1 DEX/bupropion ER Studies for TRD

In 2020, the sponsor of Auvelity announced topline results from STRIDE-1 (NCT02741791; N=312), a phase 3 RCT switching study. Patients with TRD (having failed 1-2 prior antidepressants, plus a 6 week trial of bupropion 150 mg twice daily) were randomized to an additional 6 weeks of treatment with bupropion or were switched to DEX 45 mg/bupropion 105 mg ER twice daily.[33] This may be considered as an enriched population inflating the effect of DEX/bupropion compared to bupropion, since patients who continued with bupropion alone were already deemed non-responders. While the study failed to meet the primary endpoint for the reduction in MADRS at week 6, the primary endpoint tended to favor DEX/bupropion, and key secondary endpoints such as the rate of remission, cognitive function, and

anxiety symptoms were significantly improved with DEX/bupropion.[34] At week 6 after randomization, a significantly greater proportion of patients achieved remission (defined as QIDS-SR-16 ≤5) with DEX/bupropion compared to bupropion (18.2% vs. 8.2%, p=0.012). A significant reduction in depressive symptoms (by MADRS) occurred by week 1 after randomization with DEX/bupropion vs. bupropion. While the study did not meet the primary endpoint time point at week 6, the average MADRS reduction from all time points combined (week 1 through week 6 after randomization) significantly favored DEX/bupropion.[34]

While the STRIDE-1 result announcement from the sponsor also expressed the intention to initiate a second phase 3 trial in TRD,[34] no other phase 3 trial records for DEX/bupropion ER in TRD have been found in ClinicalTrials.gov or the sponsor's website.

The sponsor also announced topline results for a phase 2 RCT study in 44 patients with TRD (defined in the study as having failed 2 or more antidepressants). This is a placebo-controlled RCT (NCT04608396, MERIT) in patients who were in stable MDD remission after ≤12 months of open-label DEX/bupropion ER treatment (prior to study entry). The study assessed whether continuation of DEX/bupropion ER was effective for relapse prevention versus switching to placebo over a period of 6 months.

Relapse was defined as meeting any of the following: "MADRS total score ≥18 for 2 consecutive assessments; a ≥2-point increase from randomization in the Clinical Global Impression of Severity, with a minimum CGI-S score of 4, for 2 consecutive assessments; hospitalization due to worsening of depression or risk of suicide; investigator determination of relapse or need for additional antidepressant or treatment switch."[35] The primary endpoint for prevention of relapse (ie, based on the time to relapse) and the key secondary endpoint, the proportion of patients without relapse, significantly favored DEX/bupropion versus placebo. At the 6-month time point, no relapses occurred in the treatment arm, whereas 36% of patients in the placebo group relapsed—suggesting the potential harm of discontinuing effective therapy.[35]

6.0 OTHER INDICATIONS UNDER INVESTIGATION

Table 4 includes other studies, identified in ClinicalTrials.gov, evaluating DEX/bupropion ER for non-MDD related indications including Alzheimer's-related agitation and smoking cessation.

Table 4. Other Indications for DEX/bupropion ER Under Study Investigation[36]

Condition	Phase NCT ID	Study Name Descriptor	Status
Agitation associated with Alzheimer's disease[a]	Phase 2/3 NCT03226522	Advance-1 DB-RCT	Completed
	Phase 3 NCT05557409	Advance-2 DB-RCT	Recruiting
Smoking behavior	Phase 2 NCT03471767	DB-RCT	Completed

[a] *The sponsor of Auvelity has received Breakthrough Therapy designation for the condition*

Abbreviations: DB-RCT; double-blind, randomized controlled trial; SR, sustained release

7.0 SAFETY

7.1 Adverse Events

The most common adverse reactions with DEX/bupropion ER (Auvelity), occurring in ≥5% of treated patients in the pivotal placebo-controlled trial (ie, the phase 3 RCT in MDD, GEMINI) and at least twice as frequent in the placebo group, included the following[1]:

- dizziness (16%)
- headache (8%)
- diarrhea (7%)
- somnolence (7%)
- dry mouth (6%)
- sexual dysfunction (6%)
- hyperhidrosis (5%)

In the phase 3 study for MDD (GEMINI), no increases in suicidality were observed. Compared to placebo, a greater proportion of patients who received DEX/bupropion ER discontinued the treatment due to adverse effects (6.2% with DEX/bupropion ER vs. 0.6% with placebo).[2] In the phase 3 study for TRD (STRIDE-1), common AEs reported by the sponsors were dizziness and nausea. Rates of discontinuation due to AEs were low (2.6% for DEX/bupropion ER vs. 1.9% for bupropion SR).[34]

A single-arm, open label, observational safety study (NCT04039022) has recently completed for DEX/bupropion ER in patients with depression but is not yet published in a peer-reviewed journal. Information from ClinicalTrials.gov shows very few serious AEs over the 1-year follow-up (2.4% [21/876] patients affected); however, it is unclear if a causative association exists. Only 1 patient each experienced the following serious psychiatric AEs: depression, mental disorder, and suicidal ideation.

Non-serious psychiatric events included anxiety (3.9% patients affected) and insomnia (3.5%). Common AEs (ie, those occurring in 10% or more patients) were nausea (12%) and dizziness (13%).[37]

7.2 Contraindications

DEX/bupropion ER is contraindicated in the following patient populations or scenarios[1]:

- Patients with seizure disorder, since bupropion can lower the seizure threshold
- Patients with a current or prior diagnosis of bulimia or anorexia nervosa; these patients have a higher risk of seizures
- During abrupt discontinuation of alcohol, benzodiazepines, barbiturates, or antiepileptic drugs, which are risk factors for seizure
- Within 14 days of monoamine oxidase inhibitor (MAOI) use
- Patients with known hypersensitivity to bupropion or DEX

7.3 Other Warnings and Precautions

As with other antidepressants, DEX/bupropion ER has a **black-box warning** for the increased risk of suicidal thoughts and behaviors in pediatric and young adult populations, based on pooled analyses of antidepressant-controlled trials of 4 months or less (including SSRIs and other antidepressants). Close monitoring is advised for all antidepressant-treated patients in order to detect clinical worsening and emergence of suicidal thoughts and behaviors.[1]

Warnings for Auvelity Related to the Bupropion Ingredient

- **Seizure**: Bupropion can decrease the seizure threshold in a dose-dependent manner. At bupropion 300 mg and 400 mg dosages (1.5 and 2 times the maximum recommended dose of bupropion in Auvelity), the seizure incidence observed was 0.1% and 0.4%, respectively based on studies with bupropion SR. Predisposing factors to seizure, such as the following, should be weighted in the decision to initiate therapy: severe head injury; arteriovenous malformation; CNS tumor or infection; severe stroke; concomitant use of other medications that lower the seizure threshold (antipsychotics, tricyclic antidepressants, theophylline, and systemic corticosteroids); metabolic disorders (hypoglycemia, hyponatremia, severe hepatic impairment, and hypoxia); use of illicit drugs such as cocaine; or abuse/misuse of CNS stimulants, alcohol, benzodiazepines, sedative/hypnotics, or opiates.
    - Auvelity is *contraindicated* in patients with a seizure disorder, current or prior diagnosis of anorexia nervosa or bulimia, or undergoing abrupt discontinuation of alcohol, benzodiazepines, barbiturates, or antiepileptic drugs.[1]
- **Elevated Blood Pressure and Hypertension:** Increased blood pressure may occur with the use of bupropion, based on smoking cessation studies using bupropion SR.[1] The risk is increased if used concomitantly with drugs that boost dopaminergic or noradrenergic activity. Blood pressure should be assessed prior to starting treatment, and regularly thereafter.[1]
- **Psychosis and Other Neuropsychiatric Reactions**: The following neuropsychiatric symptoms have been reported in depressed patients treated with bupropion: delusions, hallucinations, psychosis, disturbance in concentration, paranoia, and confusion. Some symptoms resolved upon dose reduction or withdrawal of treatment. If concomitant use of DEX/bupropion ER with other

bupropion- or DEX-containing products is clinically warranted, patients should be warned of neuropsychiatric reactions and alert to signs of overdose.[1]
    - Publications for the pivotal phase 2 and phase 3 trials for DEX/bupropion ER for MDD briefly mentioned that the agent was not associated with psychotomimetic effects (ie, psychosis); however, because the full study protocol was not available, it is unclear if a systematic method was used to assess these effects. This point also applies to dissociative effects related to DEX.[2,38] For example, other clinical trials on drugs with dissociative effects (eg, esketamine) have employed the Clinician Administered Dissociative States Scale to assess such effects.[18]
- **Dizziness**: The incidence of dizziness in placebo-controlled studies of Auvelity was 16% with treatment versus 6% with placebo. Precautions should be taken with regard to the risk of falls. Patients should also avoid operating dangerous machinery, including motor vehicles, until they are reasonably certain that the medication does not adversely affect them.[1]
- **Hypersensitivity**: Serious reactions including anaphylactoid/anaphylactic reactions and Stevens-Johnson syndrome have been reported with bupropion. Delayed hypersensitivity is also possible with bupropion; signs include arthralgia, myalgia, fever, rash, and other serum sickness-like symptoms.[1]

Warnings for Auvelity Labeled for Antidepressants in General

- **Activation of Mania or Hypomania**: Antidepressants can precipitate a manic, mixed, or hypomanic episode. Prior to starting treatment, patients should be screened for bipolar disorder and the presence of risk factors for bipolar disorder (eg, family history of bipolar disorder, suicide, or depression).[1]
- **Angle-closure Glaucoma**: Many antidepressants including bupropion may cause pupillary dilation, which can lead to an angle closure attack in certain at-risk patients; avoid use in patients with untreated anatomically narrow angles.[1]

Warnings for Auvelity Related to the DEX Ingredient

- **Signs of DEX overdose** include toxic psychosis, stupor, coma, and hyperexcitability. Patients should be screened for the use of other DEX-containing products to prevent potential overdose.[1]
- **Serotonin Syndrome**: DEX can potentiate serotonin levels; therefore, caution is advised when used with SSRIs or tricyclic antidepressants; patients should be warned of the risk for serotonin syndrome and signs/symptoms.
    - Concomitant use with MAOIs, including linezolid, is contraindicated.
    - If concomitant use of DEX/bupropion ER with other serotonergic agents is clinically warranted, including with other DEX products, patients should be monitored more closely and warned of neuropsychiatric reactions and signs of overdose.[1]
- **Embryo-fetal Toxicity**: The effect of DEX on developmental toxicity at the recommended clinical dose is unclear. However, based on animal studies, a combination of DEX/quinidine resulted in fetal malformation. Due to this finding, the use of DEX/bupropion ER is not recommended during pregnancy.[1]

7.4 Drug Interactions[1]

- **strong CYP inhibitors**
- **strong CYP2B6 inducers (avoid)**
- **CYP2D6 substrates**
- **MAOIs**
- **digoxin**
- **drugs that lower seizure threshold**
- **dopaminergic drugs**
- **laboratory test for amphetamines (false positives)**

- DEX/bupropion ER should be avoided in combination with strong CYP2B6 inducers.
- Dose reductions are recommended when DEX/bupropion ER is used with strong CYP2D6 inhibitors; the recommended dose is one tablet once daily (rather than twice daily).
- Caution is advised when DEX/bupropion ER is used in combination with CYP2D6 substrates because it increases the exposure for such substrates[39]
- Concomitant MAOI use with DEX/bupropion ER (or within 14 days of stopping) should be avoided, since this combination increases the risk of possibly fatal toxicity, including hypertensive crisis and serotonin syndrome. Use with linezolid or intravenous methylene blue is contraindicated.
- DEX/bupropion ER may decrease plasma digoxin levels; thus, closer monitoring of digoxin levels should be considered.
- Caution is advised with the coadministration of drugs that lower seizure threshold, since the combination may increase risk of seizure.
- Central nervous system toxicity (eg, restlessness, agitation, tremor, ataxia, gait disturbance, vertigo, dizziness) can occur with concomitant use of dopaminergic drugs (eg, levodopa or amantadine).
- Drug-laboratory test interactions: Bupropion can cause false-positive urine test results for amphetamines. Gas chromatography/mass spectrometry can be used to better distinguish bupropion from amphetamines.

7.5 Special Populations

- **Pregnancy**: The effect of DEX, at the recommended clinical dose, on developmental toxicity is unclear. A combination of DEX/quinidine resulted in fetal malformation in animal studies.[1] Due to this finding, the use of DEX/bupropion ER is not recommended during pregnancy.

  Epidemiological studies of pregnant women exposed to bupropion in the first trimester have not suggested a clear increased risk of congenital malformations. If the potential benefit of this medication outweighs the risk for a pregnant patient, the prescriber and patient should consider contributing data to the pregnancy-exposure registry in place for antidepressants: National Pregnancy Registry for Antidepressants.[1]
- **Lactation**: Published literature shows that bupropion is excreted into human milk. It is unknown whether DEX is excreted into human milk. Because the effects on breastfed infants or maternal milk production are not clear, use of DEX/bupropion ER during breastfeeding is not recommended. Labeling recommends to avoid breastfeeding while on this medication and for 5 days following its discontinuation.[1]
- **Pediatric use**: The safety and effectiveness of DEX/bupropion ER is not established in pediatric patients (<18 years of age).

- **Renal or hepatic impairment**: The use of DEX/bupropion ER is not recommended in severe renal or hepatic impairment. Dose adjustments are recommended for moderate renal impairment (up to 1 tablet once daily), and no adjustment is required for mild or moderate hepatic impairment.[1]

7.6 Abuse Potential

DEX/bupropion ER (Auvelity) has not been scheduled as a controlled substance, although DEX (eg, in cough suppressant formulations) has a history of abuse and misuse in the general population.[40-45] The labeling for DEX/bupropion ER states that the potential for abuse, tolerance, and physical dependence of this formulation have not been systematically evaluated in animals or humans.[1] While not the primary objective, the phase 2 trial reported that DEX/bupropion ER was not associated with abuse-related events, while the phase 3 trial lacked mention of such outcomes.[2,3] An observational study of 1 year duration of DEX/bupropion ER use also recorded no abuse-related events.[3,46] Yet, based on the statement in the package insert and lack of published information, it is likely that a robust investigation of potential dependence, abuse, or dissociative effects of DEX/bupropion ER has yet to occur.[1-3]

With little safety information in at risk populations, experts in the field call for more studies on the abuse potential of this medication, especially in at-risk paitents.[24] Patients with substance abuse history in the prior year were excluded from the pivotal trials for Auvelity, so it is unclear if abuse or drug-seeking events would arise in populations with such at-risk characteristics. Auvelity labeling recommends "…patients with a history of drug abuse should be observed closely for signs of AUVELITY misuse or abuse (e.g., development of tolerance, increases in dose, drug-seeking behavior)."[1] Experts in the field opine that the abuse potential of this product should be systematically studied, especially in those with abuse risk/history.[24]

8.0 UTILIZATION

Upon our query for pharmacy claims in the Utah Medicaid population for 2022 (through October), no pharmacy utilization was observed for Auvelity in either fee-for-service (FFS) or accountable-care-organization (ACO) patients[††].

[††] Antidepressants are carved-out medications; pharmacy coverage for ACO patients is handled through the Medicaid FFS benefit.

9.0 CONSIDERATIONS FOR PRIOR AUTHORIZATION (PA) CRITERIA

The Drug Utilization Review (DUR) board may consider implementing the following PA criteria for Auvelity:

1. An age requirement, for use in adults only, to align with the labeled indication
2. A diagnosis requirement for major depressive disorder (MDD), to align with the labeled indication
3. For the purposes of cost containment, step therapy (ie, a trial of an SSRI or SNRI before DEX/bupropion ER) may be considered. However, in pivotal clinical trials for MDD, patients were not required to fail a prior antidepressant before receiving DEX/bupropion ER.

The following attestation fields or educational notes can be considered to help ensure that safety precautions are taken:

4. Attestation that the provider has made effort to ensure that the patient is not taking any other DEX- or bupropion containing products, to prevent possible toxicity and dissociation adverse events.
5. Attestation that the provider has considered/weighed possible abuse risk/behaviors of the patient.
    a. Auvelity is not classified as a controlled substance despite the known history of abuse of dextromethorphan (as a cough suppressant) in the US.
    b. Although the risk of seizures associated with bupropion is very low, there are medical conditions‡‡ and medications[§§] that can increase the risk of seizure including the use of illicit drugs (eg, cocaine), excessive use of alcohol, or misuse or abuse of prescription drugs such as CNS stimulants, benzodiazepines, sedative/hypnotics, or opiates.
6. Attestation that the provider has screened patients for contraindicated medical conditions (ie, seizure disorder, current or prior diagnosis of anorexia nervosa or bulimia, or undergoing abrupt discontinuation of alcohol, benzodiazepines, barbiturates, and antiepileptic drugs)
7. Caution regarding CYP 2D6 and 2B6 related drug interactions with DEX/bupropion ER
8. Lastly, there is no robust evidence to support the concurrent use of DEX/bupropion ER with esketamine or ketamine treatments. Utah Medicaid may consider developing a mechanism to flag such use, and consult with all prescribers involved with concurrent prescriptions/requests, since it is possible that each prescriber may be unaware of the others' intended treatment.

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‡‡ Examples of conditions that increase seizure risk include metabolic disorders such as hypoglycemia, hyponatremia, severe hepatic impairment, and hypoxia. For a fuller list of examples, consult the Auvelity package insert.

§§ Examples of seizure threshold lowing drugs include antipsychotics, tricyclic antidepressants, and systemic corticosteroids.

10.0 SUMMARY

Treatment of depression is an area of high unmet medical need, as many patients (55-70%) do not achieve remission with initial trials of traditional antidepressant therapies (eg, SSRIs, SNRIs).[14] Even if attained, remission is often temporary, as high rates of patients appear to relapse within 6 months after remitting.[15] Thus, patients may require additional options in the iterative trial of therapies.

Auvelity, containing dextromethorphan (DEX) 45 mg with bupropion 105 mg, is the first *oral* NMDA antagonist approved for the treatment of major depressive disorder (MDD) in adults.[1] Dextromethorphan exerts mechanisms of action implicated in alleviating depression that are unique from traditional antidepressants, plus some that are overlapping. Co-formulation with bupropion, an inhibitor of CYP 2D6, serves to increase the plasma concentration of DEX to achieve therapeutic levels for MDD. Bupropion also has antidepressant properties as a norepinephrine and dopamine reuptake inhibitor (NDRI). This extended-release (ER) medication (Auvelity) is approved for adult use only and is taken on a daily basis. Clinical practice guidelines predate Auvelity FDA-approval, and thus, do not comment on its use.

Pivotal clinical trials leading to FDA approval were conducted in populations with moderate to severe depression, with DEX/bupropion ER (Auvelity) either as a first-line antidepressant, as a switch from a prior antidepressant, or after no more than 1 failed antidepressant in the current depressive episode.[2,3] Patients with treatment-resistant depression (TRD; ie, having failed 2 or more antidepressants) were excluded, as were patients with clinically significant risk of suicide, seizure history, or alcohol or substance use disorder in the prior year. In the phase 3 RCT (GEMINI), DEX 45 mg/bupropion 105 mg ER twice daily outperformed placebo for reducing depression severity (as measured by MADRS) and resulted in a greater proportion of responders and remitters at week 6. A significant effect in depression symptom reduction was seen as early as week 1, and the difference was maintained to week 6.[2] In the phase 2 RCT (ASCEND), DEX/bupropion ER outperformed bupropion SR 105 mg monotherapy for symptom reduction (measured by MADRS) by week 2 and through week 6, and led to a significantly greater remission rate and a numerically greater response rate at week 6.[3]

An additional, unpublished phase 3 RCT of DEX/bupropion ER (STRIDE-1) has been conducted in patients with TRD and insufficient response to 6 weeks of bupropion monotherapy. While the study failed to meet the primary endpoint for the reduction in MADRS at week 6, the primary endpoint did tend to favor DEX/bupropion compared to continued bupropion monotherapy. Key secondary endpoints such as the rate of remission, cognitive function, and anxiety symptoms were significantly improved with DEX/bupropion versus continued bupropion.[34]

Auvelity has not been studied in the pediatric population, nor in combination with other antidepressant therapies (including other NMDA antagonists such as esketamine/ketamine). Unpublished or in-progress phase 2 or 3 studies are assessing Auvelity for smoking cessation and agitation associated with Alzheimer's disease.[4]

Dizziness (occurring in 18%) was the only adverse reaction occurring in ≥10% of DEX/bupropion-treated patients with MDD and at least twice as frequent in the placebo group.[1] Other AEs occurring in 5-8% of DEX/bupropion-treated patients (and at least twice that of the placebo group) were headache, diarrhea, somnolence, dry mouth, sexual dysfunction, and hyperhidrosis.[1]

Auvelity (DEX/bupropion) is contraindicated in patients with seizure disorder and certain at-risk populations (eg, those with current or prior diagnosis of bulimia or anorexia nervosa; those undergoing abrupt discontinuation of alcohol, benzodiazepines, barbiturates, or antiepileptic drugs).[1] Drug interactions related to CYP 2D6 and 2B6 are relevant to DEX/bupropion, as summarized in section 7.4. Use of DEX/bupropion during or within 14 days of an MAOI is contraindicated. As with many antidepressants, DEX/bupropion has a black-box warning for the increased risk of suicidal thoughts and behaviors in pediatric and young adult populations. Antidepressants, including DEX/bupropion, also have warnings for possible activation of mania or hypomania and risk for angle-closure glaucoma in certain at-risk populations. Warnings for other AEs associated with the bupropion ingredient include the potential to lower the seizure threshold; elevate blood pressure; or induce psychosis, neuropsychiatric reactions, or hypersensitivity. A warning related to the DEX ingredient includes increased risk of serotonin syndrome when combined with serotonergic drugs. The package insert advises avoiding DEX/bupropion during pregnancy, as well as screening patients for other DEX- or bupropion-containing products that they may be taking.[1]

The abuse history of DEX-containing cough syrups in the general population—for its dissociative effects— would suggest that Auvelity has the potential for abuse. However, Auvelity has not yet been scheduled as a controlled substance. No formal abuse-potential studies, particularly in at-risk populations, have been conducted with Auvelity. The package insert of Auvelity advises that patients with substance abuse history should be monitored for misuse or abuse.[1]

Although studies are ongoing for other non-depressive disorders, prior authorization (PA) criteria for Auvelity may help ensure that prescribing is in line with the current approved indication (for adults with major depression) until other uses become established. Additionally, attestation fields in the PA form can be considered to remind prescribers of precautions to prevent overdoses, other AEs, and drug interactions (refer to section 9.0).

REFERENCES

1. AUVELITY (dextromethorphan hydrobromide and bupropion hydrochloride) extended-release tablets, for oral use. Package Insert. Axsome Therapeutics Inc.; 2022.

2. Iosifescu DV, Jones A, O'Gorman C, et al. Efficacy and Safety of AXS-05 (Dextromethorphan-Bupropion) in Patients With Major Depressive Disorder: A Phase 3 Randomized Clinical Trial (GEMINI). *J Clin Psychiatry*. 2022;83(4)doi:10.4088/JCP.21m14345

3. Tabuteau H, Jones A, Anderson A, Jacobson M, Iosifescu DV. Effect of AXS-05 (Dextromethorphan-Bupropion) in Major Depressive Disorder: A Randomized Double-Blind Controlled Trial. *Am J Psychiatry*. 2022;179(7):490-499. doi:10.1176/appi.ajp.21080800

4. Ward K, Citrome L. AXS-05: an investigational treatment for Alzheimer's disease-associated agitation. *Expert opinion on investigational drugs*. 2022;31(8):773-780. doi:10.1080/13543784.2022.2096006 Accessed July 6, 2022. Available at http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=35763451

5. Gabriel FC, Stein AT, de Melo DO, et al. Quality of clinical practice guidelines for inadequate response to first-line treatment for depression according to AGREE II checklist and comparison of recommendations: a systematic review. *BMJ Open*. 2022;12(4):e051918. doi:10.1136/bmjopen-2021-051918

6. Gabriel FC, de Melo DO, Fráguas R, Leite-Santos NC, Mantovani da Silva RA, Ribeiro E. Pharmacological treatment of depression: A systematic review comparing clinical practice guideline recommendations. *PLoS One*. 2020;15(4):e0231700-e0231700. doi:10.1371/journal.pone.0231700

7. Villarroel MA, Terlizzi EP. Symptoms of Depression Among Adults: United States, 2019. NCHS Data Brief No. 379. September 2020. Accessed October 4, 2022. Available at https://www.cdc.gov/nchs/products/databriefs/db379.htm

8. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders text revsision (DSM-5-TR).* 5th ed., American Psychiatric Association; 2022. Accessed October 20, 2022. Available at https://www.appi.org/Products/DSM-Library/Diagnostic-and-Statistical-Manual-of-Mental-Di-(1)

9. American Psychological Association, Guideline Development Panel for the Treatment of Depressive Disorders. Summary of the clinical practice guideline for the treatment of depression across three age cohorts. *The American psychologist*. 2022;77(6):770-780. doi:10.1037/amp0000904

10. McQuaid JR, Lin EH, Barber JP, Breland-Noble AM. *Clinical practice guideline for the treatment of depression across three age cohorts*. American Psychological Association; 2019. Accessed October 19, 2022. Available at https://www.apa.org/depression-guideline

11. National Institute for Health and Care Excellence: Guidelines. National Institute for Health and Care Excellence (NICE) Copyright © NICE 2022.; 2022.

12. Malhi GS, Bell E, Bassett D, et al. The 2020 Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders. *Aust N Z J Psychiatry*. 2021;55(1):7-117. doi:10.1177/0004867420979353

13. Bayes A, Parker G. How to choose an antidepressant medication. *Acta Psychiatr Scand*. 2019;139(3):280-291. doi:10.1111/acps.13001

14. Bennabi D, Charpeaud T, Yrondi A, et al. Clinical guidelines for the management of treatment-resistant depression: French recommendations from experts, the French Association for Biological Psychiatry and Neuropsychopharmacology and the fondation FondaMental. *BMC Psychiatry*. 2019;19(1):262. doi:10.1186/s12888-019-2237-x

15. Rush AJ, Warden D, Wisniewski SR, et al. STAR*D: revising conventional wisdom. *CNS Drugs*. 2009;23(8):627-647. doi:10.2165/00023210-200923080-00001

16. Ruberto VL, Jha MK, Murrough JW. Pharmacological Treatments for Patients with Treatment-Resistant Depression. *Pharmaceuticals (Basel)*. 2020;13(6):116. doi:10.3390/ph13060116

17. Conway CR, George MS, Sackeim HA. Toward an Evidence-Based, Operational Definition of Treatment-Resistant Depression: When Enough Is Enough. *JAMA Psychiatry*. 2017;74(1):9-10. doi:10.1001/jamapsychiatry.2016.2586 Accessed October 5, 2022. Available at https://doi.org/10.1001/jamapsychiatry.2016.2586

18. Spravato (esketamine) nasal spray. Package Insert. Janssen Pharmaceuticals Inc; 2020.

19. Lengvenyte A, Strumila R, Olié E, Courtet P. Ketamine and esketamine for crisis management in patients with depression: Why, whom, and how? *Eur Neuropsychopharmacol*. 2022;57:88-104. doi:10.1016/j.euroneuro.2022.02.004 Accessed October 15, 2022. Available at https://www.sciencedirect.com/science/article/pii/S0924977X22001298

20. Lam RW, Kennedy SH, Parikh SV, MacQueen GM, Milev RV, Ravindran AV. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder: Introduction and Methods. *Can J Psychiatry*. 2016;61(9):506-509. doi:10.1177/0706743716659061

21. Keitner GI, Mansfield AK. Management of treatment-resistant depression. *Psychiatr Clin North Am*. 2012;35(1):249-265. doi:10.1016/j.psc.2011.11.004

22. Rottenberg J, Devendorf AR, Kashdan TB, Disabato DJ. The Curious Neglect of High Functioning After Psychopathology: The Case of Depression. *Perspect Psychol Sci*. 2018;13(5):549-566. doi:10.1177/1745691618769868 Accessed October 27, 2022. Available at https://doi.org/10.1177/1745691618769868

23. Wilkinson ST, Sanacora G. A new generation of antidepressants: an update on the pharmaceutical pipeline for novel and rapid-acting therapeutics in mood disorders based on glutamate/GABA neurotransmitter systems. *Drug discovery today*. 2019;24(2):606-615. doi:10.1016/j.drudis.2018.11.007 Accessed October 20, 2022. Available at http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med16&NEWS=N&AN=30447328

24. Schatzberg AF. Understanding the Efficacy and Mechanism of Action of a Dextromethorphan-Bupropion Combination: Where Does It Fit in the NMDA Versus mu-Opioid Story? *Am J Psychiatry*. 2022;179(7):448-450. doi:10.1176/appi.ajp.20220434

25. Dean RL, Hurducas C, Hawton K, et al. Ketamine and other glutamate receptor modulators for depression in adults with unipolar major depressive disorder. *Cochrane Database Syst Rev*. 2021;9(9):Cd011612. doi:10.1002/14651858.CD011612.pub3

26. Nguyen L, Thomas KL, Lucke-Wold BP, Cavendish JZ, Crowe MS, Matsumoto RR. Dextromethorphan: An update on its utility for neurological and neuropsychiatric disorders. *Pharmacol Ther*. 2016;159:1-22. doi:10.1016/j.pharmthera.2016.01.016 Accessed October 14, 2022. Available at http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med13&NEWS=N&AN=26826604

27. Nguyen L, Lucke-Wold BP, Mookerjee S, Kaushal N, Matsumoto RR. Sigma-1 Receptors and Neurodegenerative Diseases: Towards a Hypothesis of Sigma-1 Receptors as Amplifiers of Neurodegeneration and Neuroprotection. *Adv Exp Med Biol*. 2017;964:133-152. doi:10.1007/978-3-319-50174-1_10

28. Seroquel XR (quetiapine extended-release) capsule. Package Insert. AstraZeneca Pharmaceuticals LP; 2022.

29. Rexulti (brexpiprazole) tablet. Package Insert. Otsuka America Pharmaceuticals Inc.; 2021.

30. Abilify (aripiprazole) tablet, oral solution, and orally disintegrating. Package Insert. Otsuka America Pharmaceuticals Inc.; 2020.

31. Lerner A, Klein M. Dependence, withdrawal and rebound of CNS drugs: an update and regulatory considerations for new drugs development. *Brain Communications*. 2019;1(1):fcz025. doi:10.1093/braincomms/fcz025 Accessed November 15, 2022. Available at https://doi.org/10.1093/braincomms/fcz025

32. Carbon M, Kane JM, Leucht S, Correll CU. Tardive dyskinesia risk with first- and second-generation antipsychotics in comparative randomized controlled trials: a meta-analysis. *World Psychiatry*. 2018;17(3):330-340. doi:10.1002/wps.20579

33. A Study to Assess the Efficacy and Safety of AXS-05 in Subjects With Treatment Resistant Major Depressive Disorder (STRIDE-1). NCT02741791. ClinicalTrials.gov. 2021. Last Updated March 24. Accessed October 24, 2022. Available at https://clinicaltrials.gov/ct2/show/NCT02741791?term=NCT02741791&draw=2&rank=1

34. Axsome Therapeutics announces topline results of the stride-1 phase 3 trial in treatment resistant depression and expert call to discuss clinical implications. Press release. Axsome Therapeutics Inc.,. 2022. Accessed October 21, 2022. Available at https://axsometherapeuticsinc.gcs-web.com/news-releases/news-release-details/axsome-therapeutics-announces-topline-results-stride-1-phase-3

35. Axsome News Release Detail. axsome therapeutics announces axs-05 achieves primary and key secondary endpoints in the merit phase 2 trial in treatment resistant depression. 2021. Accessed October 21, 2022. Available at https://axsometherapeuticsinc.gcs-web.com/news-

releases/news-release-details/axsome-therapeutics-announces-axs-05-achieves-primary-and-key

36. ClinicalTrials.gov. Search Results for "AXS-05". ClinicalTrials.gov. Accessed October 10, 2022. Available at https://www.clinicaltrials.gov/ct2/results?term=AXS-05&age_v=&gndr=&type=&rslt=&phase=1&phase=2&phase=3&Search=Apply

37. Open-Label Safety Study of AXS-05 in Subjects With Depression, NCT04039022. ClinicalTrials.gov. Accessed October 19, 2022. Available at https://clinicaltrials.gov/ct2/show/results/NCT04039022?term=NCT04039022&draw=2&rank=1

38. A Trial of AXS-05 in Patients With Major Depressive Disorder (GEMINI), NCT04019704. ClinicalTrials.gov. Accessed October 5, 2022. Available at https://www.clinicaltrials.gov/ct2/show/NCT04019704?term=GEMINI+bupropion&draw=2&rank=1

39. Guzey C, Norstrom A, Spigset O. Change from the CYP2D6 extensive metabolizer to the poor metabolizer phenotype during treatment With bupropion. *Ther Drug Monit*. 2002;24(3):436-437. Accessed October 23, 2022. Available at http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=12021638

40. Schwartz RH. Adolescent abuse of dextromethorphan. *Clin Pediatr (Phila)*. 2005;44(7):565-568. doi:10.1177/000992280504400702

41. Martinak B, Bolis RA, Black JR, Fargason RE, Birur B. Dextromethorphan in Cough Syrup: The Poor Man's Psychosis. *Psychopharmacol Bull*. 2017;47(4):59-63.

42. Stanciu CN, Penders TM, Rouse EM. Recreational use of dextromethorphan, "Robotripping"-A brief review. *Am J Addict*. 2016;25(5):374-377. doi:10.1111/ajad.12389

43. Xu J, Ou H, Sun P, Qin S, Yuan T-F. Brief Report: Predictors of Relapse for Patients With Dextromethorphan Dependence. *The American journal on addictions*. 2021;30(2):192-194. doi:10.1111/ajad.13114 Accessed October 15, 2022. Available at http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med18&NEWS=N&AN=33225556

44. Romanelli F, Smith KM. Dextromethorphan abuse: clinical effects and management. *Journal of the American Pharmacists Association : JAPhA*. 2009;49(2):e20-27. doi:10.1331/JAPhA.2009.08091 Accessed October 2, 2022. Available at http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med7&NEWS=N&AN=19289333

45. Gershman JA, Fass AD. Dextromethorphan Abuse: A Literature Review. *J Pharm Technol*. 2013;30(4):66-71. Accessed October 15, 2022. Available at http://www.epistemonikos.org/documents/d689f4593cadaa3e567f2b271508cfa915ed2a2b

46. Open-Label Safety Study of AXS-05 in Subjects With Depression. NCT04039022. ClinicalTrials.gov; 2022. Last Updated October 12, 2022. Accessed November 15, 2022. Available at https://clinicaltrials.gov/ct2/show/results/NCT04039022

47. Assessing Symptomatic Clinical Episodes in Depression (ASCEND), NCT03595579. ClinicalTrials.gov. Accessed October 5, 2022. Available at

https://www.clinicaltrials.gov/ct2/show/NCT03595579?term=ASCEND+bupropion&draw=2&rank=1

APPENDIX A – LITERATURE SEARCHES

Ovid-Medline (searched October 13th, 2022, updated search on November 7th, 2022)

1. (AXS-05 or bupropion).ti. AND (dextromethorphan).ti,ab,kw,kf.
    - 15 results
2. AXS-05.ti,ab,kw,kf. or (bupropion.ti. and dextromethorphan.ti,ab,kw,kf.) or (dextromethorphan.ti. and bupropion.ti,ab,kw,kf.)
    - 27 results
3. (AXS-05 or (bupropion and dextromethorphan)).ti,ab,kw,kf.
    - 98 results
4. (depress* and dextromethorphan).ti,ab,kw,kf
    - 167 results

Epistomonikos.org (searched October 13, 2022)

(title:(dextromethorphan AND depress*) OR abstract:(dextromethorphan AND depress*))

- Limited to systematic reviews the internal databse filter (7 results)

Embase (searched October 14, 2022)

- dextromethorphan:ti,ab,kw AND depress*:ti
    - 44 results

APPENDIX B – INCLUSION CRITERIA OF PIVOTAL CLINICAL STUDIES IN MDD

Table B1. Inclusion and Exclusion Criteria of Auvelity Pivotal Studies for Depression

Key Inclusion Criteria	Key Exclusion Criteria
Phase 3 Study (GEMINI)[2,38]	
• Adults 18-65 years of age • Major depression diagnosis per (DSM-5) of at least 4 weeks duration, without psychotic features • MADRS of 25 or higher at baseline (ie, moderate to severe disease) • CGI-S of 4 or higher • BMI 18-40 kg/m^2	• Bipolar disorder • Psychotic disorder • Panic disorder, obsessive-compulsive disorder • **Treatment-resistant depression (defined as ≥ 2 adequate failed antidepressant treatments in the current major depressive episode)** • Alcohol/substance use disorder within the past year • **Clinically significant risk of suicide** • History of seizure disorder • History of electroconvulsive therapy, vagus nerve stimulation, transcranial magnetic stimulation or any experimental central nervous system treatment during the current depressive episode or in the past 6 months • Pregnant, breastfeeding, or planning to become pregnant or breastfeed during the study
Phase 2 Study (ASCEND)[3,47]	
• Adults 18-65 years of age • Major depression diagnosis without psychotic features per DSM-5; and a current major depressive episode of moderate or greater severity • MADRS of 25 or higher at baseline (ie, moderate to severe disease) • CGI-S of 4 or higher • BMI 18-40 kg/m^2 • Previously used antidepressants were required to be completely weaned off, with a washout of at least 1 week (and 5 half-lives of the medication) prior to the baseline visit	• Bipolar disorder • History of psychotic disorder • Panic disorder, obsessive-compulsive disorder • **Treatment-resistant depression (defined as ≥ 2 failed adequate antidepressant treatments in the current major depressive episode)** • Substance use disorder within the past year • **Clinically significant risk of suicide** • History of seizure disorder • History of electroconvulsive therapy, vagus nerve stimulation, transcranial magnetic stimulation or any experimental central nervous system treatment during the current depressive episode or in the past 6 months • Pregnant, breastfeeding, or planning to become pregnant or breastfeed during the study

Abbreviations: BMI, body mass index; CGI-S, Clinician Global Impression-Severity; DSM-5; Diagnostic and Statistical Manual of Mental Disorders, 5th Edition; MADRS, Montgomery-Asberg Depression Rating Scale