Auvelity® (dextromethorphan and bupropion)

Axsome Therapeutics Inc, FDA approved Sep 2022

Background & Medication Description

- Auvelity is a new formulation of dextromethorphan and bupropion approved in August 2022 for the treatment of Major Depressive Disorder (MDD) in adults
- Unlike traditional antidepressants that mainly act on the monoamine pathway by blocking the reuptake of serotonin, norepinephrine, or dopamine (or modulating their receptors), dextromethorphan works differently. The rate of dextromethorphan's rapid metabolism can be reduced with the use of CYP2D6 inhibitors such as quinidine or bupropion.
  - Dextromethorphan works as an uncompetitive NMDA receptor antagonist (increasing glutamate levels) & sigma-1 receptor agonist with an unclear mechanism of action
  - Bupropion may have noradrenergic and dopaminergic effects and increases plasma levels of dextromethorphan by inhibiting CYP2D6
  - Bupropion weakly inhibits norepinephrine and dopamine reuptake but does not inhibit monoamine oxidase or serotonin reuptake
  - Both dextromethorphan & bupropion increase the availability of norepinephrine by inhibiting its reuptake and also act as alpha-4-beta-2 nicotinic (nACh) antagonists
  - Bupropion also increases the availability of dopamine by blocking its reuptake
  - Dextromethorphan boosts serotonin levels by blocking its reuptake and increasing its action via sigma-1 agonism

Clinical Efficacy

- Dextromethorphan-bupropion combination, was approved based on results from two 6-week trials
  - The first trial was placebo-controlled and showed that Auvelity improved depression symptoms with a decrease in MADRS score of -3.9 points more than placebo
  - The second trial compared Auvelity to bupropion alone and showed that dextromethorphan played a primary role in the antidepressant effect
  - Results suggest that Auvelity works faster than traditional antidepressants, with clinical efficacy starting at 1 week

Safety & Tolerability

- Dextromethorphan-bupropion has a tolerable safety profile with common side effects including dizziness, nausea, headache, diarrhea, somnolence, dry mouth, sexual dysfunction, and hyperhidrosis. Discontinuation due to adverse events occurred in 6.2% of cases compared to 0.6% with placebo
- Monitoring includes blood pressure, symptom changes, and potential suicidal thoughts/behavior. Also monitor for neuropsychiatric reactions, serotonin syndrome, and

digoxin levels (when taking with bupropion, dextromethorphan, serotonergic drugs, or digoxin)

Dosing & Administration

- Prior to initiating treatment: assess blood pressure; screen patients for history of bipolar disorder, mania, or hypomania; and determine if patients are receiving any other medications that contain bupropion or dextromethorphan.
- Assess history of dextromethorphan abuse
- Contraindications:
    - Seizure disorder
    - Current or prior diagnosis of bulimia or anorexia nervosa
    - Abrupt discontinuation of alcohol, benzodiazepines, barbiturates, and antiepileptic drugs
    - Use with an MAOI or within 14 days of stopping treatment with Auvelity.
    - Known hypersensitivity to bupropion, dextromethorphan, or other components of Auvelity.
- Starting dosage is one tablet once daily in the morning. After 3 days, increase to the maximum recommended dosage of one tablet twice daily, separated by at least 8 hours. Do not exceed two doses within the same day
- Swallow tablets whole, do not crush, divide, or chew
- Dosage should be adjusted for clients with moderate renal impairment and should not be used in those with severe renal or liver problems (untested). Poor CYP2D6 metabolizers also require dose adjustment due to higher dextromethorphan levels compared to those with extensive/intermediate metabolism.
- Not safe for use during pregnancy (may harm fetus) and while breastfeeding (and for 5 days after the final dose. Alternative treatment is recommended for females planning pregnancy

Role in Therapy

- A trial sponsored by Axsome found no significant difference between Auvelity and placebo for treatment-resistant depression after 6 weeks
- Auvelity is being tested as a treatment for agitation in Alzheimer's patients, smoking cessation, and TRD
- Dextromethorphan abuse has been reported and is a growing concern among US law enforcement, primarily among adolescents due to its cheap availability and lack of awareness of its potential harm
- Likely candidates for Auvelity
    - Clients who need quick response to treatment with fewer side effects, such as sexual dysfunction, weight gain, metabolic problems, or help with comorbid tobacco dependence
    - Likely to be recommended for clients who failed first-line treatments

    - Possibility of using as a rescue drug in case of relapse of symptoms or maintenance treatment after ketamine
    - May also have off-label uses for Seasonal Affective Disorder, Generalized Anxiety Disorder, sexual dysfunction caused by SSRIs, Bipolar Disorder, ADHD, smoking cessation, cough, and pain (but only FDA uses would be approved by health plans)
- The combination of dextromethorphan and quinidine was initially developed for the treatment of Pseudobulbar Affect and showed potential as an antidepressant treatment

Comparative Value to Other Therapies

- Comparison with esketamine & ketamine
    - Ketamine have potential psychomimetic and dissociation side effects, which could limit its clinical application, and requires close monitoring and frequent treatments. Auvelity doesn't have such side effects and can be self-administered
    - Esketamine is indicated for treatment-resistant depression, but limitations include restrictions in administration, higher sedation risk, dissociation, feeling drunk, and a potential for abuse and misuse. It is only available through REMs program and must be taken under the supervision of a healthcare provider (twice a week to once weekly)
    - Not a replacement drug – to be given in conjunction with an oral antidepressant
    - Faster relief of depression symptoms compared to traditional antidepressants
    - To be administered at certified physician's office or clinic
- Auvelity did not result in weight gain commonly associated with antidepressants
- No head-to-head comparisons have been made to assess Auvelity's relative advantage compared to first-line therapies like SSRIs or SNRIs

Pricing Comparison

Drug and Manufacturer	Dosage Form(s) & Strength(s)	Dosing Regimen	Cost per 30 Days[a]
NDMA Receptor Antagonist + Aminoketone			
Auvelity (dextromethorphan hydrobromide and bupropion hydrochloride) *[Axsome]*	• Oral tablet: 45 mg (dextromethorphan)/105 mg (bupropion)	• Starting dosage is 1 tablet once daily in the morning. After 3 days, increase to the maximum recommended dosage of 1 tablet twice daily, separated by at least 8 hours. Do not exceed two doses within the same day.	Brand: $1050
Aminoketone			
Bupropion hydrochloride *[Various]*	• Oral tablet: 75 mg, 100 mg	• 100 mg orally twice daily for 3 days, may increase to 100 mg 3 times daily • Max dose is 450 mg orally per day given as 150 mg 3 times daily or 100 mg 4 times daily; separate all doses by at least 6 hours • Max single dose is 150 mg orally	Generic: $42.80 - $85.61
Wellbutrin SR (bupropion hydrochloride) *[GlaxoSmithKline]*	• Oral tablet, 12 hour: 100 mg, 150 mg, 200 mg	• 150 mg orally once daily in the morning for 3 days, may increase to 150 mg twice daily • Max dose is 400 mg orally per day given as 200 mg twice daily; separate all doses by at least 8 hours • Max single dose is 200 mg orally	Brand: $ 275.18 - $1,021.99 Generic: $7.70 - $18.00
Wellbutrin XL, Forfivo XL (bupropion hydrochloride extended-release) *[Almatica; GlaxoSmithKline]*	• Wellbutrin XL: Oral tablet, 24 hour: 150 mg, 300 mg • Forfivo XL: Oral tablet, 24 hour: 450 mg	• Wellbutrin XL: 150 mg orally once daily in the morning for 3 days, may increase to 300 mg once daily; Max dose is 450 mg/day given as a single dose • Forfivo XL: Maintenance only, 450 mg orally once daily	Wellbutrin XL: Brand: $2,053.40 - $4,763.97 Generic: $5.50 - $12.35 Forfivo XL: Brand: $563.14 Generic: $250.00
NDMA Receptor Antagonist			
Spravato (Esketamine) *[Janssen]*	• Nasal Spray: 28 mg/0.2 ml	• MDD with acute suicidal ideation or behavior: 84 mg intranasally twice per week for 4 weeks. Dosage may be reduced to 56 mg twice per week based on tolerability. • TRD: 56 mg intranasally on day 1, then 56 or 84 mg intranasally twice a week during weeks 1 through 4 based on efficacy and tolerability. Then 56 or 84 mg intranasally once a week during weeks 5 through 8, then 56 or 84 mg intranasally every 2 weeks or once a week during week 9 and after. • Take a 5-minute rest between use of each device	MDD: $6,563.20 - $9,844.80 TRD: $1,640.80 - $4,922.40

[a] Estimated cost based on AWP for brands and WAC for generics per Medispan as of 08/29/2022 based on the maintenance dosing in the prescribing information.

Formulary Considerations

- BHRS Formulary: recommend adding Auvelity with PA Criteria
- CMC Formulary: required to add as protected class by CMS, need to establish PA criteria

Prior Authorization Approval Criteria

- FDA approved indication of Major Depressive Disorder
- Previous adequate trials (at maximum dose for at least 4-6 weeks) of at least two antidepressants from different classes of antidepressants (eg. one from SSRI and one from SNRI)
- No contraindication to bupropion such as seizure disorder or conditions that increase risk of seizures
- Not pregnant, breastfeeding, or planning pregnancy
    - Not taking/stopped MAOIs in last 14 days
    - No abrupt discontinuation of alcohol, benzodiazepines, barbiturates, or antiepileptic drugs
    - Prescriber attestation of screening for personal/family history of bipolar disorder, mania/hypomania, other meds containing bupropion/dextromethorphan
    - No history of dextromethorphan abuse
    - Quantity Limit: 2 tabs per day
    - Age Limit: adults only

References

- Auvelity Package Insert. Axsome Therapeutics, Inc., New York, NY. August 2022.
- Chaki, Shigeyuki, and Mai Watanabe. "Antidepressants in the post-ketamine Era: Pharmacological approaches targeting the glutamatergic system." *Neuropharmacology* (2022): 109348.
- Khabir, Yumna[1,*]; Hashmi, Mahnoor Rehan[1]; Asghar, Adam Ali[1]. Rapid-acting oral drug (Auvelity) for major depressive disorder. Annals of Medicine & Surgery 82():p 104629, October 2022. | DOI: 10.1016/j.amsu.2022.104629
- Iosifescu, Dan V., et al. "Efficacy and safety of AXS-05 (dextromethorphan-bupropion) in patients with major depressive disorder: A phase 3 randomized clinical trial (GEMINI)." *The Journal of Clinical Psychiatry* 83.4 (2022): 41226.
- Highmark Inc. Iris Tan, PharmD, Auvelity Medication Review, 2022
- O'Gorman, Cedric, et al. "Efficacy and safety of AXS-05, a novel, oral, NMDA-receptor antagonist with multimodal activity, in agitation associated with Alzheimer's disease: Results from ADVANCE-1, a phase 2/3, double-blind, active and placebo-controlled trial: Developments in clinical trials and cognitive assessment." Alzheimer's & Dementia 16 (2020): e047684.
- Rădulescu I, Drăgoi AM, Trifu SC, Cristea MB. Neuroplasticity and depression: Rewiring the brain's networks through pharmacological therapy (Review). Exp Ther Med. 2021 Oct;22(4):1131. doi: 10.3892/etm.2021.10565. Epub 2021 Aug 5. PMID: 34504581; PMCID: PMC8383338.
- Tabuteau H, Jones A, Anderson A, et al. Effect of AXS-05 (Dextromethorphan-Bupropion) in major depressive disorder: a randomized double-blind controlled trial. Am J Psychiatry. 2022 Jul;179(7):490-499.
- U.S. Department of Justice. National Drug Intelligence Center. (2004). Bulletin Intelligence.
- Zagorski, N. (2022, October 24). FDA Approves Rapid-Acting Oral Antidepressant. Psychiatric News, American Psychiatric Association. https://doi.org/10.1176/appi.pn.2022.11.11.13.