Dextromethorphan and Bupropion Extended-Release Tablets (AUVELITY) National Drug Monograph November 2022

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA Approval Information

Description/Mechanism of Action

- Dextromethorphan is an uncompetitive N-methyl D-aspartate (NMDA) receptor antagonist and sigma-1 receptor agonist, and bupropion, an aminoketone antidepressant and CYP450 2D6 inhibitor

Indication(s) Under Review in This Document

- Dextromethorphan and bupropion extended-release tablets (Dex/Bup) is indicated for the treatment of major depressive disorder (MDD) in adults

Dosage Form(s) Under Review

- Extended-release tablets: : 45 mg/105 mg dextromethorphan hydrobromide/ bupropion hydrochloride

Clinical Evidence Summary

Efficacy Considerations [1,3,4]

- The efficacy of Dex/Bup, supporting its FDA approved indication for the treatment of MDD in adults, was based on data from one phase 3, multicenter, randomized, double-blind, placebo-controlled, 6 week industry-sponsored trial (Study 1, NCT04019704) and a 6 week randomized, double-blind, active-controlled industry-sponsored, phase 2 trial (Study 2, NCT03595579)
- In Study 1, patients were 18-65 years of age with a primary diagnosis of MDD and a Montgomery-Asberg Depression Rating Scale (MADRS) total score of 25 or higher (moderate or greater severity) as well as a Clinician Global Impression-Severity (CGI-S) scale score of 4 or higher. Patients were randomly assigned to receive Dex/Bup (45mg-105mg) or placebo orally for 6 weeks. Study medication was given once daily for 3 days, then twice daily thereafter. The primary endpoint was the change from baseline to week 6 in the MADRS total score.

- The MADRS is a 10-item clinician rated questionnaire ranging from 0-60, with higher scores representing more severe depression. The CGI-S scale ranges from 1-7 with higher scores indicating greater severity of illness.
- The modified intent to treat population included 318 patients (Dex/Bup, 156; placebo, 162). Patients had a median age of 41 years and were 67% female, 55% Caucasian, 35% Black, and 5% Asian.
- The change from baseline (reduction) in the MADRS total score to week 6 was statistically significantly greater in patients treated with Dex/Bup than in those who received placebo (Table 1).
- In Study 2, patients were 18-65 years of age with a primary diagnosis of MDD and a MADRS total score of 25 or higher as well as a CGI-S scale score of 4 or higher. Bupropion was used as an active control. Patients were randomly assigned to receive Dex/Bup (45mg-105mg) or sustained-release bupropion (105mg) orally for 6 weeks. Study medication was given once daily for 3 days, then twice daily thereafter. The primary efficacy measure was the change from baseline to week 6 in the MADRS total score.
- The modified intent to treat population included 80 patients (Dex/Bup, 43; sustained-release bupropion, 37). Patients had a mean age of 37 years and were 64% female, 63% Caucasian, 33% Black, and 1% Asian.
- The change from baseline (reduction) in the MADRS total score to week 6 was statistically significantly greater in patients treated with Dex/Bup than in those who received sustained-release bupropion (Table 2). However, the dose of bupropion (210mg) used in this study is lower than the usual recommended dose for sustained release bupropion for the treatment of MDD (300-400mg/day).

Table 1. Primary Efficacy; Change from Baseline MADRS Total Score Week 6 (Study 1).[4]

	Dex/Bup N=156	Placebo N=162
MADRS baseline score Mean (SD)	33.6 (4.4)	33.2 (4.4)
LS mean (SE) change from baseline at week 6	-15.9 (0.9)	- 12.0 (0.9)
Difference vs. placebo (95% CI)	-3.9 (-1.4, -6.4)	
p-value (vs. placebo)	P=0.002	

MADRS: Montgomery-Asberg Depression Rating Scale; N: sample size; SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: confidence interval

Table 2. Primary Efficacy; Change form Baseline MADRS Total Score Week 6 (Study 2).[3]

	Dex/Bup N=43	Bupropion N=37
MADRS baseline score Mean (SD)	31.8 (4.0)	32.2 (4.5)
LS mean (SE) change from baseline at week 6	-13.7 (0.6)	- 8.8 (0.7)
Difference vs. placebo (95% CI)	-4.9 (-3.1, -6.8)	
p-value (vs. placebo)	P<0.001	

MADRS: Montgomery-Asberg Depression Rating Scale; N: sample size; SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: confidence interval

Safety Considerations

Table 3. Adverse Reactions, Adults [1,4]

Adverse reaction	Dex/Bup N=162 (%)	Placebo N=164 (%)
Dizziness	16	6
Nausea	13	9
Headache	8	4
Diarrhea	7	3
Somnolence	7	3
Dry mouth	6	2
Sexual dysfunction	6	0
Hyperhidrosis	5	0
Anxiety	4	1
Constipation	4	2
Decreased appetite	4	1
Insomnia	4	2
Arthralgia	3	0
Fatigue	3	2
Paraesthesia	3	0
Blurred vision	3	0

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 dextromethorphan and/or bupropion. Do not use dextromethorphan and/or bupropion within 14 days of discontinuing an MAOI
- Known hypersensitivity to bupropion, dextromethorphan, or other components of Dex/Bup

Other warnings / precautions:[1]

- Suicidal thought and behaviors in adolescents and young adults – box warning
- Seizure
- Increased blood pressure and hypertension – blood pressures should be assessed prior to initiation of treatment and monitored periodically throughout therapy
- Activation of mania or hypomania – prior to initiation of treatment, patients should be screened for a personal or family history of bipolar disorder, mania, or hypomania
- Psychosis and other neuropsychiatric reactions
- Angle-closure glaucoma – avoid use in patients with untreated anatomically narrow angles
- Dizziness
- Serotonin syndrome
- Embryo-fetal toxicity – may cause fetal harm; not recommended during pregnancy

Select Other Therapeutic Options

Table 4.

Drug	Formulary status	Clinical Guidance/ Indication
Dex/Bup	NF	MDD
Bupropion	F	MDD, Seasonal AD, smoking cessation
Citalopram	F	MDD
Duloxetine	F	MDD, GAD, fibromyalgia, musculoskeletal pain, neuropathic pain with DM
Escitalopram	F	MDD, GAD
Mirtazapine	F	MDD
Sertraline	F	MDD, OCD, PD, PTSD, PMDD, SAD
Venlafaxine	F	MDD, GAD, PD, SAD
Vilazodone	NF	MDD
Vortioxetine	NF	MDD

MDD: major depressive disorder; AD: affective disorder; GAD: generalized anxiety disorder; DM: diabetes mellitus; OCD: obsessive-compulsive disorder; PD: panic disorder; PTSD: posttraumatic stress disorder; PMDD: premenstrual dysphoric disorder; SAD: social anxiety disorder

Projected Place in Therapy

- Major depression is one of the most common mental disorders in the United States and can result in severe impairment that interferes with one's ability to conduct life activities. An estimated 21 million adults (8.4% of adult population) in the United States had at least one major depressive episode.[6] The main treatment approach includes antidepressant drugs, behavioral therapy (e.g., CBT) and other somatic treatments (e.g., ECT, rTMS). Antidepressant drugs, used for the management of MDD, have similar efficacy but vary in their adverse effect profile.
- The results from Study 1 and 2 support the efficacy of Dex/Bup in reducing MADRS scores in adult patients with MDD
- The effectiveness of Dex/Bup compared to alternative treatments has not been established; there is no evidence for superiority compared to other agents
- Dex/Bup has a boxed warning for suicidal thoughts and behavior
- The most common adverse reactions include dizziness, nausea, headache, diarrhea, somnolence, dry mouth, sexual dysfunction, and hyperhidrosis
- The use of Dex/Bup should be avoided in seizure disorder, patients with a current or prior diagnosis of bulimia or anorexia nervosa, during abrupt discontinuation of alcohol, benzodiazepines, barbiturates, and antiepileptic drugs, with an MAOI or within 14 days of stopping treatment with Dex/Bup, with co-administration with strong CYP2B6 inducers, and in patients with a known hypersensitivity to bupropion, dextromethorphan, or other components of Dex/Bup
- The use of Dex/Bup has not been discussed in current MDD guidelines; Dex/Bup was not available when guidelines were developed
- Long-term published safety and efficacy data are lacking
- A trial in refractory depression (STRIDE-1) failed, and information related to the potential abuse liability with long term use in vulnerable patients is needed [5]
- Dex/Bup represents an antidepressant drug combination, with a unique mechanism of action, for the management of MDD. It adds to the long list of medications approved for the management of MDD

References

1. AUVELITY (dextromethorphan hydrobromide and bupropion hydrochloride) extended-release capsules) [prescribing information]. Axsome Therapeutics, Inc. New York, NY. August 2022.
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3. Tabuteau H, Jones A, Anderson A et al. Effects of AXS-05 (Dextromethorphan-Bupropion) in major depressive disorder: a randomized double-blind controlled trail. Am J Psychiatry 2022;179:490-499.
4. 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):21m14345.

5. 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;179:448-450.
6. National Institute of Mental Health. Mental Health Information. NIMH » Major Depression (nih.gov) accessed Sept 2022.

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