VENTURA COUNTY
HEALTH CARE PLAN

PRIOR AUTHORIZATION POLICY

POLICY: Attention Deficit Hyperactivity Disorder Non-Stimulant Medications Prior Authorization Policy

- Intuniv® (guanfacine extended-release tablets – Shire, generic)
- Kapvay® (clonidine hydrochloride extended-release tablets – Concordia, generic)
- Strattera® (atomoxetine capsules – Eli Lilly, generic)
- Qelbree™ (viloxazine extended-release capsules – Supernus)

REVIEW DATE: 08/05/2020; selected revision 05/05/2021

OVERVIEW

Atomoxetine capsules (Strattera, generic), guanfacine extended-release (ER) tablets (Intuniv, generic), clonidine ER tablets (Kapvay, generic), and Qelbree are non-stimulant medications approved for the **treatment of attention deficit hyperactivity disorder** (ADHD).[1-4] Atomoxetine capsules, a selective norepinephrine reuptake inhibitor, is indicated for the treatment of ADHD in children ≥ 6 years of age, adolescents, and adults.[1] Guanfacine ER tablets and clonidine ER tablets, both alpha agonists, and Qelbree, a selective norepinephrine reuptake inhibitor, are approved for use in children and adolescents aged 6 to 17 years with ADHD.[2-4] Guanfacine ER tablets and clonidine ER tablets are indicated for use as monotherapy or as adjunctive therapy to stimulant medications.

Clinical Efficacy

Patients with pervasive developmental disorders who have symptoms of ADHD respond to ADHD medications at a reduced rate compared with typically developing peers and often with undesirable side effects.[5,6] However, there is evidence to support use of these agents (e.g., stimulants, atomoxetine capsules, guanfacine ER tablets, and clonidine ER tablets) in this patient population.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of atomoxetine capsules (Strattera, generic), clonidine ER tablets (Kapvay, generic), guanfacine ER tablets (Intuniv, generic), and Qelbree. All approvals are provided for the duration noted below.

Automation: An age edit targeting patients < 6 or > 18 years of age is recommended. Therefore, patients between the ages of 6 and 18 years will be approved at the point-of-service. For patients < 6 or > 18 years of age, coverage will be determined by Prior Authorization criteria.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of atomoxetine capsules (Strattera, generic), clonidine ER tablets (Kapvay, generic), guanfacine ER tablets (Intuniv, generic), or Qelbree is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Attention Deficit Hyperactivity Disorder.** Approve for 3 years if the patient is ≥ 6 years of age.

Other Uses with Supportive Evidence – Only For Atomoxetine Capsules (Strattera, generic), Clonidine ER Tablets (Kapvay, generic), or Guanfacine ER Tablets (Intuniv, generic)

2. **Pervasive Developmental Disorders (e.g., autism spectrum disorder, Asperger's disorder).** Approve atomoxetine capsules (Strattera, generic), clonidine ER tablets (Kapvay, generic), or guanfacine ER tablets (Intuniv, generic) for 3 years in patients with symptoms of attention deficit hyperactivity disorder (e.g., inattention, hyperactivity).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of atomoxetine capsules (Strattera, generic), clonidine ER tablets (Kapvay, generic), guanfacine ER tablets (Intuniv, generic), or Qelbree is not recommended in the following situations:

1. **Binge-Eating Disorder.** In one 10-week, placebo-controlled study in outpatients with binge-eating disorder (n = 40), atomoxetine was associated with a significantly greater reduction in binge-eating episode frequency vs. placebo.[7] Additional studies with atomoxetine are needed. There are no data with guanfacine ER tablets, clonidine ER tablets, or Qelbree.

2. **Depression Without Attention Deficit/Hyperactivity Disorder.** Limited information is available on the use of atomoxetine for the treatment of major depressive disorder. In three case reports and one case series in 15 patients with depressive disorders, adding atomoxetine to a selective serotonin reuptake inhibitor (SSRI) resulted in further improvement.[8,9] However, in a published controlled trial, patients with major depressive disorder (without ADHD) [n =276] were treated with sertraline at doses up to 200 mg/day.[10] Patients who continued to experience depressive symptoms (n = 146) were then randomly assigned to either treatment with atomoxetine 40 to 120 mg/day or placebo for an additional 8 weeks. There was no difference between the atomoxetine/sertraline and placebo/sertraline treatment groups in mean change in depressive symptom severity or in the number of patients whose depressive symptoms remitted (40.3% vs. 37.8%, respectively; P = 0.865). Atomoxetine did not improve clinically significant depression in patients with Parkinson disease (n = 55) in one study.[11] There are no data with guanfacine ER tablets, clonidine ER tablets, or Qelbree.

3. **Fibromyalgia.** In case reports, atomoxetine was effective in reducing fatigue and pain in fibromyalgia syndrome.[12] Well-controlled trials with atomoxetine are needed to establish safety and efficacy. There are no data with guanfacine ER tablets, clonidine ER tablets, or Qelbree.

4. **Improve Cognitive Function (or Neuroenhancement).** The use of prescription medication to augment cognitive or affective function in otherwise healthy individuals (also known as neuroenhancement) is increasing in adult and pediatric populations.[20] A 2013 Ethics, Law, and Humanities Committee position paper, endorsed by the American Academy of Neurology (AAN) indicates that based on currently available data and the balance of ethics issues, neuroenhancement in children and adolescents without a diagnosis of a neurologic disorder is not justifiable. The prescription of neuroenhancements is inadvisable due to numerous social, developmental, and professional integrity issues. Several studies have evaluated atomoxetine for cognitive function in various patient populations, including patients with Huntington disease[12], Alzheimer's disease[14], schizophrenia[15,16], and Parkinson's disease.[17] However, atomoxetine has not demonstrated clinical benefit.

5. **Long-Term Combination Therapy (i.e., > 2 months) with atomoxetine (Strattera, generic) and Central Nervous System (CNS) Stimulants used for the Treatment of Attention Deficit/Hyperactivity Disorder (e.g., mixed amphetamine salts ER capsules [Adderall XR®, generic], methylphenidate ER tablets, methylphenidate immediate-release tablets).** Currently, data do not support using atomoxetine and CNS stimulant medications concomitantly.[18,19] Short-term drug therapy (2 months or less) with both atomoxetine and CNS stimulant medications are allowed for transitioning the patient to only one drug. Guanfacine ER tablets and clonidine ER tablets are indicated

for use as monotherapy or as adjunctive therapy to CNS stimulant medications; therefore, long-term combination therapy with either agent and CNS stimulants is appropriate.[2-3] Qelbree labeling does not address combination use with CNS stimulants at this time.[4]

6. **Nocturnal Enuresis.** In case reports, children with ADHD and other comorbid psychiatric diagnoses who had nocturnal enuresis and were treated with atomoxetine had resolution of their enuresis.[21] In one controlled trial in pediatric patients (n = 87) with nocturnal enuresis, atomoxetine increased the average number of dry nights per week by 1.47 vs. 0.60 for placebo (P = 0.01).[22] Additional controlled trials with atomoxetine are needed. There are no data with guanfacine ER tablets, clonidine ER tablets, or Qelbree.

7. **Weight Loss.** In one 12-week, placebo-controlled study in obese women (n = 30), atomoxetine resulted in a mean -3.7% loss vs. 0.2% gain with placebo when combined with a hypocaloric diet (500 kcal/day deficit).[23] Atomoxetine did not demonstrate efficacy for weight reduction in patients with schizophrenia (n = 37) treated with antipsychotics (clozapine or olanzapine).[24] Additional studies are needed.

8. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Strattera® capsules [prescribing information]. Indianapolis, IN: Eli Lilly and Company; February 2020.
2. Intuniv® extended-release tablets [prescribing information]. Lexington, MA: Shire US Inc.; December 2019.
3. Kapvay® extended-release tablets, oral [prescribing information]. Overland Park, KS: Concordia Pharmaceuticals Inc.; February 2020.
4. Qelbree™ extended-release capsules [prescribing information].
5. Nash K, Carter KJ. Treatment options for the management of pervasive developmental disorders. *Int J Psychiatry Med*. 2016;51(2):201-210.
6. Goel R, Hong JS, Findling RL. An update on pharmacotherapy of autism spectrum disorder in children and adolescents. *Int Rev Psychiatry*. 2018;30(1):78-95.
7. McElroy SL, Guerdjikova A, Kotwal R, et al. Atomoxetine in the treatment of binge-eating disorder: a randomized placebo-controlled trial. *J Clin Psychiatry.* 2007;68:390-398.
8. Berigan TR. Atomoxetine used adjunctively with selective serotonin reuptake inhibitors to treat depression. *Prim Care Companion J Clin Psychiatry.* 2004;6:93-94.
9. Carpenter LL, Milosavljevic N, Jordan JD, Schecter JM, Tyrka AR, Price LH. Augmentation with open-label atomoxetine for partial or nonresponse to antidepressants. *J Clin Psychiatry*. 2005;66:1234-1238.
10. Michelson D, Adler LA, Amsterdam JD, et al. Addition of atomoxetine for depression incompletely responsive to sertraline: a randomized, double-blind, placebo-controlled study. *J Clin Psychiatry*. 2007;68:582-587.
11. Weintraub D, Mavandadi S, Mamikonyan E, et al. Atomoxetine for depression and other neuropsychiatric symptoms in Parkinson disease. *Neurology.* 2010;75:448-455.
12. Berigan T. The use of atomoxetine adjunctively in fibromyalgia syndrome. *Can J Psychiatry.* 2004;49:499-500.
13. Beglinger LJ, Adams WH, Paulson H, et al. Randomized controlled trial of atomoxetine for cognitive dysfunction in early Huntington disease. *J Clin Psychopharmacol.* 2009;29:484-487.
14. Mohs R, Shiovitz TM, Tariot PN, et al. Atomoxetine augmentation of cholinesterase inhibitor therapy in patients with Alzheimer disease: 6-month, randomized, double-blind, placebo-controlled, parallel-trial study. *Am J Geriatr Psychiatry.* 2009;17:752-759.
15. Kelly DL, Buchanan RW, Boggs DL, et al. A randomized double-blind trial of atomoxetine for cognitive impairments in 32 people with schizophrenia. *J Clin Psychiatry.* 2009;70:518-525.
16. Friedman JI, Carpenter D, Lu J, et al. A pilot study of adjunctive atomoxetine treatment to second-generation antipsychotics for cognitive impairment in schizophrenia. *J Clin Psychopharmacol.* 2008;28:59-63.
17. Marsh L, Biglan K, Gerstenhaber M, Williams JR. Atomoxetine for the treatment of executive dysfunction in Parkinson's disease: a pilot open-label study. *Mov Disord.* 2009;30:277-282.
18. Treuer T, Gau SS-F, Mendez L, et al. A systematic review of combination therapy with stimulants and atomoxetine for attention-deficit/hyperactivity disorder, including patient characteristics, treatment strategies, effectiveness, and tolerability. *J Child Adolesc Psychopharmacol*. 2013;23(3):179-193.

19. Clemow DB, Mason OW, Sarkis EH, et al. Atomoxetine monotherapy compared with combination therapy for the treatment of ADHD: a retrospective chart review study. *Expert Rev Neurother.* 2015;15(11):1353-1366.
20. Graf WD, Nagel SK, Epstein LG, et al. Pediatric neuroenhancement: ethical, legal, social, and neurodevelopmental implications. *Neurology.* 2013;80:1251-1260.
21. Shatkin JP. Atomoxetine for the treatment of pediatric nocturnal enuresis. *J Child Adolesc Psychopharmacol.* 2004;14(3):443-447.
22. Sumner CR, Schuh KJ, Sutton VK, et al. Placebo-controlled study of the effects of atomoxetine on bladder control in children with nocturnal enuresis. *J Child Adolesc Psychopharmacol.* 2006;16:699-711.
23. Gadde KM, Yonish GM, Wagner HR, et al. Atomoxetine for weight reduction in obese women: a preliminary randomized controlled trial. *Int J Obes (Lond).* 2006;30:1138-1142.
24. Ball MP, Warren KR, Feldman S, et al. Placebo-controlled trial of atomoxetine for weight reduction in people with schizophrenia treated with clozapine or olanzapine. *Clin Schizophr Relat Psychoses.* 2011;5:17-25.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	06/27/2018
Annual Revision	**Pervasive Developmental Disorders:** The "such as" statement was revised from e.g., autism, autistic disorder, Asperger's disorder to e.g., autism spectrum disorder, Asperger's disorder.	07/24/2019
Annual Revision	No criteria changes.	08/05/2020
Selected Revision	• Addition of Qelbree to the policy. • **Pervasive Developmental Disorders:** Restricted approval to atomoxetine (Strattera, generic), clonidine extended-release tablets (Kapvay, generic), or guanfacine extended-release tablets (Intuniv, generic).	05/05/2021