ADHD Non-Stimulant Medications Step Therapy Program

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Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will BCBSKC will provide coverage for brand name non-stimulant when the following criteria are met. The brand name medications affected are:

- Strattera® (atomoxetine capsules – Eli Lilly and Company)
- Intuniv® (guanfacine extended-release tablets – Shire Pharmaceuticals)
- Kapvay® (clonidine hydrochloride extended-release tablets – Shionogi Pharma, generics)

When Policy Topic is covered
Strattera, Intuniv, and Kapvay may be reserved for use in patients who have not responded to or cannot tolerate stimulants. A step therapy program has been developed to encourage use of a central nervous system (CNS) stimulant medication for ADHD prior to Strattera, Intuniv, or Kapvay. If the step therapy rule is not met at the point of service, coverage will be determined by prior authorization criteria.

Step 1: Amphetamines
- Mixed amphetamine salts [dextroampheta mine sulfate, dextroamphetamine saccharate, amphetamine sulfate, amphetamine aspartate] immediate-release tablets (Adderall®, generics)/ extended-release capsules (Adderall XR®, generics)
- Dextroamphetamine immediate release tablets (Dexedrine®, generics)/sustained-release capsules (Dexedrine® Spansules®, generics)
- Dextroamphetamine sulfate oral solution
- Methamphetamine (Desoxyn®, generics)
- Lisdexamfetamine (Vyvanse™)

Methylphenidate/dexmethylphenidate
- methylphenidate extended-release tablets or capsules (Concerta®, Methylin® ER, Methylin® Chewable, Metadate® CD, Metadate® ER, Ritalin® LA, Ritalin-SR®, generics)
- methylphenidate immediate release (Ritalin, Methylin, generics)
- dexmethylphenidate immediate-release tablets (Focalin®, generics)
- dexmethylphenidate extended-release capsules (Focalin XR®)
- methylphenidate transdermal system (Daytrana®)
- methylphenidate extended-release oral suspension (Quillivant™ XR)

Step 2: Strattera, Intuniv, Kapvay (brand and generic)

Exceptions for a Step 2 agent can be made for patients with one of the following conditions/situations:

1. If the patient has tried a Step 1 agent, then authorization for a Step 2 agent may be given.
2. Authorization for a Step 2 agent may be given if the patient has a documented history of addiction to controlled substances.

3. Authorization for a Step 2 agent may be given if the patient has a history of seizures. According to the product labeling, methylphenidate and amphetamine may lower the seizure threshold in patients with a prior history of seizures, in patients with prior EEG abnormalities (with absence of seizures), and very rarely, in the absence of history of seizures and no prior EEG evidence of seizures. Product labeling for Strattera, Intuniv, and Kapvay do not contain this warning.

4. Authorization for a Step 2 agent may be given if the patient has a history of motor tics or a family history or diagnosis of Tourette’s syndrome. According to product labeling, methylphenidate is contraindicated in patients with motor tics or with a family history or diagnosis of Tourette’s syndrome. Amphetamines may exacerbate motor and phonic tics and Tourette’s syndrome. Strattera, Intuniv, and Kapvay do not contain warnings regarding tics or Tourette’s syndrome. In the professional opinion of specialist physicians reviewing the data, we have adopted this criterion.

5. Authorization for Strattera may be given if the patient has ADHD or ADD and co-morbid anxiety. The 2007 AACAP ADHD treatment guidelines and the 2006 Texas Children’s Medication Algorithm for the pharmacotherapy of ADHD state that Strattera is one of the first-line medication options for the treatment of ADHD with comorbid anxiety. In the professional opinion of specialist physicians reviewing the data, we have adopted this criterion.

Exceptions are not recommended for a Step 2 agent without first trying a Step 1 agent in the following conditions/situations:

a. Patient/parent/primary caregiver has concern of drug abuse or dependence with stimulant medications in situations where there is no documented history of addiction to controlled substances. According to the 2011 AAP guidelines on treatment of ADHD in children and adolescents, for cases (especially in adolescents) in which there is concern of misuse or diversion of the medication, clinicians should consider prescribing medications with no abuse potential, such as Strattera and Intuniv or Kapvay, or stimulant medications with less abuse potential, such as lisdexamfetamine (Vyvanse), dermal methylphenidate (Daytrana), or OROS methylphenidate (Concerta).

b. Depression without ADHD or ADD and does not meet any of the exception criteria above. Limited information is available on Strattera’s use for treatment of major depressive disorder. In three case reports and one case series in 15 patients with depressive disorders, adding Strattera to an SSRI resulted in further improvement. However, in a published controlled trial patients with major depressive disorder (without ADHD) [n = 276] were treated with the SSRI sertraline at doses up to 200 mg/day. Patients who continued to experience depressive symptoms (n = 146) were then randomly assigned to either treatment with Strattera 40 to 120 mg/day or placebo for an additional 8 weeks. There was no difference between the Strattera-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). There are no data with Intuniv or Kapvay.

c. Nocturnal enuresis. In case reports, children with ADHD and other comorbid psychiatric diagnoses who had nocturnal enuresis and were treated with Strattera had resolution of their enuresis. Controlled trials with Strattera are needed. There are no data with Intuniv or Kapvay.

d. Fibromyalgia. In case reports, Strattera was effective in reducing fatigue and pain in fibromyalgia syndrome. Well-controlled trials with Strattera are need to establish safety and efficacy. There are no data with Intuniv or Kapvay.
**When Policy Topic is not covered**
The use of brand name non-stimulant medications is considered investigative for all other indications.

**Considerations**
ADHD non-stimulant medications require prior authorization through the Clinical Pharmacy Department.

This Blue Cross and Blue Shield of Kansas City policy Statement was developed using available resources such as, but not limited to: Food and Drug Administration (FDA) approvals, Facts and Comparisons, National specialty guidelines, Local medical policies of other health plans, Medicare (CMS), Local providers.

**Description of Procedure or Service**
Attention-deficit hyperactivity disorder (ADHD) is a neurobehavioral disorder that typically begins in childhood and often persists into adulthood. ADHD is characterized by developmentally inappropriate levels of inattention and hyperactivity resulting in functional impairment in academic, family, and social settings. ADHD is the most commonly diagnosed neurobehavioral disorder of childhood.

**Treatment**
The American Academy of Pediatrics (AAP) clinical practice guideline for the diagnosis, evaluation, and treatment of ADHD in children and adolescents (2011) indicate that stimulants have the most evidence for efficacy and safety in the treatment of ADHD, and remain the first choice of medication treatment. Individuals may respond to one stimulant but not to another, and it cannot be predicted which stimulant will be best in an individual. Therefore, if a trial with one group is unsuccessful (poor efficacy or adverse events [AEs]), a trial on a medication from the other group should be undertaken. At least one-half of the patients whose symptoms fail to respond to one stimulant medication may have a positive response to the alternative medication. The dose of medication should be titrated to achieve maximum benefit with minimum AEs. More than 70% of children and youth with ADHD respond to one of the stimulant medications at an optimal dose when a systematic trial is used. Titration to maximum doses that control symptoms without AEs is recommended instead of titration strictly on a mg-per-kg basis.

The 2006 Texas Children’s Medication Algorithm for the pharmacotherapy of ADHD and the 2007 American Academy of Child and Adolescent Psychiatry (AACAP) ADHD treatment guidelines recommend stimulants as first line treatment for ADHD followed by a trial of another stimulant if the first stimulant is not effective. The Texas Children’s Medication Algorithm states that Strattera may be considered in patients after one stimulant trial if the patient experienced severe AEs.

According the AACAP guidelines, if patients do not achieve satisfactory treatment response to stimulants or Strattera, use of other medications may be considered. The guidelines indicate that alpha-agonists (guanfacine immediate-release, clonidine) are often used in the treatment of ADHD even though they were not approved by the Food and Drug Administration (FDA) at the time of publication. However, alpha-agonists (along with other second-line agents) have effect sizes considerably less than those of the first-line agents and comparable with behavioral therapy. Alpha-agonists are widely used for ADHD itself, for comorbid aggression, or to combat AEs such as tics or insomnia, although data are lacking. These guidelines also indicate that children with ADHD and a comorbid tic disorder, on average, show a decline in tics when treated with a stimulant. If a patient has treatment emergent tics during a trial of a stimulant, an alternative stimulant or a nonstimulant should be tried. If the patient’s ADHD symptoms only respond to a stimulant that induces tics, adding an alpha-agonist is recommended.

The Texas Children’s Medication Algorithm states that for ADHD an alpha agonist may be used after a trial of two stimulants, Strattera® (atomoxetine capsules), bupropion, and a tricyclic antidepressant (TCA). Hence, alpha agonists are the last stage in the algorithm. For ADHD with comorbid tic
disorders, stimulant monotherapy is still first-line therapy. However, if tics continue to impair, an alpha agonist may be added.

Several stimulants are approved for the treatment of ADHD in adolescents, as well as adults. Strattera is indicated for the treatment of ADHD in children ≥ 6 years of age, adolescents, and adults. Limited data are available with Strattera in children < 6 years of age.

Overall, studies with Strattera in ADHD have been short term (about 3 to 10 weeks); a 12 month trial in children; an 18 month trial in children and adolescents; and a 97 week open-label study in adults have been published. In contrast, the stimulants have been well studied, especially in children with ADHD, and their safety and efficacy for long-term therapy are well established.

Two alpha agonists are currently approved for the treatment of ADHD: Intuniv® (guanfacine extended-release tablets) and Kapvay. Both of these agents are approved for use in children and adolescents aged 6 to 17 years. No controlled studies have studied Intuniv or Kapvay in children < 6 years of age or adults. The effectiveness of Intuniv and Kapvay for longer-term use (more than 9 weeks and 5 weeks, respectively) has not been systematically evaluated in controlled trials. However, long-term efficacy of Intuniv was assessed in two 24-month open-label extension studies.

Rationale

Comparative Efficacy

Intuniv or Kapvay have not been compared to any of the stimulants in head-to-head studies.

In total, there are six published studies comparing Strattera to a stimulant. More well-designed studies are needed that directly compare Strattera to methylphenidate and amphetamine-type products. A review article (published in 2006) evaluated five of the head-to-head comparison studies between Strattera and stimulants. Overall, there was no difference between Strattera and methylphenidate immediate-release in efficacy as measured by ADHD rating scale total score; methylphenidate osmotic oral release system (OROS) showed significantly greater improvement at Weeks 1 and 2 compared to Strattera and more patients treated with methylphenidate OROS were considered responders; and both Strattera and mixed amphetamine salts (MAS) extended-release (XR) showed significant improvements at endpoint; however, Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP) scores were significantly better with MAS XR.

Tics/Tourette's Syndrome

According to product labeling, methylphenidate is contraindicated in patients with motor tics or with a family history or diagnosis of Tourette's syndrome. However, controlled trials have not found that methylphenidate worsens motor tics in children with ADHD with or without Tourette's syndrome. In uncontrolled studies with Concerta® (methylphenidate extended-release), the cumulative incidence of new onset of tics was 9% after 27 months in one study and 1% in a second study with a treatment period of up to 9 months. In three controlled studies in children with ADHD, the percentage of patients experiencing tics was not significantly different between Concerta (4.0%), methylphenidate three times daily (2.3%), and placebo (3.7%) [P = 0.5249]; none of the patients had Tourette's syndrome and those with mild or moderate tics could enroll. Most patients who reported tics during the studies had a prior history of tics. According to product labeling, amphetamines may exacerbate motor and phonic tics and Tourette's syndrome. In a review of seven studies that compared stimulants to placebo or with other medications, there was no increase in tics in children who received stimulants.

Studies that compared Strattera with placebo in ADHD did not specify whether patients with motor tics or with a family history or diagnosis of Tourette's syndrome were included or excluded. One 18-week, randomized, double-blind, placebo-controlled study enrolled 148 children with ADHD and concurrent Tourette syndrome or chronic motor tic disorder (of mostly mild to moderate severity). The primary objective of the study was to test the hypothesis that Strattera does not worsen tics (non-inferiority study design). Both treatment groups decreased tic severity from baseline and Strattera was
found to be non-inferior to placebo. In both open label trials that compared Strattera with methylphenidate as well as the controlled trial that compared Strattera with Adderall XR, patients with motor tics or a family history of Tourette’s syndrome were excluded; motor and vocal tics were not reported as adverse events.22-24 Tics are not included as an AE in the product labeling for Strattera.7 However, there are case reports of children with ADHD who had developed tics on stimulant medications and in whom tics reappeared or were exacerbated on Strattera,38 and case reports of worsening of tics with Strattera.39

Practice guidelines for ADHD state that the effects of medication on tics is unpredictable, and the presence of tics before or during medical management of ADHD is not a contraindication to the use of stimulant drugs.2,7 The 2007 AACAP ADHD treatment guidelines state that Strattera may be considered first-line medication for individuals with ADHD and tics.2 In treating patients with ADHD and tic disorder, the 2006 Texas Children’s Medication Algorithm for the pharmacotherapy of ADHD still recommends first line treatment with a stimulant.5 However, if tics continue to impair, an alpha agonist may be added to stimulant therapy.

Seizures
According to a warning in the product labeling, amphetamine and methylphenidate may lower the seizure threshold in patients with a prior history of seizures, in patients with prior electroencephalogram (EEG) abnormalities in absence of seizures, and very rarely, in the absence of history of seizures and no prior EEG evidence of seizures.27,30 Many studies have reported that methylphenidate is safe in children with active or well-controlled epilepsy and that methylphenidate does not increase the risk of developing seizures in children with ADHD.40-43 Practice guidelines for ADHD also state that methylphenidate has not caused an increase in seizure frequency or severity when it is added to appropriate anticonvulsant medications.14 Although amphetamine and methylphenidate are not contraindicated in children with pre-existing epilepsy, it is important to monitor seizure frequency when initiating therapy.27,30 Strattera has not been systematically evaluated in controlled trials in patients with seizure disorders. During the clinical development program, seizures occurred in 0.2% of children (mean age 10 years).7 Placebo-controlled efficacy and safety trials with Strattera excluded patients with a history of seizures32,34 or other serious medical illnesses.22,33,35-36 Seizures have been reported with Strattera in the postmarket period.7 The postmarketing seizure cases include patients with preexisting seizure disorders and those with identified risk factors for seizures, as well as patients with neither a history of nor identified risk factors for seizures. The exact relationship between Strattera and seizures is difficult to evaluate due to uncertainty about the background risk of seizures in patients with ADHD. Intuniv and Kapvay also have not been evaluated in controlled trials in patients with seizure disorders. During the clinical development programs for Intuniv and Kapvay there were no reports of seizures.16-17

Cardiovascular (CV)
In 2011, the FDA issued safety communications regarding medications used to treated ADHD (stimulants [methylphenidate and amphetamine products] and Strattera) and cardiovascular safety.44-47 Based on large retrospective cohort studies, the FDA recommendations include: stimulant products and Strattera should generally not be used in patients with serious heart problems, or for whom an increase in blood pressure or heart rate would be problematic; and, patients treated with ADHD medications should be periodically monitored for changes in heart rate or blood pressure.

Methylphenidate products should generally not be used in children or adolescents with known serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac problems due to reports of sudden cardiac death in association with stimulants.27 Caution should be used in treating patients with methylphenidate who have underlying medical conditions that might be compromised by increases in blood pressure or heart rate (e.g., preexisting hypertension, heart failure, recent myocardial infarction, or ventricular arrhythmia). Amphetamines are contraindicated in patients with advanced arteriosclerosis, symptomatic CV disease, moderate to severe hypertension, and hyperthyroidism.30
Strattera is contraindicated in patients with severe CV disorders whose condition would be expected to
deteriorate if they experience clinically important increases in blood pressure or heart rate (e.g., 15 to
20 mmHg in blood pressure or 20 beats per minute [bpm] in heart rate). In addition, Strattera should
be used with caution in patients with hypertension, tachycardia, or CV or cerebrovascular disease. In
pediatric trials, patients on Strattera had a mean increase in heart rate of 5.0 bpm and 9.4 bpm for
extensive and poor metabolizers, respectively, and tachycardia was an AE in 0.3% of Strattera patients
vs. 0% on placebo. In adult trials, tachycardia was an AE in 1.5% of Strattera patients vs. 0.5% on
placebo. In short-term, placebo-controlled clinical trials, the proportions of pediatric and adults patients
having an increase in diastolic blood pressure ≥ 15 mmHg were 21.5% and 12.6%, respectively, at any
one time, and 9.3% and 4.8%, respectively, at endpoint. The proportions of pediatric and adults patients
having an increase in systolic blood pressure ≥ 20 mmHg were 12.5% and 12.4%, respectively, at any
one time, and 4.9% and 4.2%, respectively, at endpoint. The proportions of pediatric and adults patients
having an increase in heart rate ≥ 20 bpm were 23.4% and 22.4%, respectively, at any one time, and 12.2% and 10.2%, respectively, at endpoint. Orthostatic hypotension
and syncope have also been reported in patients taking Strattera; therefore, Strattera should be used
with caution in any condition that may predispose patients to hypotension, or conditions associated with
abrupt heart rate or blood pressure changes.

Intuniv and Kapvay should be used with caution in patients with a history of hypotension, heart block,
bradyarrhythmia, CV disease, or syncope because it can decrease blood pressure and heart rate. These
alpha agonists should also be used with caution in patients treated concomitantly with
antihypertensives or other drugs that can reduce blood pressure or heart rate or increase the risk of
syncope. Patients should be advised to avoid becoming dehydrated or overheated. In the pediatric,
short-term, controlled trials with Intuniv, the maximum mean changes from baseline in systolic blood
pressure, diastolic blood pressure, and pulse were -5 mmHg, -3 mmHg, and -6 bpm, respectively. Hypotension was reported as an AE for 7% of the Intuniv group vs. 3% of the placebo group.
Orthostatic hypotension was reported for 1% and 0% on the Intuniv and placebo groups, respectively.
In pediatric patients that completed 5 weeks of treatment in a controlled, fixed-dose, monotherapy trial
with Kapvay, the maximum placebo-subtracted mean changes in systolic blood pressure, diastolic
blood pressure, and heart rate for the 0.2 and 0.4 mg/day doses were -4.0 and -8.8 mmHg, -4.0 and -
7.3 mmHg, and -4.0 and -7.7 bpm, respectively. Bradycardia was reported as an AE for 4% of the
Kapvay 0.4 mg/day group, and 0% for both the Kapvay 0.2 mg/day and placebo groups.

Comorbid Anxiety
Anxiety disorders reportedly occur in up to one third of patients with ADHD. There are data showing
treatment with Strattera, either as monotherapy or in combination with a selective serotonin receptor
antagonist (SSRI), significantly reduces ADHD and anxiety symptom scores.

Initial reports showed an increased placebo response rate, a greater incidence of side effects, and
smaller improvements on cognitive tests in children with ADHD and comorbid anxiety disorder treated
with methylphenidate. However, more recent controlled studies do not support these findings. There are data from recent controlled trials showing improvement in anxiety symptoms as well as
ADHD symptoms in children treated with methylphenidate. Treatment guidelines state that the
contraindication of anxiety disorder in the methylphenidate prescribing information has not been
supported by data from recent randomized, controlled trials which actually showed children with
comorbid anxiety disorder to improve on methylphenidate. Anxiety is not listed as a
contraindication, warning, or precaution in amphetamine product labeling.

A trial with a stimulant is one of the first-line treatment options in this patient population. If the stimulant
improves ADHD symptoms but the anxiety symptoms remain, an SSRI or other anti-anxiety medication
should be added. In a recently published small, double-blind, placebo-controlled study there was no
improvement in residual anxiety symptoms when the SSRI fluvoxamine was added to existing
methylphenidate therapy compared to placebo. As a result of this study, the 2007 AACAP ADHD
treatment guidelines now state that using Strattera for the treatment of ADHD with comorbid anxiety is
a viable alternative approach to the practice of first treating with a stimulant and then adding an SSRI if
necessary. In treating patients with ADHD and comorbid anxiety, the 2006 Texas Children’s Medication Algorithm for the pharmacotherapy of ADHD recommends either first treating the ADHD with a stimulant and then adding an SSRI to treat residual anxiety symptoms or treating with Strattera initially; either approach is considered acceptable as initial treatment.\(^4\)

References:

7. Strattera® capsules [prescribing information]. Indianapolis, IN: Eli Lilly and Company; February 20, 2014.

**Billing Coding/Physician Documentation Information**

N/A Brand name non-stimulant medications are considered a pharmacy benefit.

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**Additional Policy Key Words**

Policy Number: 5.01.596
Policy Implementation/Update Information

07/2014  New Policy titled ADHD Non-Stimulant Medications Step Therapy Program
07/2015  Annual Review- no changes
07/2016  Annual Review- no changes
07/2017  Annual Review- no changes

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