NEW DRUG APPROVAL

Brand Name	Xelstrym™
Generic Name	dextroamphetamine
Drug Manufacturer	Noven Pharmaceuticals Inc.

New Drug Approval

FDA approval date: March 22, 2022

Review designation: Standard

Type of review: Type 3 - New Dosage Form; New Drug Application (NDA): 215401

Dispensing restriction: N/A

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Attention Deficit-Hyperactivity Disorder (ADHD) is a psychiatric condition that has long been recognized as affecting children's ability to function. Individuals suffering from this disorder show patterns of developmentally inappropriate levels of inattentiveness, hyperactivity, or impulsivity. Although there used to be two different diagnoses of attention deficit disorder vs. attention deficit hyperactivity disorder, the DSM IV combined this into one disorder with three subtypes: predominantly inattentive, predominantly hyperactive, or combined type.

The symptoms begin at a young age and usually include lack of attention, lack of concentration, disorganization, difficulty completing tasks, being forgetful, and losing things. These symptoms should be present before the age of 12, have lasted six months, and interfere with daily life activities to be labelled as 'ADHD.' This must be present in more than one setting (i.e., at home and school, or school and after-school activities). It can have large consequences, including social interactions, increased risky behaviours, loss of jobs, and difficulty achieving in school.

The subtypes of attention deficit disorders are found to have a different rate of prevalence in a group of individuals suffering from the disorders. It is found that the inattentive subtype is prevalent in about 18.3% of the total patients while hyperactive/impulsive and combined represent 8.3% and 70%, respectively. It is also found that the inattentive subtype is more common amongst the female population. The disorders (collectively) are found in a 2:1 male to female ratio as per different research. It is prevalent in around 3%-6% of the adult population. It is one of the most prevalent disorders found in childhood. There is some evidence that ADHD is more prevalent in the United States than in other developed countries.

Efficacy

The efficacy of Xelstrym™ for the treatment of ADHD in adults and pediatric patients 6 to 17 years was established in a study with Xelstrym™ in pediatric patients and also based on adequate and well-controlled studies of lisdexamfetamine in pediatric and adult patients. Efficacy of lisdexamfetamine in the treatment of ADHD has been established in three short-term trials in pediatric patients 6 to 12 years, one short-term trial in pediatric patients 13 to 17 years, one short-term trial in pediatric patients 6 to 17 years, two short-term trials in adults 18 to 55 years, and two randomized withdrawal trials in pediatric patients 6 to 17 years and adults 18 to 55 years.

Pediatric Patients 6 to 17 years with ADHD-

The efficacy of Xelstrym™ for the treatment of ADHD in pediatric patients 6 to 17 years was evaluated in a multi-center, randomized, double-blind, placebo-controlled, cross-over design, modified analog classroom study (Study 1; NCT01711021). The study was conducted in 110 patients who met DSM-IV-TR criteria for ADHD.

Following a 5-week open-label, dose optimization phase with Xelstrym™ (4.5 mg/9 hours, 9 mg/9 hours, 13.5 mg/9 hours and 18 mg/9 hours), patients were randomized to one of two treatment sequences: 1) Xelstrym™ (optimized dose) followed by placebo, each for one week, or 2) placebo followed by Xelstrym™ (optimized dose), each for one week. Efficacy was assessed at the end of each week using the Swanson, Kotkin, Agler, M.Flynn, and Pelham (SKAMP) total score, a validated 13-item rating scale to assess manifestations of ADHD in a classroom setting. Items are specific to place (classroom setting) and time (during a typical classroom period), and the scale is used to assess multiple ratings taken within a day.

Efficacy was solely based on data from Period 1, which was the first week of the two-week double-blind, placebo-controlled, crossover treatment phase. A statistically significant separation from placebo was observed with use of Xelstrym™ in Period 1 (Table 1). Changes in SKAMP total scores assessed at pre-dose (-0.5 hours) and at 1, 2, 3, 4.5, 6, 7, 9, 10, and 12 hours post application are presented in Figure 1.

Table 1: Summary of Primary Efficacy Results: SKAMP Total Score Averaged Over Classroom Day in Pediatric Patients (6 to 17 years) with ADHD (Period 1 Data only)

Study Number	Treatment Group	Pre-Dose Score on Classroom Day[b] Mean (SD)	LS Mean[c] (SE)	Placebo-subtracted Differenced[d] (95% CI)
Study 1	Xelstrym™[a]	13.6 (5.9)	12.4 (1.2)	-4.7 (-8.0, -1.4)
	Placebo	12.7 (7.9)	17.1 (1.2)	--------

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: confidence interval

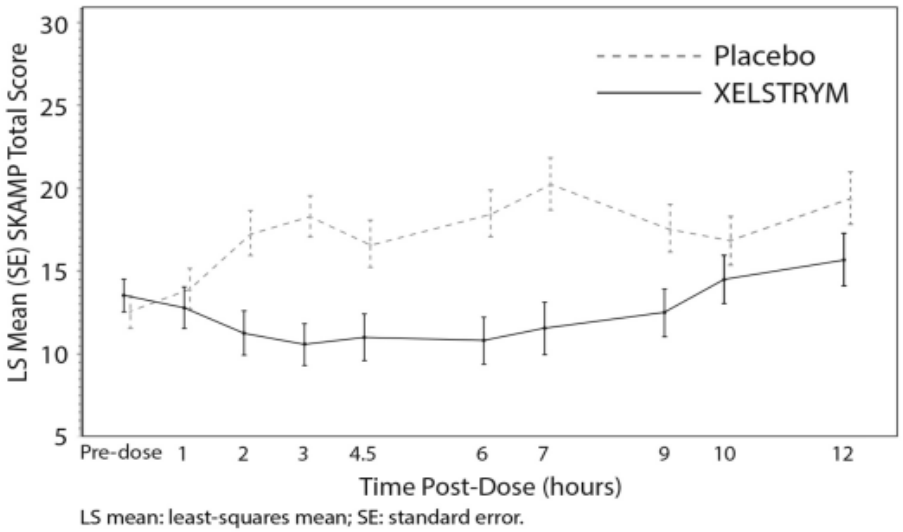
[a] Statistically significant to placebo.

[b] Pre-dose score on Period 1 classroom day.

[c] LS mean over hours 1, 2, 3, 4.5, 6, 7, 9, 10, and 12 hours post-dose on Period 1 classroom day.

[d] Difference (drug minus placebo) in least-squares means on Period 1 classroom day.

Figure 1. LS Mean SKAMP Total Score After Treatment with Xelstrym™ or Placebo in Period 1 Classroom Day in Pediatric Patients (6 to 17 years) with ADHD (Study 1)



LS mean: least-squares mean; SE: standard error.

Adhesion- Based on a clinical study in adult subjects wearing Xelstrym™ 18 mg/9 hours, 233 of 238 transdermal systems (98%) exhibited 75% or greater surface area adhesion at all timepoints evaluated (every hour) throughout the 9-hour wear period. In another study in which pediatric patients 6 to 17 years and adult patients wearing Xelstrym™ 4.5 mg/9 hours or 18 mg/9 hours were not confined to the clinical unit, 50 out of 58 transdermal systems (86%) exhibited 75% or greater surface area adhesion at 9 hours; 3 transdermal systems (5%) were reported as fully detached during the study.

Safety

ADVERSE EVENTS

The safety of Xelstrym™ for the treatment of ADHD in adults and pediatric patients 6 to 17 years is based on a study with Xelstrym™ in pediatric patients and adequate and well-controlled studies of lisdexamfetamine in adult and pediatric patients with ADHD. The safety data are from a 7-week study including a 5-week open-label dose optimization phase (n=110) followed by a 2-week randomized, parallel-group, crossover, placebo-controlled double-blind treatment phase (n=105).

Adverse Reactions Leading to Discontinuation of Treatment- In the dose-optimization phase (no placebo comparator in this phase), 2.7% (3/110) of patients treated with Xelstrym™ discontinued due to adverse reactions. These adverse reactions reported in one patient each were abdominal pain (0.9%), irritability (0.9%) and decreased appetite (0.9%). There were no discontinuations due to adverse reactions during the double-blind phase.

Adverse Reactions Occurring at an Incidence of 5% or More in Xelstrym™ Treated Pediatric Patients Ages 6 to 17 Years During Dose-optimized Treatment- Adverse reactions (incidence of ≥ 5%) that occurred during the dose-optimization phase of the clinical study include: decreased appetite (54%), insomnia1 (32%), headache (21%), irritability (16%), abdominal pain (16%) affect lability (16%), application site pain (13%), nausea (9%), application site pruritus (7%), and fatigue (5%).

Adverse Reactions Occurring at an Incidence of 2% or More of Xelstrym™-Treated Pediatric Patients Ages 6 to 17 Years During Double-blind Treatment- Adverse reactions (incidence of ≥ 2% and incidence greater than placebo) that occurred during the double-blind, placebo-controlled phase of the clinical study are shown in Table 2.

Table 2: Adverse Reactions Reported by ≥ 2% of Pediatric Patients 6 to 17 Years with ADHD Receiving Xelstrym™ and Greater Incidence Than Placebo in the Double-Blind Phase

System Organ Class Preferred Term	Xelstrym™ All Doses (n = 105)	Placebo (n = 105) %
Metabolism and nutrition disorders		
Decreased appetite	12	2
Nervous system disorders		
Headache	6	4
Psychiatric disorders		
Insomnia	8	6
Affect lability	3	0
Tic	2	0
Gastrointestinal Disorders		
Vomiting	4	0

Abdominal pain	4	2
Nausea	3	1
General disorders and administration site conditions		
Irritability	2	1
Investigations/Cardiac Disorders		
Blood pressure increased	2	1
Heart rate increased	2	0

Application Site Reactions- Based on daily patient diaries and dermal reaction scales at clinic assessments, local skin reactions were reported with Xelstrym™. During the wear time or immediately after removal of Xelstrym™, patients experienced pain, pruritus, burning sensation, erythema, discomfort, edema, and swelling. During the dose-optimization phase of the clinical study, 45% of patients reported application site discomfort associated with the use of Xelstrym™ in daily patient diaries; 72% of patients reported discomfort at clinic visit assessments; and 13% of patients reported severe discomfort at clinic visit assessments. During the dose-optimization phase, 73% of patients reported application site irritation. Application site reactions that occurred during the double-blind phase of the clinical study are presented in Table 3.

Table 3: Summary of Application Site Reactions During the Double-Blind Phase

	Xelstrym™ n/N	Placebo n/N
Discomfort		
Reported in patient diaries	8/96 (8%)	8/98 (8%)
Clinic assessments		
Any discomfort	72/104 (69%)	9/101 (9%)
Severe discomfort	10/104 (10%)	4/101 (4%)
Irritation		
Reported in patient diaries	64/103 (62%)	41/105 (39%)
Reported at Clinic assessments	97/103 (94%)	55/101 (54%)

Weight Loss and Slowing Growth Rate- In a 7-week trial of Xelstrym™ with a 5-week dose optimization phase and a 2-week crossover placebo-controlled phase in pediatric patients ages 6 to 17 years, patients had a mean weight loss from baseline of -3.1 pounds after 5 weeks of Xelstrym™.

Leukopenia and Neutropenia- In the 2-week crossover phase of the 7-week trial of Xelstrym™ in pediatric patients ages 6 to 17 years, shifts in WBCs from normal to low occurred in 10% of patients treated with Xelstrym™ and 2% of patients treated with placebo. Shifts in neutrophils from normal to low occurred in 14% of patients treated with Xelstrym™ and 6% of patients treated with placebo.

Weight Loss and Slowing Growth Rate in Pediatric Patients with ADHD with Lisdexamfetamine and Other Stimulants- In a controlled trial of lisdexamfetamine in pediatric patients 6 to 12 years, mean weight loss from baseline after 4 weeks of therapy was -0.9, -1.9, and -2.5 pounds, respectively, for patients receiving 30 mg, 50 mg, and 70 mg of lisdexamfetamine, compared to 1 pound weight gain for patients receiving placebo.

WARNINGS & PRECAUTIONS

Potential for Abuse and Dependence- CNS stimulants, including Xelstrym™, other amphetamine-containing products, and methylphenidate, have a high potential for abuse and dependence. Assess the risk of abuse prior to prescribing and monitor for signs of abuse and dependence while on therapy.

Serious Cardiovascular Reactions- Sudden death, stroke and myocardial infarction have been reported in adults with CNS stimulant treatment at recommended doses. Sudden death has been reported in pediatric patients with structural cardiac abnormalities and other serious heart problems taking CNS stimulants at recommended doses for ADHD. Avoid use in patients with known structural cardiac abnormalities, cardiomyopathy, serious heart arrhythmia, coronary artery disease, and other serious heart problems.

Blood Pressure and Heart Rate Increases- CNS stimulants cause an increase in blood pressure (mean increase about 2 to 4 mm Hg) and heart rate (mean increase about 3 to 6 bpm). Monitor all patients for potential tachycardia and hypertension.

Psychiatric Adverse Reactions- CNS stimulants may exacerbate symptoms of behaviour disturbance and thought disorder in patients with a pre-existing psychotic disorder. CNS stimulants may induce a mixed/manic episode in patients with bipolar disorder. Prior to initiating treatment, screen patients for risk factors for developing a manic episode (e.g., comorbid or history of depressive symptoms or a family history of suicide, bipolar disorder, and depression). CNS stimulants, at recommended doses, may cause psychotic or manic symptoms (e.g., hallucinations, delusional thinking, or mania) in patients without a prior history of psychotic illness or mania. If such symptoms occur, consider discontinuing Xelstrym™.

Suppression of Growth- CNS stimulants have been associated with weight loss and slowing of growth rate in pediatric patients. Closely monitor growth (weight and height) in pediatric patients treated with CNS stimulants, including Xelstrym™. Patients who are not growing or gaining height or weight as expected may need to have their treatment interrupted. Xelstrym™ is not approved for use in pediatric patients below 6 years of age.

Peripheral Vasculopathy, including Raynaud's Phenomenon- Stimulants, including Xelstrym™, are associated with peripheral vasculopathy, including Raynaud's phenomenon. Signs and symptoms are usually intermittent and mild; however, very rare sequelae include digital ulceration and/or soft tissue breakdown. Effects of peripheral vasculopathy, including Raynaud's phenomenon, were observed in post-marketing reports at different times and at therapeutic doses in all age groups throughout the course of treatment. Signs and symptoms generally improve after reduction in dose or discontinuation of drug.

Serotonin Syndrome- Serotonin syndrome, a potentially life-threatening reaction, may occur when amphetamines are used in combination with other drugs that affect the serotonergic neurotransmitter systems such as monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, and St. John's Wort. The co-administration with cytochrome P450 2D6 (CYP2D6) inhibitors may also increase the risk with increased exposure to Xelstrym™.

Contact Sensitization- Use of Xelstrym™ may lead to contact sensitization (allergic contact dermatitis). Erythema is commonly seen with use of Xelstrym™ and is not by itself an indication of sensitization. However, contact sensitization should be suspected if erythema is accompanied by evidence of a more intense local reaction (edema, papules, vesicles) that does not significantly improve within 48 hours or spreads beyond the application site.

Application Site Reactions- Local skin reactions, such as pain, pruritus, burning sensation, erythema, discomfort, edema, and/or swelling were reported during the wear time or immediately after removal of Xelstrym™.

Use of External Heat- When heat is applied to Xelstrym™ after application, both the rate and extent of absorption are increased. After application of a heating pad, amphetamine exposure (AUC0-9h) was about 1.5- times greater than without heating pad application.

CONTRAINDICATIONS

- Known hypersensitivity to amphetamine products or other components of Xelstrym™. Anaphylactic reactions, Stevens-Johnson Syndrome, angioedema, and urticaria have been observed in post marketing reports.
- Patients taking monoamine oxidase inhibitors (MAOI), or within 14 days of stopping MAOIs (including MAOIs such as linezolid or intravenous methylene blue), because of an increased risk of hypertensive crisis.

Clinical Pharmacology

MECHANISMS OF ACTION

Amphetamines are non-catecholamine sympathomimetic amines with CNS stimulant activity. The exact mode of therapeutic action in ADHD is not known.

Dose & Administration

ADULTS

Apply one transdermal system at a time for not more than 9 hours. Use only one per 24 hours. Starting dose in adults is 9 mg per 9 hours. Dosage may be adjusted up to a maximum recommended dose of 18 mg per 9 hours.

PEDIATRICS

Apply one transdermal system at a time for not more than 9 hours. Use only one per 24 hours. Starting dose in n pediatric patients 6 to 17 years is 4.5 mg per 9 hours. Dosage may be adjusted in weekly increments of 4.5 mg up to a maximum recommended dose of 18 mg per 9 hours.

GERIATRICS

None.

RENAL IMPAIRMENT

In patients with severe renal impairment (GFR 15 to < 30 mL/min/1.73 m^2), the maximum dose should not exceed 13.5 mg per 9 hours. The maximum recommended dose in end stage renal disease (GFR < 15 mL/min/1.73 m^2) patients is 9 mg per 9 hours.

HEPATIC IMPAIRMENT

None.

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Transdermal system: 4.5 mg/9 hours, 9 mg/9 hours, 13.5 mg/9 hours, 18 mg/9 hours.