

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use KAPVAY safely and effectively. See full prescribing information for KAPVAY.

KAPVAY (clonidine hydrochloride) extended-release tablets, oral **Initial U.S. Approval: 1974**

-----INDICATIONS AND USAGE-----

KAPVAY™ is a centrally acting alpha₂-adrenergic agonist indicated for the treatment of attention deficit hyperactivity disorder (ADHD) as monotherapy or as adjunctive therapy to stimulant medications. (1)

The efficacy of KAPVAY is based on the results of two clinical trials in children and adolescents. (14) Maintenance efficacy has not been systematically evaluated, and patients who are continued on longer-term treatment require periodic reassessment. (1)

This extended-release formulation of clonidine hydrochloride is also approved for the treatment of hypertension under the trade name JENLOGA. (1)

-----DOSAGE AND ADMINISTRATION-----

Dosing should be initiated with one 0.1 mg tablet at bedtime, and the daily dosage should be adjusted in increments of 0.1 mg/day at weekly intervals until the desired response is achieved. Doses should be taken twice a day, with either an equal or higher split dosage being given at bedtime, as depicted below (2.1)

Total Daily Dose	Morning Dose	Bedtime Dose
0.1 mg/day		0.1 mg
0.2 mg/day	0.1 mg	0.1 mg
0.3 mg/day	0.1 mg	0.2 mg
0.4 mg/day	0.2 mg	0.2 mg

- Tablets should not be crushed, chewed or broken before swallowing. (2.1)
- Do not substitute for other clonidine products on a mg-per-mg basis, because of differing pharmacokinetic profiles. (2.1)
- When discontinuing, taper the dose in decrements of no more than 0.1 mg every 3 to 7 days. (2.4)

-----DOSAGE FORMS AND STRENGTHS-----

Extended-release tablets: 0.1 mg and 0.2 mg, not scored. (3)

-----CONTRAINDICATIONS-----

Clonidine hydrochloride tablets should not be used in patients with known hypersensitivity to clonidine. (4)

-----WARNINGS AND PRECAUTIONS-----

- Hypotension/bradycardia: Use KAPVAY with caution in patients at risk for hypotension, bradycardia, and heart block. Measure heart rate and blood pressure prior to initiation of therapy, following dose increases, and periodically while on therapy. Advise patients to avoid becoming dehydrated or overheated. (5.1)
- Somnolence/Sedation: Has been observed with KAPVAY. Consider the potential for additive sedative effects with CNS depressant drugs. Caution

patients against operating heavy equipment or driving until they know how they respond to KAPVAY. (5.2)

- Abrupt Discontinuation: Patients should be instructed not to discontinue KAPVAY therapy without consulting their physician due to the potential risk of withdrawal effects. KAPVAY should be discontinued slowly in decrements of no more than 0.1 mg every 3 to 7 days. (5.3)
- Allergic Reactions: In patients who have developed localized contact sensitization or other allergic reaction to clonidine in a transdermal system, substitution of oral clonidine hydrochloride therapy may be associated with the development of a generalized skin rash, urticaria, or angioedema. (5.4)
- Use in patients with vascular disease, cardiac conduction disease, or chronic renal failure: Monitor carefully and uptitrate slowly. (5.5)
- Other clonidine containing products: Do not use KAPVAY concomitantly with other products containing clonidine, (e.g. Catapres®). (5.6)

-----ADVERSE REACTIONS-----

Common and drug related adverse reactions (incidence at least 5% and twice the rate of placebo) reported with the use of KAPVAY include (6.1):
Somnolence, fatigue, upper respiratory tract infection (cough, rhinitis, sneezing), irritability, throat pain (sore throat), insomnia, nightmares, emotional disorder, constipation, nasal congestion, increased body temperature, dry mouth, and ear pain.

To report SUSPECTED ADVERSE REACTIONS, contact Shionogi Pharma, Inc. at 1-800-849-9707 ext. 1454 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

-----DRUG INTERACTIONS-----

- Sedating Drugs: Clonidine may potentiate the CNS-depressive effects of alcohol, barbiturates or other sedating drugs. (7.1)
- Tricyclic Antidepressants: May reduce the hypotensive effect of clonidine. (7.2)
- Drugs Known to Affect Sinus Node Function or AV Nodal Conduction: Caution is warranted in patients receiving clonidine concomitantly with agents known to affect sinus node function or AV nodal conduction (e.g., digitalis, calcium channel blockers and beta-blockers) due to a potential for additive effects such as bradycardia and AV block. (7.3)
- Use with other products containing clonidine: Do not use KAPVAY concomitantly with other products containing clonidine (e.g. Catapres®). (7.4)
- Antihypertensive drugs: Use caution when coadministered with KAPVAY. (7.5)

-----USE IN SPECIFIC POPULATIONS-----

- Since clonidine hydrochloride is excreted in human milk, caution should be exercised when KAPVAY is administered to a nursing woman. (8.3)
- KAPVAY has not been studied in children less than 6 years old. (8.4)
- Renal Insufficiency: The dosage of KAPVAY must be adjusted according to the degree of impairment, and patients should be carefully monitored. (8.6)

See page XX for Patient Counseling Information

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FULL PRESCRIBING INFORMATION

1. INDICATIONS AND USAGE

KAPVAY™ (clonidine hydrochloride) extended-release is indicated for the treatment of attention deficit hyperactivity disorder (ADHD) as monotherapy and as adjunctive therapy to stimulant medications.

The efficacy of KAPVAY in the treatment of ADHD is based on two controlled trials (one monotherapy and one adjunctive to stimulant medication) in children and adolescents ages 6-17 who met DSM-IV criteria for ADHD hyperactive or combined hyperactive/inattentive subtypes [see Clinical Studies (14)]. In the adjunctive study, KAPVAY was administered to patients who had been on a stable regimen of either methylphenidate or amphetamine (or their derivatives) and who had not achieved an optimal response. The effectiveness of KAPVAY for longer-term use (more than 5 weeks) has not been systematically evaluated in controlled trials.

A diagnosis of ADHD implies the presence of hyperactive-impulsive and/or inattentive symptoms that cause impairment and were present before the age of 7 years. The symptoms must cause clinically significant impairment, e.g., in social, academic, or occupational functioning, and be present in two or more settings, e.g., school (or work) and at home. The symptoms must not be better accounted for by another mental disorder. For the Inattentive Type, at least six of the following symptoms must have persisted for at least 6 months: lack of attention to details/careless mistakes; lack of sustained attention; poor listener; failure to follow through on tasks; poor organization; avoids tasks requiring sustained mental effort; loses things; easily distracted; forgetful. For the Hyperactive-Impulsive Type, at least six of the following symptoms must have persisted for at least 6 months: fidgeting/squirming; leaving seat; inappropriate running/climbing; difficulty with quiet activities; "on the go"; excessive talking; blurting answers; can't wait turn; intrusive. The Combined Type requires both inattentive and hyperactive-impulsive criteria to be met.

Special Diagnostic Considerations

Specific etiology of this syndrome is unknown, and there is no single diagnostic test. Adequate diagnosis requires the use not only of medical but also of special psychological, educational, and social resources. Learning may or may not be impaired. The diagnosis must be based upon a complete history and evaluation of the patient and not solely on the presence of the required number of DSM-IV® characteristics.

Need for Comprehensive Treatment program

KAPVAY is indicated as an integral part of a total treatment program for ADHD that may include other measures (psychological, educational, and social) for patients with this syndrome. Drug treatment may not be indicated for all patients with this syndrome. KAPVAY is not intended for use in patients who exhibit symptoms secondary to environmental factors and/or other primary psychiatric disorders, including psychosis. Appropriate educational/vocational placement is essential and psychosocial intervention is often helpful. When remedial measures alone are insufficient, the decision to prescribe KAPVAY will depend upon the physician's assessment of the chronicity and severity of the patient's symptoms and on the level of functional impairment.

NOTE: This extended-release formulation of clonidine hydrochloride is also approved for the treatment of hypertension in adults under the trade name JENLOGA.

2. DOSAGE AND ADMINISTRATION

KAPVAY is an extended-release tablet formulation of clonidine hydrochloride. While it is dosed twice a day, the same as the immediate-release clonidine formulation, it is not to be used interchangeably with the immediate-release formulation.

2.1 General Dosing Information

KAPVAY is an extended-release tablet and, therefore, must be swallowed whole and never crushed, cut or chewed. KAPVAY may be taken with or without food.

Due to the lack of controlled clinical trial data and differing pharmacokinetic profiles, substitution of KAPVAY for other clonidine products on a mg-per-mg basis is not recommended.

2.2 Dose Selection

The dose of KAPVAY, administered either as monotherapy or as adjunctive therapy to a psychostimulant, should be individualized according to the therapeutic needs and response of the patient. Dosing should be initiated with one 0.1 mg tablet at bedtime, and the daily dosage should be adjusted in increments of 0.1 mg/day at weekly intervals until the desired response is achieved. Doses should be taken twice a day, with either an equal or higher split dosage being given at bedtime (see Table 1).

Table 1 KAPVAY Dosing Guidance

Total Daily Dose	Morning Dose	Bedtime Dose
0.1 mg/day		0.1 mg
0.2 mg/day	0.1 mg	0.1 mg
0.3 mg/day	0.1 mg	0.2 mg
0.4 mg/day	0.2 mg	0.2 mg

Doses of KAPVAY higher than 0.4 mg/day (0.2 mg twice daily) were not evaluated in clinical trials for ADHD and are not recommended.

When KAPVAY is being added-on to a psychostimulant, the dose of the psychostimulant can be adjusted depending on the patient's response to KAPVAY.

2.3 Maintenance Treatment

The effectiveness of KAPVAY for longer-term use (more than 5 weeks) has not been systematically evaluated in controlled trials. Therefore the physician electing to use KAPVAY for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

2.4 Discontinuation

When discontinuing KAPVAY, the total daily dose should be tapered in decrements of no more than 0.1 mg every 3 to 7 days.

3. DOSAGE FORM AND STRENGTHS

KAPVAY tablets are available in two strengths, 0.1 mg and 0.2 mg as an extended-release formulation. Both the 0.1 mg and 0.2 mg tablets are white, non-scored, standard convex with debossing on one side. The 0.1 mg tablets are round and the 0.2 mg tablets are oval. KAPVAY tablets must be swallowed whole and never crushed, cut or chewed.

4. CONTRAINDICATIONS

KAPVAY should not be used in patients with known hypersensitivity to clonidine.

5. WARNINGS AND PRECAUTIONS

5.1 Hypotension/Bradycardia

Treatment with KAPVAY can cause dose related decreases in blood pressure and heart rate. In patients that completed 5 weeks of treatment in a controlled, fixed-dose monotherapy study in pediatric patients, during the treatment period the maximum placebo-subtracted mean change in systolic blood pressure was -4.0 mmHg on KAPVAY 0.2 mg/day and -8.8 mmHg on KAPVAY 0.4 mg/day. The maximum placebo-subtracted mean change in diastolic blood pressure was -4.0 mmHg on KAPVAY 0.2 mg/day and -7.3 mmHg on KAPVAY 0.4 mg/day. The maximum placebo-subtracted mean change in heart rate was -4.0 beats per minute on KAPVAY 0.2 mg/day and -7.7 beats per minute on KAPVAY 0.4 mg/day.

During the taper period of the fixed-dose monotherapy study the maximum placebo-subtracted mean change in systolic blood pressure was +3.4 mmHg on KAPVAY 0.2 mg/day and -5.6 mmHg on KAPVAY 0.4 mg/day. The maximum placebo-subtracted mean change in diastolic blood pressure was +3.3 mmHg on KAPVAY 0.2 mg/day and -5.4 mmHg on KAPVAY 0.4 mg/day. The maximum placebo-subtracted mean change in heart rate was -0.6 beats per minute on KAPVAY 0.2 mg/day and -3.0 beats per minute on KAPVAY 0.4 mg/day.

Measure heart rate and blood pressure prior to initiation of therapy, following dose increases, and periodically while on therapy. Use KAPVAY with caution in patients with a history of hypotension, heart block, bradycardia, or cardiovascular disease, because it can decrease blood pressure and heart rate. Use caution in treating patients who have a history of syncope or may have a condition that predisposes them to syncope, such as hypotension, orthostatic hypotension, bradycardia, or dehydration. Use KAPVAY 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. Advise patients to avoid becoming dehydrated or overheated.

5.2 Sedation and Somnolence

Somnolence and sedation were commonly reported adverse reactions in clinical studies. In patients that completed 5 weeks of therapy in a controlled fixed dose pediatric monotherapy study, 31% of patients treated with 0.4 mg/day and 38% treated with 0.2 mg/day vs 7% of placebo treated patients reported somnolence as an adverse event. In patients that completed 5 weeks of therapy in a controlled flexible dose pediatric adjunctive to stimulants study, 19% of patients treated with KAPVAY+stimulant vs 8% treated with placebo+stimulant reported somnolence. Before using KAPVAY with other centrally active depressants (such as phenothiazines, barbiturates, or benzodiazepines), consider the potential for additive sedative effects. Caution patients against operating heavy equipment or driving until they know how they respond to treatment with KAPVAY. Advise patients to avoid use with alcohol.

5.3 Abrupt Discontinuation

No studies evaluating abrupt discontinuation of KAPVAY in children with ADHD have been conducted. In children and adolescents with ADHD, physicians should gradually reduce the dose of KAPVAY in decrements of no more than 0.1 mg every 3 to 7 days. Patients should be instructed not to discontinue KAPVAY therapy without consulting their physician due to the potential risk of withdrawal effects.

In adults with hypertension, sudden cessation of clonidine hydrochloride extended-release formulation treatment in the 0.2 to 0.6 mg/day range resulted in reports of headache, tachycardia, nausea, flushing, warm feeling, brief lightheadedness, tightness in chest, and anxiety.

In adults with hypertension, sudden cessation of treatment with immediate-release clonidine has, in some cases, resulted in symptoms such as nervousness, agitation, headache, and tremor

accompanied or followed by a rapid rise in blood pressure and elevated catecholamine concentrations in the plasma.

5.4 Allergic Reactions

In patients who have developed localized contact sensitization to clonidine transdermal system, continuation of clonidine transdermal system or substitution of oral clonidine hydrochloride therapy may be associated with the development of a generalized skin rash.

In patients who develop an allergic reaction from clonidine transdermal system, substitution of oral clonidine hydrochloride may also elicit an allergic reaction (including generalized rash, urticaria, or angioedema).

5.5 Patients with Vascular Disease, Cardiac Conduction Disease, or Renal Failure

Clonidine hydrochloride should be used with caution in patients with severe coronary insufficiency, conduction disturbances, recent myocardial infarction, cerebrovascular disease or chronic renal failure.

5.6 Other Clonidine-Containing Products

Clonidine, the active ingredient in KAPVAY, is also approved as an antihypertensive. Do not use KAPVAY in patients concomitantly taking other clonidine-containing products, (e.g. Catapres®).

6. ADVERSE REACTIONS

6.1 Clinical Trial Experience

Two KAPVAY ADHD clinical studies evaluated 256 patients who received active therapy, in one of the two placebo-controlled studies (Studies 1 and 2) with primary efficacy end-points at 5-weeks.

Study 1: Fixed-dose KAPVAY Monotherapy

Study 1 was a multi-center, randomized, double-blind, placebo-controlled study with primary efficacy endpoint at 5 weeks, of two fixed doses (0.2 mg/day or 0.4 mg/day) of KAPVAY in children and adolescents (6 to 17 years of age) who met DSM-IV criteria for ADHD hyperactive or combined inattentive/hyperactive subtypes.

Commonly observed adverse reactions (incidence of $\geq 2\%$ in either active treatment group and greater than the rate on placebo) during the treatment period are listed in Table 2.

Table 2 Common Adverse Reactions in the Fixed-Dose Monotherapy Trial- Treatment period (Study 1)

Preferred Term	Percentage of Patients Reporting Event		
	KAPVAY 0.4 mg/day N=78	KAPVAY 0.2 mg/day N=76	Placebo (N=76)
Somnolence ¹	31%	38%	5%
Headache	19%	29%	18%
Upper Abdominal Pain	13%	20%	17%
Fatigue ²	13%	16%	1%
Upper Respiratory Tract Infection	6%	11%	4%
Irritability	6%	9%	3%

Table 2 Common Adverse Reactions in the Fixed-Dose Monotherapy Trial- Treatment period (Study 1)

Throat Pain	6%	8%	3%
Nausea	8%	5%	4%
Nightmare	9%	3%	0
Dizziness	3%	7%	5%
Insomnia	6%	4%	1%
Emotional Disorder	5%	4%	1%
Constipation	6%	1%	0
Dry Mouth	5%	0	1%
Nasal Congestion	5%	3%	1%
Body Temperature Increased	1%	5%	3%
Gastrointestinal Viral	0%	7%	4%
Diarrhea	1%	4%	3%
Ear Pain	0	5%	1%
Nasopharyngitis	3%	3%	1%
Abnormal Sleep-Related Event	1%	3%	0
Aggression	1%	3%	1%
Asthma	1%	3%	1%
Bradycardia	4%	0	0
Enuresis	4%	0	0
Influenza like Illness	3%	1%	1%
Tearfulness	3%	1%	0
Thirst	3%	1%	0
Tremor	3%	1%	0
Epistaxis	0	3%	0
Lower Respiratory Tract Infection	0	3%	1%
Pollakiuria	0	3%	0
Sleep Terror	0	3%	0

1. Somnolence includes the terms “somnolence” and “sedation”.
2. Fatigue includes the terms “fatigue” and “lethargy”.

Commonly observed adverse reactions (incidence of $\geq 2\%$ in either active treatment group and greater than the rate on placebo) during the taper period are listed in Table 3.

Table 3 Common Adverse Reactions in the Fixed-Dose Monotherapy Trial- Taper period* (Study 1)

Preferred Term	Percentage of Patients Reporting Event		
	KAPVAY 0.4 mg/day N=78	KAPVAY 0.2 mg/day N=76	Placebo (N=76)
Abdominal Pain Upper	6%	0	3%
Headache	2%	5%	3%
Gastrointestinal Viral	5%	0	0
Somnolence	3%	2%	0
Heart Rate Increased	3%	0	0
Otitis Media Acute	0	3%	0

*Taper Period: 0.2 mg dose, week 8; 0.4 mg dose, weeks 6-8; Placebo dose, weeks 6-8

Study 2: Flexible-dose KAPVAY as Adjunctive Therapy to Psychostimulants

Study 2 was a multi-center, randomized, double-blind, placebo-controlled study, with primary efficacy endpoint at 5 weeks, of a flexible dose of KAPVAY as adjunctive therapy to a psychostimulant in children and adolescents (6 to 17 years) who met DSM-IV criteria for ADHD hyperactive or combined

inattentive/hyperactive subtypes. KAPVAY was initiated at 0.1 mg/day and titrated up to 0.4 mg/day over a 3-week period. Most KAPVAY treated patients (75.5%) were escalated to the maximum dose of 0.4 mg/day.

Commonly observed adverse reactions (incidence of $\geq 2\%$ in the treatment group and greater than the rate on placebo) during the treatment period are listed in Table 4.

Table 4 Common Adverse Reactions in the Flexible-Dose Adjunctive to Stimulant Therapy Trial- Treatment Period (Study 2)

Preferred Term	Percentage of Patients Reporting Event	
	KAPVAY+STM (N=102)	PBO+STM (N=96)
Somnolence ¹	19%	8%
Fatigue ²	16%	4%
Abdominal Pain Upper	12%	7%
Nasal Congestion	6%	5%
Throat Pain	6%	3%
Decreased Appetite	5%	4%
Body Temperature Increased	4%	2%
Dizziness	4%	2%
Insomnia	4%	2%
Epistaxis	3%	0
Rhinorrhea	3%	0
Abdominal Pain	2%	1%
Anxiety	2%	0
Pain in Extremity	2%	0

1. Somnolence includes the terms: "somnolence" and "sedation".
2. Fatigue includes the terms "fatigue" and "lethargy".

Commonly observed adverse reactions (incidence of $\geq 2\%$ in the treatment group and greater than the rate on placebo) during the taper period are listed in Table 5.

Table 5 Common Adverse Reactions in the Flexible-Dose Adjunctive to Stimulant Therapy Trial- Taper Period* (Study 2)

Preferred Term	Percentage of Patients Reporting Event	
	KAPVAY+STM (N=102)	PBO+STM (N=96)
Nasal Congestion	4%	2%
Headache	3%	1%
Irritability	3%	2%
Throat Pain	3%	1%
Gastroenteritis Viral	2%	0
Rash	2%	0

*Taper Period: weeks 6-8

Most common adverse reactions, defined as events that were reported in at least 5% of drug-treated patients and at least twice the rate as in placebo patients, during the treatment period were somnolence, fatigue, upper respiratory tract infection, irritability, throat pain, insomnia, nightmares, emotional disorder, constipation, nasal congestion, increased body temperature, dry mouth, and ear pain. The most common adverse reactions that were reported during the taper phase were upper abdominal pain and gastrointestinal virus.

Adverse Reactions Leading to Discontinuation

Thirteen percent (13%) of patients receiving KAPVAY discontinued from the pediatric monotherapy study due to adverse events, compared to 1% in the placebo group. The most common adverse reactions leading to discontinuation of KAPVAY monotherapy treated patients were from somnolence/sedation (5%) and fatigue (4%). Less common adverse reactions leading to discontinuation (occurring in approximately 1% of patients) included: formication, vomiting, prolonged QT, increased heart rate, and rash. In the pediatric adjunctive treatment to stimulants study, one patient discontinued from KAPVAY + stimulant group because of bradyphrenia.

Effects on Laboratory Tests, Vital Signs, and Electrocardiograms

KAPVAY treatment was not associated with any clinically important effects on any laboratory parameters in either of the placebo-controlled studies.

Mean decreases in blood pressure and heart rate were seen [see Warnings and Precautions (5.1)].

There were no changes on ECGs to suggest a drug-related effect.

7. DRUG INTERACTIONS

No drug interaction studies have been conducted with KAPVAY in children. The following have been reported with other oral immediate release formulations of clonidine.

7.1 Interactions with CNS-depressant Drugs

Clonidine may potentiate the CNS-depressive effects of alcohol, barbiturates or other sedating drugs.

7.2 Interactions with Tricyclic Antidepressants

If a patient is receiving clonidine hydrochloride and also taking tricyclic antidepressants the hypotensive effects of clonidine may be reduced.

7.3 Interactions with Drugs Known to Affect Sinus Node Function or AV Nodal Conduction

Due to a potential for additive effects such as bradycardia and AV block, caution is warranted in patients receiving clonidine concomitantly with agents known to affect sinus node function or AV nodal conduction (e.g., digitalis, calcium channel blockers and beta-blockers).

7.4 Use with other products containing clonidine

Do not use KAPVAY concomitantly with other products containing clonidine (e.g. Catapres®).

7.5 Antihypertensive Drugs

Use caution when KAPVAY is administered concomitantly with antihypertensive drugs, due to the potential for additive pharmacodynamic effects (e.g., hypotension, syncope) [see *Warnings and Precautions* (5.2)].

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C: Oral administration of clonidine hydrochloride to pregnant rabbits during the period of embryo/fetal organogenesis at doses of up to 80 mcg/kg/day (approximately 3 times the oral maximum recommended daily dose [MRHD] of 0.4 mg/day on a mg/m² basis) produced no evidence of teratogenic or embryotoxic potential. In pregnant rats, however, doses as low as 15 mcg/kg/day (1/3 the MRHD on a mg/m² basis) were associated with increased resorptions in a study in which dams were treated continuously from 2 months prior to mating and throughout gestation. Increased resorptions were not associated with treatment at the same or at higher dose levels (up to 3 times the MRHD) when treatment of the dams was restricted to gestation days 6-15. Increases in resorptions were observed in both rats and mice at 500 mcg/kg/day (10 and 5 times the MRHD in rats and mice, respectively) or higher when the animals were treated on gestation days 1-14; 500 mcg/kg/day was the lowest dose employed in this study. No adequate and well-controlled studies have been conducted in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should not be used during pregnancy unless clearly needed.

8.3 Nursing Mothers

Since clonidine hydrochloride is excreted in human milk, caution should be exercised when KAPVAY is administered to a nursing woman.

8.4 Pediatric Use

A study was conducted in which young rats were treated orally with clonidine hydrochloride from day 21 of age to adulthood at doses of up to 300 mcg/kg/day, which is approximately 3 times the maximum recommended human dose (MRHD) of 0.4 mg/day on a mg/m² basis. A slight delay in onset of preputial separation was seen in males treated with the highest dose (with a no-effect dose of 100 mcg/kg/day, which is approximately equal to the MRHD), but there were no drug effects on fertility or on other measures of sexual or neurobehavioral development.

KAPVAY has not been studied in children with ADHD less than 6 years old.

8.6 Patients with Renal Impairment

The impact of renal impairment on the pharmacokinetics of clonidine in children has not been assessed. The initial dosage of KAPVAY should be based on degree of impairment. Monitor patients carefully for hypotension and bradycardia, and titrate to higher doses cautiously. Since only a minimal amount of clonidine is removed during routine hemodialysis, there is no need to give supplemental KAPVAY following dialysis.

8.7 Adult Use in ADHD

KAPVAY has not been studied in adult patients with ADHD.

9.0 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

KAPVAY is not a controlled substance and has no known potential for abuse or dependence.

10. OVERDOSAGE

Symptoms

Clonidine overdose: hypertension may develop early and may be followed by hypotension, bradycardia, respiratory depression, hypothermia, drowsiness, decreased or absent reflexes, weakness, irritability and miosis. The frequency of CNS depression may be higher in children than adults. Large overdoses may result in reversible cardiac conduction defects or dysrhythmias, apnea, coma and seizures. Signs and symptoms of overdose generally occur within 30 minutes to two hours after exposure.

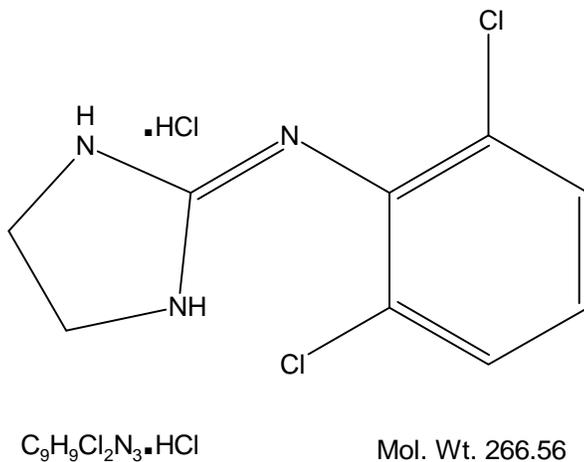
Treatment

Consult with a Certified Poison Control Center for up-to-date guidance and advice.

11. DESCRIPTION

KAPVAY (clonidine hydrochloride) extended-release is a centrally acting α_2 -adrenergic agonist available as 0.1 mg or 0.2 mg extended-release tablets for oral administration. Each 0.1 mg and 0.2 mg tablet is equivalent to 0.087 mg and 0.174 mg, respectively, of the free base.

The inactive ingredients are sodium lauryl sulfate, lactose monohydrate, hypromellose type 2208, partially pregelatinized starch, colloidal silicon dioxide, and magnesium stearate. The formulation is designed to delay the absorption of active drug in order to decrease peak to trough plasma concentration differences. Clonidine hydrochloride is an imidazoline derivative and exists as a mesomeric compound. The chemical name is 2-(2,6-dichlorophenylamino)-2-imidazoline hydrochloride. The following is the structural formula:



Clonidine hydrochloride is an odorless, bitter, white, crystalline substance soluble in water and alcohol.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Clonidine stimulates α_2 -adrenergic receptors in the brain. Clonidine is not a central nervous system stimulant. The mechanism of action of clonidine in ADHD is not known.

12.2 Pharmacodynamics

Clonidine is a known antihypertensive agent. By stimulating alpha₂-adrenergic receptors in the brain stem, clonidine reduces sympathetic outflow from the central nervous system and decreases peripheral resistance, renal vascular resistance, heart rate, and blood pressure.

12.3 Pharmacokinetics

Single-dose Pharmacokinetics in Adults

Immediate-release clonidine hydrochloride and KAPVAY have different pharmacokinetic characteristics; dose substitution on a milligram for milligram basis will result in differences in exposure. A comparison across studies suggests that the C_{max} is 50% lower for KAPVAY compared to immediate-release clonidine hydrochloride.

Following oral administration of an immediate release formulation, plasma clonidine concentration peaks in approximately 3 to 5 hours and the plasma half-life ranges from 12 to 16 hours. The half-life increases up to 41 hours in patients with severe impairment of renal function. Following oral administration about 40-60% of the absorbed dose is recovered in the urine as unchanged drug in 24 hours. About 50% of the absorbed dose is metabolized in the liver. Although studies of the effect of renal impairment and studies of clonidine excretion have not been performed with KAPVAY, results are likely to be similar to those of the immediate release formulation.

The pharmacokinetic profile of KAPVAY administration was evaluated in an open-label, three-period, randomized, crossover study of 15 healthy adult subjects who received three single dose regimens of clonidine: 0.1 mg of KAPVAY under fasted conditions, 0.1 mg of KAPVAY following a high fat meal, and 0.1 mg of clonidine immediate-release (Catapres[®]) under fasted conditions. Treatments were separated by one-week washout periods.

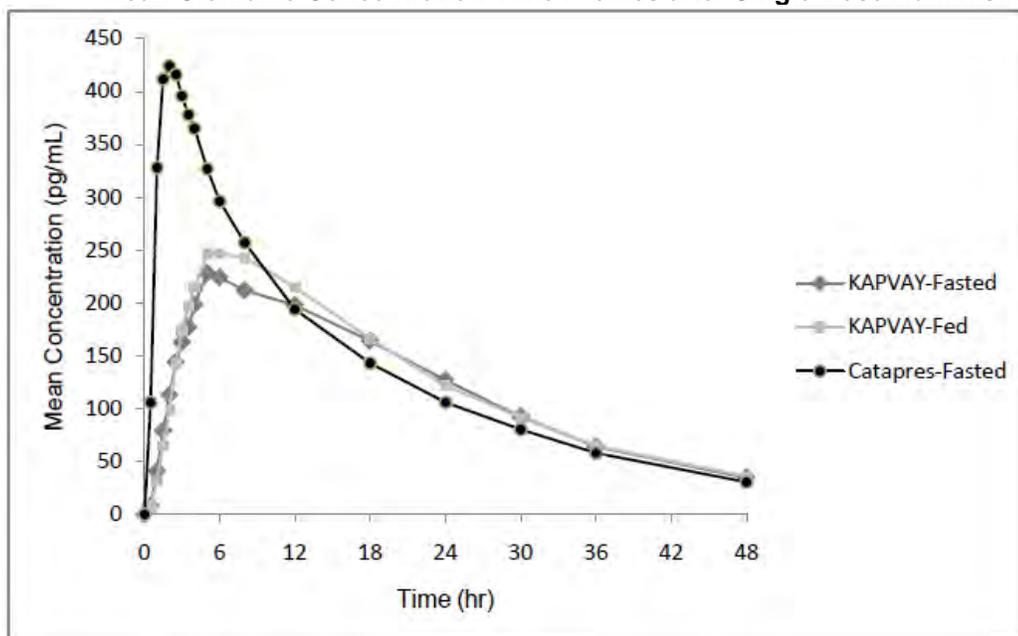
Mean concentration-time data from the 3 treatments are shown in Table 6 and Figure 1. After administration of KAPVAY, maximum clonidine concentrations were approximately 50% of the Catapres maximum concentrations and occurred approximately 5 hours later relative to Catapres. Similar elimination half-lives were observed and total systemic bioavailability following KAPVAY was approximately 89% of that following Catapres.

Food had no effect on plasma concentrations, bioavailability, or elimination half-life.

Table 6 Pharmacokinetic Parameters of Clonidine in Healthy Adult Volunteers

Parameter	CATAPRES-Fasted n=15		KAPVAY-Fed n=15		KAPVAY-Fasted n=14	
	Mean	SD	Mean	SD	MEAN	SD
C _{max} (pg/mL)	443	59.6	235	34.7	258	33.3
AUC _{inf} (hr*pg/mL)	7313	1812	6505	1728	6729	1650
hT _{max} (hr)	2.07	0.5	6.80	3.61	6.50	1.23
T _{1/2} (hr)	12.57	3.11	12.67	3.76	12.65	3.56

Figure 1 Mean Clonidine Concentration-Time Profiles after Single Dose Administration



Multiple-dose Pharmacokinetics in Children and Adolescents

Plasma clonidine concentrations in children and adolescents (0.1 mg bid and 0.2 mg bid) with ADHD are greater than those of adults with hypertension with children and adolescents receiving higher doses on a mg/kg basis. Body weight normalized clearance (CL/F) in children and adolescents was higher than CL/F observed in adults with hypertension. Clonidine concentrations in plasma increased with increases in dose over the dose range of 0.2 to 0.4 mg/day. Clonidine CL/F was independent of dose administered over the 0.2 to 0.4 mg/day dose range. Clonidine CL/F appeared to decrease slightly with increases in age over the range of 6 to 17 years, and females had a 23% lower CL/F than males. The incidence of “sedation-like” AEs (somnolence and fatigue) appeared to be independent of clonidine dose or concentration within the studied dose range in the titration study. Results from the add-on study showed that clonidine CL/F was 11% higher in patients who were receiving methylphenidate and 44% lower in those receiving amphetamine compared to subjects not on adjunctive therapy.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis and Impairment of Fertility

Clonidine HCl was not carcinogenic when administered in the diet of rats (for up to 132 weeks) or mice (for up to 78 weeks) at doses of up to 1620 (male rats), 2040 (female rats), or 2500 (mice) mcg/kg/day. These doses are approximately 20, 25, and 15 times, respectively, the maximum recommended human dose (MRHD) of 0.4 mg/day on a mg/m² basis.

There was no evidence of genotoxicity in the Ames test for mutagenicity or mouse micronucleus test for clastogenicity.

Fertility of male or female rats was unaffected by clonidine HCl doses as high as 150 mcg/kg/day (approximately 3 times the MRDHD on a mg/m² basis). In a separate experiment, fertility of female rats appeared to be adversely affected at dose levels of 500 and 2000 mcg/kg/day (10 and 40 times the MRHD on a mg/m² basis).

13.2 Ocular Toxicity

In several studies with oral clonidine hydrochloride, a dose-dependent increase in the incidence and severity of spontaneous retinal degeneration was seen in albino rats treated for six months or longer. Tissue distribution studies in dogs and monkeys showed a concentration of clonidine in the choroid. In combination with amitriptyline, clonidine hydrochloride administration led to the development of corneal lesions in rats within 5 days.

In view of the retinal degeneration seen in rats, eye examinations were performed during clinical trials in 908 adult patients before, and periodically after, the start of clonidine therapy for hypertension. In 353 of these 908 patients, the eye examinations were carried out over periods of 24 months or longer. Except for some dryness of the eyes, no drug-related abnormal ophthalmological findings were recorded and, according to specialized tests such as electroretinography and macular dazzle, retinal function was unchanged.

14. CLINICAL STUDIES

The efficacy of KAPVAY in the treatment of ADHD was established in 2 (one monotherapy and one adjunctive therapy) placebo-controlled trials in pediatric patients aged 6 to 17, who met DSM-IV criteria of ADHD hyperactive or combined hyperactive/inattentive subtypes. Signs and symptoms of ADHD were evaluated using the investigator administered and scored ADHD Rating Scale-IV-Parent Version (ADHDRS-IV) total score including hyperactive/impulsivity and inattentive subscales.

Study 1 was an 8-week randomized, double-blind, placebo-controlled, fixed dose study of children and adolescents aged 6 to 17 (N=236) with a 5-week primary efficacy endpoint. Patients were randomly assigned to one of the following three treatment groups: KAPVAY (CLON) 0.2 mg/day (N=78), KAPVAY 0.4 mg/day (N=80), or placebo (N=78). Dosing for the KAPVAY groups started at 0.1 mg/day and was titrated in increments of 0.1 mg/week to their respective dose (as divided doses). Patients were maintained at their dose for a minimum of 2 weeks before being gradually tapered down to 0.1 mg/day at the last week of treatment. At both doses, improvements in ADHD symptoms were statistically significantly superior in KAPVAY-treated patients compared with placebo-treated patients at the end of 5 weeks as measured by the ADHDRS-IV total score.

Study 2 was an 8-week randomized, double-blind, placebo-controlled, flexible dose study in children and adolescents aged 6 to 17 (N=198) with a 5-week primary efficacy end point. Patients had been treated with a psychostimulant (methylphenidate or amphetamine) for four weeks with inadequate response. Patients were randomly assigned to one of two treatment groups: KAPVAY adjunct to a psychostimulant (N=102) or psychostimulant alone (N=96). The KAPVAY dose was initiated at 0.1 mg/day and doses were titrated in increments of 0.1 mg/week up to 0.4 mg/day, as divided doses, over a 3-week period based on tolerability and clinical response. The dose was maintained for a minimum of 2 weeks before being gradually tapered to 0.1 mg/day at the last week of treatment. ADHD symptoms were statistically significantly improved in KAPVAY plus stimulant group compared with the stimulant alone group at the end of 5 weeks as measured by the ADHDRS-IV total score.

16 HOW SUPPLIED/STORAGE AND HANDLING

KAPVAY extended-release tablets are white, non-scored, standard convex with debossing ("651" for 0.1 mg and "652" for 0.2 mg) on one side.

The 0.1 mg are round tablets supplied in bottles containing 60 (NDC 59630-658-60) or 180 tablets (NDC 59630-658-18).

The 0.2 mg are oval tablets supplied in bottles containing 60 (NDC 59630-659-60) or 180 tablets (NDC 59630-659-18).

Store at 20°-25°C (68°-77°F) [see USP Controlled Room Temperature].
Dispense in a tight, light-resistant container.

17 PATIENT COUNSELING INFORMATION

See FDA-approved Patient Labeling

17.1 General Information

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with KAPVAY and should counsel them in its appropriate use. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Patient Information and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Patient Information and to obtain answers to any questions they may have. The complete text of the Patient Information is attached to the package insert.

17.2 Abrupt Discontinuation

Patients should be advised not to discontinue KAPVAY abruptly. In order to minimize potential withdrawal effects (see Warnings and Precautions), when discontinuing KAPVAY therapy, patients should be instructed to decrease their total daily dose of KAPVAY in decrements of no more than 0.1 mg every 3 to 7 days.

17.3 Allergic Reactions

In patients who have developed an allergic reaction from clonidine transdermal system, substitution of oral clonidine hydrochloride may also elicit an allergic reaction (including generalized rash, urticaria, or angioedema).

17.4 Dosing

If the total daily dose of KAPVAY does not allow equal doses to be given in the morning and at bedtime (e.g., if the total daily dose is 0.3 mg/day), the higher of the two doses should be taken at bedtime (e.g., in a patient on 0.3 mg/day, a 0.1 mg dose should be taken in the morning and a 0.2 mg dose should be taken at bedtime). KAPVAY must be swallowed whole and never crushed, cut, or chewed.

17.5 Pregnancy

Patients should be instructed to consult a physician if they are nursing, pregnant, or thinking of becoming pregnant while taking KAPVAY.

17.6 Food

Patients may take KAPVAY with or without food.

17.7 Missed Dose

If patients miss a dose of KAPVAY, they should skip the dose and take the next dose as scheduled. Do not take more than the prescribed total daily amount of KAPVAY in any 24-hour period.

17.8 Impairment in Ability to Operate Machinery or Vehicles

No evaluation of the effects of KAPVAY on the ability to drive or operate machinery was performed during the development program. However, given the observed incidence of somnolence with KAPVAY, patients should be instructed to use caution when driving a car or operating hazardous machinery until they know how they will respond to treatment with KAPVAY.

Patient Information

KAPVAY™ (KAP-vay) (clonidine hydrochloride) Extended-Release Tablets

Read the Patient Information that comes with KAPVAY before you start taking it and each time you get a refill. There may be new information. This Patient Information leaflet does not take the place of talking to your doctor about your medical condition or treatment.

What is KAPVAY?

KAPVAY is a prescription medicine used for the treatment of Attention-Deficit Hyperactivity Disorder (ADHD). Your doctor may prescribe KAPVAY alone or together with certain other ADHD medicines.

- KAPVAY is not a central nervous system (CNS) stimulant.
- KAPVAY should be used as part of a total treatment program for ADHD that may include counseling or other therapies.

Who should not take KAPVAY?

- Do not take KAPVAY if you are allergic to clonidine in KAPVAY. See the end of this leaflet for a complete list of ingredients in KAPVAY.

What should I tell my doctor before taking KAPVAY?

Before you take KAPVAY, tell your doctor if you:

- have kidney problems
- have low or high blood pressure
- have a history of passing out (syncope)
- have heart problems, including history of heart attack
- have had a stroke or have stroke symptoms
- had a skin reaction (such as a rash) after taking clonidine in a transdermal form (skin patch)
- have any other medical conditions
- are pregnant or plan to become pregnant. It is not known if KAPVAY will harm your unborn baby. Talk to your doctor if you are pregnant or plan to become pregnant.
- are breastfeeding or plan to breastfeed. KAPVAY can pass into your breast milk. Talk to your doctor about the best way to feed your baby if you take KAPVAY.

Tell your doctor about all of the medicines that you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

KAPVAY and certain other medicines may affect each other causing serious side effects. Sometimes the doses of other medicines may need to be changed while taking KAPVAY.

Especially tell your doctor if you take:

- anti-depression medicines
- heart or blood pressure medicine
- other medicines that contain clonidine
- a medicine that makes you sleepy (sedation)

Ask your doctor or pharmacist for a list of these medicines, if you are not sure if your medicine is listed above.

Know the medicines that you take. Keep a list of your medicines with you to show your doctor and pharmacist when you get a new medicine.

How should I take KAPVAY?

- Take KAPVAY exactly as your doctor tells you to take it.
- Your doctor will tell you how many KAPVAY tablets to take and when to take them. Your doctor may change your dose of KAPVAY. Do not change your dose of KAPVAY without talking to your doctor.
- Do not stop taking KAPVAY without talking to your doctor.
- KAPVAY can be taken with or without food
- KAPVAY should be taken 2 times a day (in the morning and at bedtime).
- If you miss a dose of KAPVAY, skip the missed dose. Just take the next dose at your regular time. Do not take two doses at the same time.
- Take KAPVAY tablets whole. Do not chew, crush or break KAPVAY tablets. Tell your doctor if you cannot swallow KAPVAY tablets whole. You may need a different medicine.
- If you take too much KAPVAY, call your Poison Control Center or go to the nearest hospital emergency room right away.

What should I avoid while taking KAPVAY?

- Do not drink alcohol or take other medicines that make you sleepy or dizzy while taking KAPVAY until you talk with your doctor. KAPVAY taken with alcohol or medicines that cause sleepiness or dizziness may make your sleepiness or dizziness worse.
- Do not drive, operate heavy machinery or do other dangerous activities until you know how KAPVAY will affect you.
- Avoid becoming dehydrated or overheated.

What are possible side effects of KAPVAY?

KAPVAY may cause serious side effects, including:

- **Low blood pressure and low heart rate.** Your doctor should check your heart rate and blood pressure before starting treatment and regularly during treatment with KAPVAY.
- Sleepiness.
- Withdrawal symptoms. Suddenly stopping KAPVAY may cause withdrawal symptoms including: increased blood pressure, headache, increased heart rate, lightheadedness, tightness in your chest and nervousness.

The most common side effects of KAPVAY include:

- sleepiness
- tiredness
- upper respiratory tract infection, symptoms may include:
 - cough
 - runny nose
 - sneezing
- irritability
- sore throat
- trouble sleeping (insomnia)
- nightmares
- change in mood
- constipation

- stuffy nose
- increased body temperature
- dry mouth
- ear pain

Tell your doctor if you have any side effects that bother you or that does not go away.

These are not all of the possible side effects of KAPVAY. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store KAPVAY?

- Store KAPVAY between 68°-77°F (20°-25°C).
- Keep KAPVAY in a tightly closed container and keep KAPVAY out of the light.

Keep KAPVAY and all medicines out of the reach of children.

General information about the safe and effective use of KAPVAY

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use KAPVAY for a condition for which it was not prescribed. Do not give KAPVAY to other people, even if they have the same symptoms that you have. It may harm them.

This Patient Information leaflet summarizes the most important information about KAPVAY. If you would like more information, talk with your doctor. You can also ask your doctor or pharmacist for information about KAPVAY that is written for healthcare professionals.

For more information about KAPVAY, go to www.KAPVAY.com or call 1-800-849-9707 ext. 1454.

What are the ingredients in KAPVAY?

- Active Ingredient: clonidine hydrochloride
- Inactive Ingredients: sodium lauryl sulfate, lactose monohydrate, hypromellose type 2208, partially pregelatinized starch, colloidal silicon dioxide, and magnesium stearate

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