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ID CONSULT

Watch for Foodborne Illness

The recent *Escherichia coli* outbreak in Germany reminds us yet again about the threat of foodborne illness and the need for awareness about the clinical manifestations, the treatment, and the

public health implications. On June 14, a 2-year-old boy became the first child and the 37th person to die in Germany's ongoing *E. coli* outbreak. Here in the United States, the Centers for Disease Control and Prevention estimates 48 million people – 1 in every 6 Americans – become ill, 128,000 are hospitalized, and 3,000 die of foodborne illness annually. About half of all foodborne illness occurs in children,

who are particularly vulnerable because of their immature immune systems, lower body weight, and reduced stomach acid production.

Norovirus has become the most common recognized foodborne pathogen, causing about 5 million illnesses a year, followed by nontyphoidal *Salmonella*, with just over 1 million annual cases, and *Clostridium perfringens*, at just under 1

million, according to the CDC. *Norovirus* illness is usually mild, but it did cause an estimated 149 annual deaths. Nontyphoidal *Salmonella* is the most common serious cause of foodborne illness with an estimated 378 annual deaths, followed by *Toxoplasma gondii* (327 deaths) and *Listeria monocytogenes* (255 deaths).

The following foodborne illnesses are frequent causes of morbidity in children.

KAPVAY (clonidine hydrochloride) extended-release tablets, oral, Rx only

Brief Summary: For complete details, please see full Prescribing Information for Kapvay.

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)

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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.

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.

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.

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).

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.

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®).

ADVERSE REACTIONS

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%
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.

Information on the possible foodborne sources and the effects of infection are from a report compiled by the Pew Health Group in collaboration with the Center for Foodborne Illness Research and Prevention.

► **Salmonella.** These infections occur in approximately 75 children/100,000 under age 4 years, according to the CDC. It is commonly associated with foods of animal origin, including beef, poultry, milk, and eggs, or cross-contamination from these with other foods. Typical symptoms include diarrhea, fever, and abdominal cramps. More serious short-

term manifestations can include colitis, meningitis, septicemia, and death. Treatment involves rehydration as needed.

In general, antibiotic therapy is not warranted, but in immunocompromised hosts and children younger than age 6 months, antimicrobial therapy may be beneficial. In such settings, ceftriaxone is effective when susceptible, specifically in high-risk populations.

► **Shigella.** This infection occurs in about 28/100,000 children under age 4 years and 26/100,000 for those aged 4-11 years, according to the CDC. It is often associated with vegetables harvested in fields

contaminated with sewage; flies that breed in infected feces and contaminate the food; and drinking, swimming, or playing in contaminated water. Short-term effects include high fever, diarrhea that is often bloody, stomach cramps, and seizures in children less than age 2 years. Reactive or chronic arthritis can be a postinfectious sequelae.

Treatment includes rehydration as necessary, and antibiotics for severe disease or dysentery, particularly in those with underlying immunosuppression. Ceftriaxone and ciprofloxacin are effective, although the latter is not licensed for use

in young children. Resistance to amoxicillin and trimethoprim-sulfamethoxazole (TMP-SMZ) is common. Treatment of mild cases may be indicated to shorten the duration of excretion.

► **Campylobacter.** This infection affects 29/100,000 children under age 4 years, similar in incidence to *Shigella*. Foodborne sources included raw or undercooked poultry or foods cross-contaminated by poultry, unpasteurized milk, and contaminated water. Symptoms include diarrhea (sometimes bloody), cramping, abdominal pain, urinary tract infection, fever, and meningitis. *Campylobacter* is also associated with Guillain-Barré syndrome or reactive/chronic arthritis. Again, treatment involves rehydration as necessary. Macrolides (azithromycin or erythromycin) can shorten duration of illness and prevent relapse.

► **E. coli or other shiga toxin-producing strains.** This foodborne infection has been in the headlines lately, and affects about 4/100,000 children between 4 and 11 years of age. Typical food sources include ground beef and other meats, green leafy vegetables, unpasteurized juices or raw milk, or soft cheeses made from raw milk. Symptoms include severe stomach cramps, diarrhea (often bloody), and vomiting. Hemolytic-uremic syndrome occurs in about 15% of children with *E. coli* 0157:H7 infection. This can result in long-term kidney damage as well as death.

In general, antibiotics have not been shown to benefit patients. Early reports of increased risk of hemolytic-uremic syndrome with antibiotic treatment have not been confirmed. As with the others, rehydration and supportive therapy are the mainstays of treatment.

► **Listeria.** This infection occurs in about 0.76/100,000 children under age 4 years, according to the CDC. About one-third of all cases involve pregnant women. Common food sources include uncooked meats, particularly cold cuts and hot dogs, as well as smoked seafood, raw milk, soft cheeses made from raw milk, and vegetables grown in contaminated soil or fertilizer. Symptoms include fever, muscle aches, nausea, and diarrhea. Headaches, stiff neck, confusion, loss of balance, and seizures can result if infection spreads to the nervous system.

For invasive disease, ampicillin plus an aminoglycoside is recommended. For penicillin-allergic patients, TMP-SMZ or high-dose vancomycin can be used. Cephalosporins are generally inactive. In the majority of patients with febrile gastroenteritis, the illness is self-limited (typical duration, 2 days or less) and therefore, generally no antibiotic treatment is necessary.

In pregnant women, listerial febrile gastroenteritis can lead to fetal death, premature birth, or infected newborns. Oral ampicillin or TMP-SMZ can be given for several days in immunocompromised or pregnant patients with listerial febrile gastroenteritis, particularly if they are still symptomatic once the culture result is known. ■

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 bradypnea.

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.

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.

Interactions with CNS-depressant Drugs

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

Interactions with Tricyclic Antidepressants

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

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).

Use with other products containing clonidine

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

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)].

USE IN SPECIFIC POPULATIONS

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.

Nursing Mothers

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

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.

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.

Adult Use in ADHD

KAPVAY has not been studied in adult patients with ADHD.

DRUG ABUSE AND DEPENDENCE

Controlled Substance

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

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.

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DR. PELTON is chief of pediatric infectious disease and also is the coordinator of the maternal-child HIV program at Boston Medical Center. He said he had no relevant financial disclosures.