HIGHLIGHTS OF PRESCRIBING INFORMATION

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

APTENSIO XR™ (methylphenidate hydrochloride extended-release) Capsules, for oral use. CII
Initial U.S. Approval: 1955

WARNING: ABUSE AND DEPENDENCE

See full prescribing information for complete boxed warning.

- **CNS stimulants, including APTENSIO XR, other methylphenidate-containing products, and amphetamines, have a high potential for abuse and dependence (5.1, 9.2, 9.3)**
- **Assess the risk of abuse prior to prescribing, and monitor for signs of abuse and dependence while on therapy (5.1, 9.2)**

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

- APTENSIO XR is a central nervous system (CNS) stimulant indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). (1)

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

- Recommended starting dose for patients 6 years and above: 10 mg once daily with or without food in the morning. Dosage may be increased weekly in increments of 10 mg per day. Daily dosage above 60 mg is not recommended. (2.1)
- Capsules may be swallowed whole or opened and the entire contents sprinkled onto applesauce. (2.1)

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

- Extended-Release Capsules: 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 50 mg, and 60 mg of methylphenidate hydrochloride, which is equivalent to 8.6 mg, 13.0 mg, 17.3 mg, 25.9 mg, 34.6 mg, 43.2 mg, and 51.9 mg of methylphenidate free base, respectively, per capsule. (3)

----------CONTRAINDICATIONS----------

- Known hypersensitivity to methylphenidate or product components (4)
- Concurrent treatment with a monoamine oxidase inhibitor (MAOI), or use of an MAOI within the preceding 14 days (4)

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

- *Serious Cardiovascular Events:* Sudden death has been reported in association with CNS stimulant treatment at recommended doses in pediatric patients with structural cardiac abnormalities or other serious heart problems. In adults, sudden death, stroke, and myocardial infarction have been reported. Avoid use in patients with known structural cardiac abnormalities, cardiomyopathy, serious heart arrhythmias, or coronary artery disease. (5.2)
- *Blood Pressure and Heart Rate Increases:* Monitor blood pressure and pulse. Consider the benefits and risks in patients for whom an increase in blood pressure or heart rate would be problematic. (5.3)
- *Psychiatric Adverse Reactions:* Use of stimulants may cause psychotic or manic symptoms in patients with no prior history, or exacerbation of symptoms in patients with pre-existing psychiatric illness. Evaluate for bipolar disorder prior to APTENSIO XR use. (5.4)
- *Priapism:* Cases of painful and prolonged penile erections and priapism have been reported with methylphenidate products. Immediate medical attention should be sought if signs or symptoms of prolonged penile erections or priapism are observed. (5.5)
- *Peripheral Vasculopathy, including Raynaud's Phenomenon:* Stimulants used to treat ADHD are associated with peripheral vasculopathy, including Raynaud's phenomenon. Careful observation for digital changes is necessary during treatment with ADHD stimulants. (5.6)
- *Long-Term Suppression of Growth:* Monitor height and weight at appropriate intervals in pediatric patients. (5.7)

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

The most common adverse reactions in double-blind clinical trials (> 5% and twice the rate of placebo) in pediatric patients 6 to 17 years were abdominal pain, decreased appetite, headache and insomnia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Rhodes Pharmaceuticals L.P. at (1-888-827-0616); or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 01/2017

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FULL PRESCRIBING INFORMATION

WARNING: ABUSE AND DEPENDENCE

CNS stimulants, including APTENSIO XR, other methylphenidate-containing products, and amphetamines, 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 *[see Warning and Precautions (5.1), Drug Abuse and Dependence (9.2, 9.3)].*

1 INDICATIONS AND USAGE

APTENSIO XR is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD*) [see Clinical Studies (14)]*.

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Information

The recommended starting dose of APTENSIO XR for patients 6 years and above is 10 mg once daily in the morning with or without food. Advise patients to establish a routine pattern with regard to meals. The dose should be individualized according to the needs and response of the patient.

The dose may be titrated weekly in increments of 10 mg. Daily doses above 60 mg have not been studied and are not recommended.

APTENSIO XR may be taken whole or the capsule may be opened and the entire contents sprinkled onto applesauce. If the patient is using the sprinkled administration method, the sprinkled applesauce should be consumed immediately; it should not be stored. Patients should take the applesauce with sprinkled beads in its entirety without chewing. The dose of a single capsule should not be divided. The contents of the entire capsule should be taken, and patients should not take anything less than one capsule per day.

Pharmacological treatment of ADHD may be needed for extended periods. Healthcare providers should periodically re-evaluate the long-term use of APTENSIO XR, and adjust dosage as needed.

2.2 Dose Reduction and Discontinuation

If paradoxical aggravation of symptoms or other adverse reactions occur; the dosage should be reduced, or, if necessary, the drug should be discontinued.

If improvement is not observed after appropriate dosage adjustment over a one-month period, the drug should be discontinued.

2.3 Important Information Prior to Initiating Treatment

Prior to treating pediatric patients and adults with CNS stimulants including APTENSIO XR, assess for the presence of cardiac disease (i.e., perform a careful history, family history of sudden death or ventricular arrhythmia, and physical exam) *[see Warnings and Precautions 5.2]*.

Assess the risk of abuse prior to prescribing, and monitor for signs of abuse and dependence while on therapy. Maintain careful prescription records, educate patients about abuse, monitor for signs of abuse and overdose, and periodically re-evaluate the need for APTENSIO XR use *[see Boxed Warning, Warnings and Precautions (5.1), and Drug Abuse and Dependence (9)]*.

3 DOSAGE FORMS AND STRENGTHS

- ***10 mg Extended-Release Capsules*** – light turquoise blue cap/white body (imprinted with "APTENSIO XR" on cap and "10 mg" on the body)
- ***15 mg Extended-Release Capsules*** – orange cap/white body (imprinted with "APTENSIO XR" on cap and "15 mg" on the body)
- ***20 mg Extended-Release Capsules*** – yellow cap/white body (imprinted with "APTENSIO XR" on cap and "20 mg" on the body)
- ***30 mg Extended-Release Capsules*** – blue violet cap/white body (imprinted with "APTENSIO XR" on cap and "30 mg" on the body)
- ***40 mg Extended-Release Capsules*** – pink cap/white body (imprinted with "APTENSIO XR" on cap and "40 mg" on the body)
- ***50 mg Extended-Release Capsules*** – green cap/white body (imprinted with "APTENSIO XR" on cap and "50 mg" on the body)
- ***60 mg Extended-Release Capsules*** – gray cap/white body (imprinted with "APTENSIO XR" on cap and "60 mg" on the body)

4 CONTRAINDICATIONS

- Hypersensitivity to methylphenidate or other components of the product. Hypersensitivity reactions such as angioedema and anaphylactic reactions have been reported in patients treated with methylphenidate products *[see Adverse Reactions (6.1)]*.
- Concomitant treatment with monoamine oxidase inhibitors, and also within 14 days following discontinuation of treatment with a monoamine oxidase inhibitor, because of the risk of hypertensive crisis *[see Drug Interactions (7.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Potential for Abuse and Dependence

CNS stimulants, including APTENSIO XR, other methylphenidate-containing products, and amphetamines, 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 *[see Boxed Warning and Drug Abuse and Dependence (9.2, 9.3)]*.

5.2 Serious Cardiovascular Events

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. Further evaluate patients who develop exertional chest pain, unexplained syncope, or arrhythmias during APTENSIO XR treatment.

5.3 Blood Pressure and Heart Rate Increases

CNS stimulants cause an increase in blood pressure (mean increase approximately 2 to 4 mmHg) and heart rate (mean increase approximately 3 to 6 bpm). Individuals may have larger increases. Monitor all patients for hypertension and tachycardia.

5.4 Psychiatric Adverse Reactions

Exacerbation of Pre-Existing Psychosis

CNS stimulants may exacerbate symptoms of behavior disturbance and thought disorder in patients with a pre-existing psychotic disorder.

Induction of a Manic Episode in Patients with Bipolar Disorder

CNS stimulants may induce a manic or mixed episode in patients. 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, or depression).

New Psychotic or Manic Symptoms

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 APTENSIO XR. In a pooled analysis of multiple short-term, placebo-controlled studies of CNS stimulants, psychotic or manic symptoms occurred in approximately 0.1% of CNS stimulant-treated patients, compared to 0 in placebo-treated patients.

5.5 Priapism

Prolonged and painful erections, sometimes requiring surgical intervention, have been reported with methylphenidate products, in both pediatric and adult patients. Priapism was not reported with drug initiation but developed after some time on the drug, often subsequent to an increase in dose. Priapism has also appeared during a period of drug withdrawal (drug holidays or during discontinuation). Patients who develop abnormally sustained or frequent and painful erections should seek immediate medical attention.

5.6 Peripheral Vasculopathy, including Raynaud's Phenomenon

Stimulants, including APTENSIO XR, used to treat ADHD 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. Careful observation for digital changes is necessary during treatment with ADHD stimulants. Further clinical evaluation (e.g., rheumatology referral) may be appropriate for certain patients.

5.7 Long-Term 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 APTENSIO XR.

Careful follow-up of weight and height in pediatric patients ages 7 to 10 years who were randomized to either methylphenidate or non-medication treatment groups over 14 months, as well as in naturalistic subgroups of newly methylphenidate-treated and non-medication treated pediatric patients over 36 months (to the ages of 10 to 13 years), suggests that consistently medicated pediatric patients (i.e., treatment for 7 days per week throughout the year) have a temporary slowing in growth rate (on average, a total of about 2 cm less growth in height and 2.7 kg less growth in weight over 3 years), without evidence of growth rebound during this period of development.

Published data are inadequate to determine whether chronic use of amphetamines may cause a similar suppression of growth, however, it is anticipated that they likely have this effect as well. Therefore, growth should be monitored during treatment with stimulants, and patients who are not growing or gaining height or weight as expected may need to have their treatment interrupted.

6 ADVERSE REACTIONS

The following are discussed in more detail in other sections of the labeling:

- Drug Dependence *[see Boxed Warning, Warnings and Precautions (5.1), and Drug Abuse and Dependence (9.2, 9.3)]*
- Hypersensitivity to Methylphenidate *[see Contraindications (4)]*
- Monoamine Oxidase Inhibitors *[see Contraindications (4) and Drug Interactions (7.1]*
- Serious Cardiovascular Events *[see Warnings and Precautions (5.2)]*
- Blood Pressure and Heart Rate Increases *[see Warnings and Precautions (5.3)]*
- Psychiatric Adverse Reactions *[see Warnings and Precautions (5.4)]*
- Priapism *[see Warnings and Precautions (5.5)]*
- Peripheral Vasculopathy, including Raynaud's Phenomenon *[see Warnings and Precautions (5.6)]*
- Long-Term Suppression of Growth *[see Warnings and Precautions (5.7)]*

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Clinical Trials Experience with Other Methylphenidate Products in Children, Adolescents, and Adults with ADHD

Commonly reported (≥2% of the methylphenidate group and at least twice the rate of the placebo group) adverse reactions from placebo-controlled trials of methylphenidate products include: decreased appetite, decreased weight, nausea, abdominal pain, dyspepsia, dry mouth, vomiting, insomnia, anxiety, nervousness, restlessness, affect lability, agitation, irritability, dizziness, vertigo, tremor, blurred vision, increased blood pressure, increased heart rate, tachycardia, palpitations, hyperhidrosis, and pyrexia.

Clinical Trials Experience with APTENSIO XR in Pediatric Patients with ADHD

The safety data in this section is based on data from two one-week controlled clinical studies of APTENSIO XR in pediatric patients with ADHD, one in children ages 6 to 12 years (RP-BP-EF001, hereafter "Study 1"), and one in children and adolescents ages 6 to 17 years (RP-BP-EF002, hereafter "Study 2").

Two APTENSIO XR clinical studies evaluated a total of 256 patients with ADHD. Two hundred and forty-three (243) patients participated in the double-blind phase of these two clinical studies.

Study 1 was a randomized, double-blind, single center, placebo-controlled, flexible-dose, cross-over study to evaluate the time of onset, duration of efficacy, tolerability and safety of APTENSIO XR 15 mg, 20 mg, 30 mg, or 40 mg administered for one week in 26 pediatric patients aged 6 to 12 years who met DSM-IV criteria for ADHD *[see Clinical Studies (14)]*.

Most Common Adverse Reactions (incidence of ≥ 5% and at a rate at least twice placebo): abdominal pain, pyrexia and headache.

Adverse Reactions Leading to Discontinuation: No subjects discontinued due to adverse reactions during the double-blind phase of this study.

Study 2 was a randomized, double-blind, multicenter, placebo-controlled, parallel group, fixed-dose study of 10 mg, 15 mg, 20 mg, and 40 mg of APTENSIO XR administered for one week in 221 pediatric patients (6 to 17 years of age) who met DSM-IV criteria for ADHD *[see Clinical Studies (14)]*.

Most Common Adverse Reactions (incidence of ≥ 5% and at a rate of at least twice placebo): abdominal pain, decreased appetite, headache and insomnia.

Adverse Reactions Leading to Discontinuation: Two patients (4.4%) in the APTENSIO XR 40 mg group discontinued due to insomnia, nausea and rapid heart rate, respectively during the double-blind phase of the study.

Table 1: Common Adverse Reactions Occurring in ≥ 2% of Pediatric Patients (6 to 17 years of age) with ADHD Taking APTENSIO XR and at a Rate Greater than Placebo (Study 2)

System Organ Class Adverse Reaction	Aptensio XR (n= 183)	Placebo (n=47)
Nervous System Disorders		
Headache	10.9%	8.5%
Insomnia	9.8%	2.1%
Dizziness	2.2%	2.1%
Gastrointestinal Disorders		
Abdominal pain upper	8.2%	0%
Nausea	3.8%	2.1%
Vomiting	3.8%	0%
Metabolism and Nutritional		
Decreased Appetite	4.9%	0%

6.2 Post-Marketing Experience

The following adverse reactions have been identified during post approval use of methylphenidate products. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These adverse reactions are as follows:

Blood and Lymphatic System Disorders: Pancytopenia, Thrombocytopenia, Thrombocytopenic purpura
Cardiac Disorders: Angina pectoris, Bradycardia, Extrasystole, Supraventricular tachycardia, Ventricular extrasystole
Eye Disorders: Diplopia, Mydriasis, Visual impairment
General Disorders: Chest pain, Chest discomfort, Hyperpyrexia
Immune System Disorders: Hypersensitivity reactions such as Angioedema, Anaphylactic reactions, Auricular swelling, Bullous conditions, Exfoliative conditions, Urticarias, Pruritus NEC, Rashes, Eruptions, and Exanthemas NEC
Investigations: Alkaline phosphatase increased, Bilirubin increased, Hepatic enzyme increased, Platelet count decreased, White blood cell count abnormal, severe hepatic injury
Musculoskeletal, Connective Tissue and Bone Disorders: Arthralgia, Myalgia, Muscle twitching, Rhabdomyolysis
Nervous System: Convulsion, Grand mal convulsion, Dyskinesia, serotonin syndrome in combination with serotonergic drugs
Psychiatric Disorders: Disorientation, Libido changes
Skin and Subcutaneous Tissue Disorders: Alopecia, Erythema

7 DRUG INTERACTIONS

7.1 Clinically Important Interactions with APTENSIO XR

Monoamine Oxidase Inhibitors (MAOIs)

Do not administer APTENSIO XR concomitantly or within 14 days after discontinuing MAOI treatment. Concomitant use of MAOIs and CNS stimulants can cause hypertensive crisis. Potential outcomes include death, stroke, myocardial infarction, aortic dissection, ophthalmological complications, eclampsia, pulmonary edema, and renal failure *[see Contraindications (4)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Limited published studies report on the use of methylphenidate in pregnant women; however, the data are insufficient to inform any drug-associated risks. No teratogenic effects were observed in embryo-fetal development studies with oral administration of methylphenidate to rats and rabbits during organogenesis at doses 2 and 11 times, respectively, the maximum recommended human dose (MRHD). However, spina bifida was observed in rabbits at a dose 40 times the MRHD. A decrease in pup body weight was observed in a pre- and post-natal development study with oral administration of methylphenidate to rats throughout pregnancy and lactation at doses 4 times the MRHD *[see Data]*. The background risk of major birth defects and miscarriage for the indicated population are unknown. However, the background risk in the U.S. general population of major birth defects is 2% to 4% and of miscarriage is 15% to 20% of clinically recognized pregnancies.

Clinical Considerations

Fetal/Neonatal adverse reactions

CNS stimulants, such as APTENSIO XR, can cause vasoconstriction and thereby decrease placental perfusion. No fetal and/or neonatal adverse reactions have been reported with the use of therapeutic doses of methylphenidate during pregnancy; however, premature delivery and low birth weight infants have been reported in amphetamine-dependent mothers.

Data

Animal Data

In studies conducted in rats and rabbits, methylphenidate was administered orally at doses of up to 75 and 200 mg/kg/day, respectively, during the period of organogenesis. Teratogenic effects (increased incidence of fetal spina bifida) were observed in rabbits at the highest dose, which is approximately 40 times the maximum recommended human dose (MRHD) on a mg/m^2 basis. The no effect level for embryo-fetal development in rabbits was 60 mg/kg/day (11 times the MRHD on a mg/m^2 basis). There was no evidence of specific teratogenic activity in rats, although increased incidences of fetal skeletal variations were seen at the highest dose level (7 times the MRHD on a mg/m^2 basis), which was also maternally toxic. The no effect level for embryo-fetal development in rats was 25 mg/kg/day (2 times the MRHD on a mg/m^2 basis). When methylphenidate was administered to rats throughout pregnancy and lactation at doses of up to 45 mg/kg/day, offspring body weight gain was decreased at the highest dose (4 times the MRHD on a mg/m^2 basis), but no other effects on postnatal development were observed. The no effect level for pre- and postnatal development in rats was 15 mg/kg/day (equal to the MRHD on a mg/m^2 basis).

8.2 Lactation

Risk Summary

Limited published literature, based on breast milk sampling from five mothers, reports that methylphenidate is present in human milk, which resulted in infant doses of 0.16% to 0.7% of the maternal weight-adjusted dosage and a milk/plasma ratio ranging between 1.1 and 2.7. There are no reports of adverse effects on the breastfed infant and no effects on milk production. However, long-term neurodevelopmental effects on infants from stimulant exposure are unknown. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for APTENSIO XR and any potential adverse effects on the breastfed infant from APTENSIO XR or from the underlying maternal condition.

Clinical Considerations

Monitor breastfeeding infants for adverse reactions, such as agitation, anorexia, and reduced weight gain.

8.4 Pediatric Use

The safety and effectiveness of APTENSIO XR in pediatric patients under six years have not been evaluated.

The safety and effectiveness of APTENSIO XR have been established in pediatric patients ages 6 to 17 years in two adequate and well-controlled clinical trials *[see Clinical Studies (14)]*. The long-term efficacy of methylphenidate in pediatric patients has not been established.

Long Term Suppression of Growth

Growth should be monitored during treatment with stimulants, including APTENSIO XR. Pediatric patients who are not growing or gaining weight as expected may need to have their treatment interrupted *[see Warnings and Precautions (5.7)]*.

Juvenile Animal Data

Rats treated with methylphenidate early in the postnatal period through sexual maturation demonstrated a decrease in spontaneous locomotor activity in adulthood. A deficit in acquisition of a specific learning task was observed in females only. The doses at which these findings were observed are at least 6 times the maximum recommended human dose (MRHD) on a mg/m^2 basis.

In the study conducted in young rats, methylphenidate was administered orally at doses of up to 100 mg/kg/day for 9 weeks, starting early in the postnatal period (postnatal day 7) and continuing through sexual maturity (postnatal week 10). When these animals were tested as adults (postnatal weeks 13-14), decreased spontaneous locomotor activity was observed in males and females previously treated with 50 mg/kg/day (approximately 6 times the maximum recommended human dose [MRHD] on a mg/m^2 basis) or greater, and a deficit in the acquisition of a specific learning task was observed in females exposed to the highest dose (12 times the MRHD on a mg/m^2 basis). The no effect level for juvenile neurobehavioral development in rats was 5 mg/kg/day (half the MRHD on a mg/m^2 basis). The clinical significance of the long-term behavioral effects observed in rats is unknown.

8.5 Geriatric Use

Clinical trials of APTENSIO XR did not include any patients aged 65 years and over. In general, dose selection for an elderly patient start at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

APTENSIO XR contains methylphenidate a Schedule II controlled substance.

9.2 Abuse

CNS stimulants including APTENSIO XR, other methylphenidate-containing products, and amphetamines have a high potential for abuse. Abuse is characterized by impaired control over drug use despite harm, and craving.

Signs and symptoms of CNS stimulant abuse include increased heart rate, respiratory rate, blood pressure, and/or sweating, dilated pupils, hyperactivity, restlessness, insomnia, decreased appetite, loss of coordination, tremors, flushed skin, vomiting, and/or abdominal pain. Anxiety, psychosis, hostility, aggression, suicidal or homicidal ideation have also been observed. Abusers of CNS stimulants may chew, snort, inject, or use other unapproved routes of administration which can result in overdose and death *[see Overdosage (10)]*.

To reduce the abuse of CNS stimulants including APTENSIO XR, assess the risk of abuse prior to prescribing. After prescribing, keep careful prescription records, educate patients and their families about abuse and on proper storage and disposal of CNS stimulants, monitor for signs of abuse while on therapy, and re-evaluate the need for APTENSIO XR use.

9.3 Dependence

Tolerance

Tolerance (a state of adaptation in which exposure to a drug results in a reduction of the drug's desired and/or undesired effects over time) can occur during chronic therapy with CNS stimulants including APTENSIO XR.

Dependence

Physical dependence (a state of adaptation manifested by a withdrawal syndrome produced by abrupt cessation, rapid dose reduction, or administration of an antagonist) can occur in patients treated with CNS stimulants including APTENSIO XR. Withdrawal symptoms after abrupt cessation following prolonged high-dosage administration of CNS stimulants include extreme fatigue and depression.

10 OVERDOSAGE

10.1 Signs and Symptoms

Signs and symptoms of acute methylphenidate overdose, resulting principally from overstimulation of the CNS and from excessive sympathomimetic effects, may include the following: nausea, vomiting, diarrhea, restlessness, anxiety, agitation, tremors, hyperreflexia, muscle twitching, convulsions (may be followed by coma), euphoria, confusion, hallucinations, delirium, sweating, flushing, headache, hyperpyrexia, tachycardia, palpitations, cardiac arrhythmias, hypertension, hypotension, tachypnea, mydriasis, dryness of mucous membranes, and rhabdomyolysis.

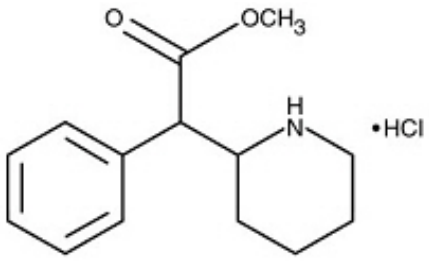
10.2 Management of Overdose

Consult with a Certified Poison Control Center (1-800-222-1222) for up-to-date guidance and advice on the management of overdosage with methylphenidate. Provide supportive care, including close medical supervision and monitoring. Treatment should consist of those general measures employed in the management of overdosage with any drug. Consider the possibility of multiple drug overdosages. Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. Use supportive and symptomatic measures.

Gastric contents may be evacuated by gastric lavage as indicated. Before performing gastric lavage, control agitation and seizures if present and protect the airway. Other measures to detoxify the gut include administration of activated charcoal and a cathartic. Intensive care must be provided to maintain adequate circulation and respiratory exchange; external cooling procedures may be required for pyrexia.

11 DESCRIPTION

APTENSIO XR is a central nervous system (CNS) stimulant. APTENSIO XR capsules contain multi layered beads, which are composed of an immediate-release layer which contains approximately 40% of the methylphenidate dose, and a controlled release layer which contains approximately 60% of the methylphenidate dose. APTENSIO XR is available in seven capsule strengths. Each extended-release capsule for once-a-day oral administration contains 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 50 mg, or 60 mg of methylphenidate HCl USP, which is equivalent to 8.6 mg, 13.0 mg, 17.3 mg, 25.9 mg, 34.6 mg, 43.2 mg, or 51.9 mg of methylphenidate free base, respectively. Chemically, methylphenidate HCl is *d*,*l* (racemic) methyl α-phenyl-2-piperidineacetate hydrochloride. Its molecular formula is $C_{14}H_{19}NO_2 \bullet HCl$. Its structural formula is:



Methylphenidate hydrochloride USP is a white to off-white, odorless, fine crystalline powder. Its solutions are acid to litmus. It is freely soluble in water and in methanol, soluble in alcohol, and slightly soluble in chloroform and in acetone. Its molecular weight is 269.77.

Inactive Ingredients: sugar spheres, hypromelloses, polyethylene glycol, ammonio methacrylate copolymer, type B; methacrylic acid copolymer, type C; triethyl citrate, talc, colloidal silicon dioxide (added if necessary), titanium oxide, and gelatin.

Each strength capsule also contains colorant ingredients in the capsule shell as follows:

10 mg: FD&C Blue No. 1
15 mg: D&C Red No. 28, D&C Yellow No. 10, FD&C Red No. 40
20 mg: D&C Red No. 33, D&C Yellow No. 10
30 mg: FD&C Blue No. 1, FD&C Red No. 3
40 mg: D&C Red No. 28, FD&C Blue No. 1, FD&C Red No. 40
50 mg: D&C Yellow No. 10, FD&C Green No. 3
60 mg: Black Iron Oxide

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Methylphenidate HCl is a central nervous system (CNS) stimulant.

12.2 Pharmacodynamics

Methylphenidate is a racemic mixture comprised of the *d*- and *l*-isomers. The *d*-isomer is more pharmacologically active than the *l*-isomer. Methylphenidate is thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space.

12.3 Pharmacokinetics

Absorption

Following oral administration of APTENSIO XR in adults, plasma methylphenidate concentrations increase rapidly, reaching an initial maximum at about 2 hours, followed by gradual descending concentrations over the next 4 to 6 hours, after which a gradual increase begins, reaching a second peak at approximately 8 hours (Figure 1). The relative bioavailability of APTENSIO XR given once daily as compared to a methylphenidate immediate-release oral product given three times daily in adults is comparable. The relative bioavailability is 102%.

The pharmacokinetic profiles and parameters of methylphenidate are similar when APTENSIO XR is administered either as a whole capsule or sprinkled onto applesauce in subjects under fasting conditions (see Table 2 and Figure 1).

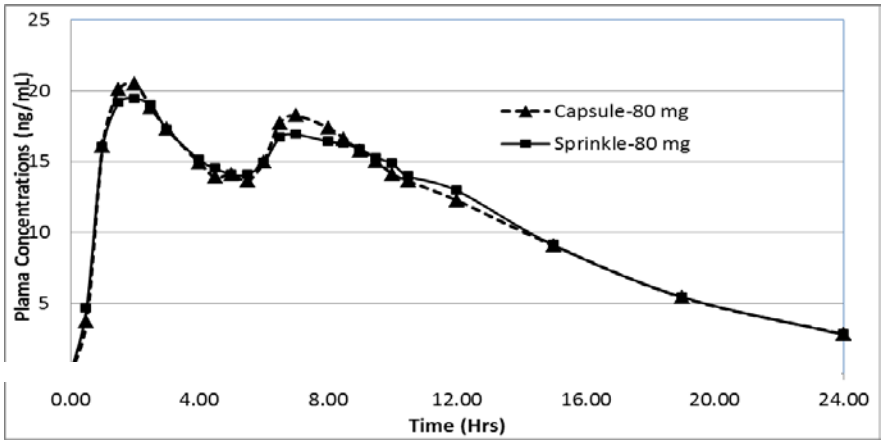
Table 2: The Single Dose Pharmacokinetics of *d,l*-Methylphenidate[1] ER Capsule and Sprinkle following an Oral Dose of 80 mg APTENSIO XR under Fast Conditions in Healthy Adults

Pharmacokinetic Parameters	Capsule	Sprinkle
C_{max}[2] (ng/mL)	23.47 ± 11.4	21.78 ± 9.5

$AUC_{(0\text{-}t)}$[2] (ng.hr/mL)	**262.7 ± 135**	**262.9 ± 128**
$AUC_{(0\text{-}inf)}$[2] (ng.hr/mL)	**258.1 ± 94.2**	**258.0 ± 84.4**
T_{max} (hr) ‡	**2.0**	**2.0**
Half-life (hr)	**5.09**	**5.43**
Relative bioavailability	**102%**	**101%**

[1] *d,l* (racemic) methylphenidate HCl
[2] C_{max}, $AUC_{(0\text{-}t)}$ $AUC_{(0\text{-}inf)}$ presented as mean ± SD
‡ data presented as median (range)

Figure 1: Mean *d,l*-Methylphenidate Plasma Concentration-Time Profiles following 80 mg Administered as Capsule and Sprinkle Dose in Healthy Adults



Metabolism and Excretion

In humans, methylphenidate is metabolized primarily via deesterification to alpha-phenyl-piperidine acetic acid (PPAA). The metabolite has little or no pharmacologic activity.

After oral dosing of radiolabeled methylphenidate in humans, about 90% of the radioactivity was recovered in urine. The main urinary metabolite was PPAA, accounting for approximately 80% of the dose.

Food Effects

Administration of APTENSIO XR with high fat meal showed a decreased or diminished second peak. A high-fat meal also increased the average C_{max} of methylphenidate by about 28% and the AUC by about 19%. In the clinical trials of APTENSIO XR, it was administered without regard to meals.

Alcohol Effect

At an alcohol concentration up to 40%, there was 96% release of methylphenidate from APTENSIO XR 80 mg capsule within two hours. The results with the 80 mg capsule are considered to be representative of the other available capsules strengths.

Studies in Specific Populations

Gender

There is insufficient experience with the use of APTENSIO XR to detect gender variations in pharmacokinetics.

Race

There is insufficient experience with the use of APTENSIO XR to detect ethnic variations in pharmacokinetics.

Age

The pharmacokinetics of methylphenidate after APTENSIO XR administration was studied in pediatric patients with ADHD between 6 and 12 years of age. Following administration of APTENSIO XR, the bi-phasic plasma methylphenidate concentration profile was qualitatively similar in healthy adult volunteers and pediatric patients with ADHD. The bi-phasic profile in both groups is characterized by an early peak due to rapid absorption of the immediate-release component followed by a delayed, secondary peak due to the controlled-release component of APTENSIO XR.

Renal Insufficiency

There is no experience with the use of APTENSIO XR in patients with renal insufficiency. After oral administration of radiolabeled methylphenidate in humans, methylphenidate was extensively metabolized and approximately 80% of the radioactivity was excreted in the urine in the form of ritalinic acid metabolite. Since renal clearance is not an important route of methylphenidate clearance, renal insufficiency is expected to have little effect on the pharmacokinetics of APTENSIO XR.

Hepatic Insufficiency

There is no experience with the use of APTENSIO XR in patients with hepatic insufficiency.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

In a lifetime carcinogenicity study carried out in B6C3F1 mice, methylphenidate caused an increase in hepatocellular adenomas and, in males only, an increase in hepatoblastomas, at a daily dose of approximately 60 mg/kg/day. This dose is approximately 4 times the maximum recommended human dose on a mg/m^2 basis. Hepatoblastoma is a relatively rare rodent malignant tumor type. There was no increase in total malignant hepatic tumors. The mouse strain used is sensitive to the development of hepatic tumors, and the significance of these results to humans is unknown.

Methylphenidate did not cause any increase in tumors in a lifetime carcinogenicity study carried out in F344 rats; the highest dose used was approximately 45 mg/kg/day, which is approximately 5 times the maximum recommended human dose on a mg/m^2 basis.

Mutagenesis

Methylphenidate was not mutagenic in the *in vitro* Ames reverse mutation assay or in the *in vitro* mouse lymphoma cell forward mutation assay. Sister chromatid exchanges and chromosome aberrations were increased, indicative of a weak clastogenic response, in an *in vitro* assay in cultured Chinese Hamster Ovary (CHO) cells. The genotoxic potential of methylphenidate has not been evaluated in an *in vivo* assay.

Impairment of Fertility

Methylphenidate did not impair fertility in male or female mice that were fed diets containing the drug in an 18-week Continuous Breeding study. The study was conducted at doses of up to 160 mg/kg/day, approximately 8-fold the maximum recommended human dose on a mg/m^2 basis.

14 CLINICAL STUDIES

The efficacy of APTENSIO XR for the treatment of ADHD was established in a randomized, double-blind, single center, placebo-controlled, flexible-dose, cross-over trial in pediatric patients aged 6 to 12 years and a second randomized, double-blind, multicenter, placebo-controlled, fixed–dose trial in pediatric patients 6 to 17 years.

Pediatric Patients

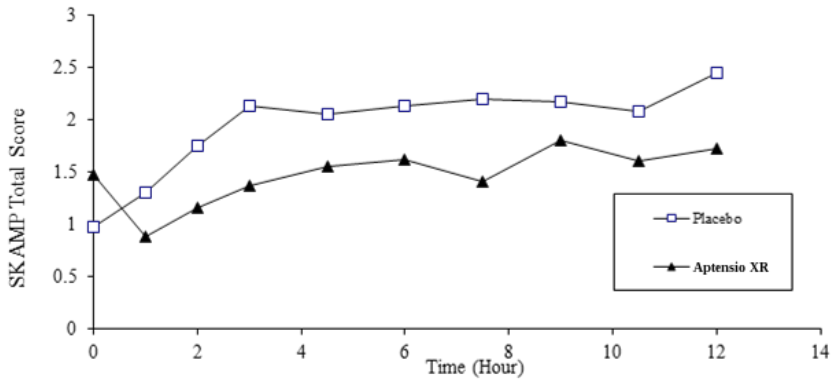
A randomized, double-blind, placebo-controlled, flexible-dose, cross-over, analog classroom study (Study 1) was conducted in pediatric patients ages 6 to 12 years (N=26) who met DSM-IV-TR criteria for ADHD inattentive, hyperactive-impulsive or combined inattentive/hyperactive-impulsive subtypes.

Following a 2 to 4 week open-label dose optimization phase in which patients received flexible-dose APTENSIO XR 15 mg, 20 mg, 30 mg, or 40 mg administered once daily in the morning, patients were randomly assigned to APTENSIO XR (dose from open-label phase) or placebo. After 1-week of treatment, patients were evaluated over a period of 12 hours. Subsequently, patients were given the opposite treatment for 1-week and returned for the second evaluation. Patients could then enter an open-label extension phase for up to 21 months.

Efficacy assessments were conducted at 1, 2, 3, 4.5, 6, 7.5, 9, 10.5 and 12 hours post-dose using the Swanson, Kotkin, Agler, M. Flynn, and Pelham Total score (SKAMP). The primary efficacy endpoint was the average SKAMP Total Score, comparing APTENSIO XR to placebo. SKAMP is a validated 13-item teacher-rated scale that assesses manifestations of ADHD in a classroom setting.

The SKAMP Total Scores were statistically significantly better (lower) for APTENSIO XR than for placebo at the test day average and at all time points (1, 2, 3, 4.5, 6, 7.5, 9, 10.5 and 12 hours) post-dosing (see Figure 2).

Figure 2: Absolute SKAMP- Total Score after treatment with APTENSIO XR or Placebo (Study 1).



A randomized, double-blind, multicenter, placebo-controlled, parallel-group, fixed-dose study (Study 2) was conducted in pediatric patients age 6 to 17 years (N=230) who met DSM-IV-TR criteria for ADHD inattentive, hyperactive-impulsive or combined inattentive/hyperactive-impulsive subtypes.

The ADHD-RS-IV is an 18-item questionnaire with a score range of 0 to 54 points that measures the core symptoms of ADHD and includes both hyperactive/impulsive and inattentive subscales.

Patients were randomized to a daily morning dose of APTENSIO XR 10 mg, 15 mg, 20 mg, or 40 mg, or placebo for 1 week. An 11-week open label phase followed the double-blind phase. Patients could then enter another open-label phase for up to 21 months.

The primary efficacy endpoint was the mean decrease from baseline to the end of Week 1 in the ADHD-RS-IV Total Score. Each of the four APTENSIO XR doses (10 mg, 15 mg, 20 mg, and 40 mg/day) was compared to placebo at the end of week 1. For both the 20 mg/day and the 40 mg/day doses, APTENSIO XR was superior to placebo in reduction of the ADHD-RS-IV Total Score, but not for the 10 mg/day or the 15 mg/day doses.

A total of 221 patients completed the 1-week double-blind phase. Among those, 200 (90.5%) completed the 11-week open label phase and 173 (86.5%) patients continued into the 21-month open-label extension phase.

Table 3: Summary of Parallel-Group Study

Study Number	Treatment Group	Primary Efficacy Measure: ADHD-RS-IV Total Score		
		Mean Baseline Score (SD)	LS Mean Reduction from Baseline (SE)	Placebo-subtracted Difference[a] (95% CI)
Study 2 (Pediatric)	APTENSIO XR 10 mg/day	37.6 (8.32)	9.1 (1.40)	3.7 (-0.31, 7.66)
	APTENSIO XR 15 mg/day	38.0 (8.64)	10.3 (1.59)	4.9 (0.63, 9.07)
	APTENSIO XR 20 mg/day*	36.2 (8.46)	11.4 (1.49)	6.0 (1.92, 10.02)

	APTENSIO XR 40 mg/day*	35.6 (9.16)	12.8 (1.49)	7.4 (3.38, 11.45)
	Placebo	33.4 (11.01)	5.4 (1.48)	--

Note: SD: standard deviation; SE: standard error; LS Mean: least-squares mean;
CI: confidence interval, not adjusted for multiple comparisons.
[a] Difference (placebo minus drug) in least-squares mean change from baseline. Positive numbers indicate reduction (improvement).
* Doses that are demonstrated to be effective.

16 HOW SUPPLIED/STORAGE AND HANDLING

APTENSIO XR (methylphenidate hydrochloride extended-release) capsules are available as follows:

10 mg Capsules – light turquoise blue cap/white body, (imprinted with "APTENSIO XR" on cap and "10 mg" on the body)
Bottles of 90 ..... NDC 42858-401-45

15 mg Capsules – orange cap/white body, (imprinted with "APTENSIO XR" on cap and "15 mg" on the body)
Bottles of 90 ..... NDC 42858-402-45

20 mg Capsules – yellow cap/white body, (imprinted with "APTENSIO XR" on cap and "20 mg" on the body)
Bottles of 90 ..... NDC 42858-403-45

30 mg Capsules – blue violet cap/white body, (imprinted with "APTENSIO XR" on cap and "30 mg" on the body)
Bottles of 90 ..... NDC 42858-404-45

40 mg Capsules – pink cap/white body, (imprinted with "APTENSIO XR" on cap and "40 mg" on the body)
Bottles of 90 ..... NDC 42858-405-45

50 mg Capsules – green cap/white body, (imprinted with "APTENSIO XR" on cap and "50 mg" on the body)
Bottles of 90 ..... NDC 42858-406-45

60 mg Capsules – gray cap/white body, (imprinted with "APTENSIO XR" on cap and "60 mg" on the body)
Bottles of 90 ..... NDC 42858-407-45

Storage and Handling

APTENSIO XR (methylphenidate hydrochloride extended-release) capsules should be stored at 20°C to 25°C (68°F to 77°F) [see USP Controlled Room Temperature]. Protect from moisture.

Dispense in tight container (USP).

17 PATIENT COUNSELING INFORMATION

Advise patients to read the FDA-approved patient labeling (Medication Guide).

Controlled Substance Status/High Potential for Abuse and Dependence

Advise patients that APTENSIO XR is a controlled substance, and it can be abused and lead to dependence. Instruct patients that they should not give APTENSIO XR to anyone else. Advise patients to store APTENSIO XR in a safe place, preferably locked, to prevent abuse. Advise patients to comply with laws and regulations on

drug disposal. Advise patients to dispose of remaining, unused, or expired APTENSIO XR by a medicine take-back program if available *[see Boxed Warning, Warnings and Precautions (5.1), Drug Abuse and Dependence (9.1, 9.2, and 9.3)*].

Dosage and Administration Instructions

Advise patients that APTENSIO XR can be taken with or without food and that they should establish a routine pattern of taking APTENSIO XR with regard to meals. For patients who take APTENSIO XR sprinkled over applesauce, the contents of the entire capsule should be consumed immediately; it should not be stored. Patients should take the applesauce with sprinkled beads in its entirety without chewing. When initiating treatment with APTENSIO XR, provide dosage escalation and administration instructions *[see Dosage and Administration (2.1)]*.

Serious Cardiovascular Risks

Advise patients that there is a potential serious cardiovascular risk including sudden death, myocardial infarction, stroke, and hypertension with APTENSIO XR use. Instruct patients to contact a healthcare provider immediately if they develop symptoms such as exertional chest pain, unexplained syncope, or other symptoms suggestive of cardiac disease *[see Warnings and Precautions (5.2)]*.

Blood Pressure and Heart Rate Increases

Instruct patients that APTENSIO XR can cause elevations of their blood pressure and pulse rate *[see Warnings and Precautions (5.3)*].

Psychiatric Risks

Advise patients that APTENSIO XR, at recommended doses, can cause psychotic or manic symptoms, even in patients without prior history of psychotic symptoms or mania *[see Warnings and Precautions (5.4)]*.

Priapism

Advise patients of the possibility of painful or prolonged penile erections (priapism). Instruct them to seek immediate medical attention in the event of priapism *[see Warnings and Precautions (5.5)]*.

Circulation problems in fingers and toes [Peripheral vasculopathy, including Raynaud's phenomenon]

Instruct patients beginning treatment with APTENSIO XR about the risk of peripheral vasculopathy, including Raynaud's Phenomenon, and associated signs and symptoms: fingers or toes may feel numb, cool, painful, and/or may change from pale, to blue, to red. Instruct patients to report to their physician any new numbness, pain, skin color change, or sensitivity to temperature in fingers or toes.

Instruct patients to call their physician immediately with any signs of unexplained wounds appearing on fingers or toes while taking APTENSIO XR. Further clinical evaluation (e.g. rheumatology referral) may be appropriate for certain patients *[see Warnings and Precautions (5.6)]*.

Suppression of Growth

Advise patients that APTENSIO XR may cause slowing of growth and weight loss *[see Warnings and Precautions (5.7)]*.

Alcohol

Advise patients to avoid alcohol while taking APTENSIO XR. Consumption of alcohol while taking APTENSIO XR may result in a more rapid release of the dose of methylphenidate *[see Clinical Pharmacology (12.3)]*.

Marketed by:
Rhodes Pharmaceuticals L.P.
Coventry, RI 02816

Manufactured by:

Patheon Manufacturing Services LLC
Greenville, North Carolina 27834

This product is covered by US patents including US Patents No. 6,419,960, 7,083,808, 7,247,318, 8,580,310 and 9,066,869.

Component # 302802-0B

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