

Once Daily

Metadate CD[®]

(methylphenidate HCl, USP)



Extended-Release Capsules

Rx Only

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use METADATE CD[®] safely and effectively. See full prescribing information for METADATE CD.

METADATE CD (methylphenidate hydrochloride) extended-release capsules, CII

Initial U.S. Approval: 1955

WARNING: ABUSE, MISUSE, AND ADDICTION

See full prescribing information for complete boxed warning.

METADATE CD has a high potential for abuse and misuse, which can lead to the development of a substance use disorder, including addiction. Misuse and abuse of CNS stimulants, including METADATE CD, can result in overdose and death (5.1, 9.2, 10):

- Before prescribing METADATE CD, assess each patient's risk for abuse, misuse, and addiction.
- Educate patients and their families about these risks, proper storage of the drug, and proper disposal of any unused drug.
- Throughout treatment, reassess each patient's risk and frequently monitor for signs and symptoms of abuse, misuse, and addiction.

RECENT MAJOR CHANGES

| | |
|---|---------|
| Boxed Warning..... | 10/2023 |
| Dosage and Administration (2.1, 2.2) | 10/2023 |
| Warnings and Precautions (5.1, 5.2, 5.8, 5.9, 5.10) | 10/2023 |

INDICATIONS AND USAGE

METADATE CD is a central nervous system (CNS) stimulant indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in pediatric patients 6 to 15 years of age (1)

DOSAGE AND ADMINISTRATION

- Take orally once daily in the morning, before breakfast.
- Swallow whole with the aid of liquids, or sprinkle contents onto a small amount of applesauce and give immediately.
- Do not crush or chew the capsule or capsule contents (2.1)
- Recommended starting dose is 20 mg once daily. Dosage may be increased 10-20 mg at weekly intervals; do not exceed 60 mg per day (2.2)

DOSAGE FORMS AND STRENGTHS

Extended-release capsules: 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg (3)

FULL PRESCRIBING INFORMATION: CONTENTS*

ABUSE, MISUSE, AND ADDICTION

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

- 2.1 Pretreatment Screening
- 2.3 Administration Instructions
- 2.4 Dosage Reduction and Discontinuation

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Abuse, Misuse, and Addiction
- 5.2 Risks to Patients with Serious Cardiac Disease
- 5.3 Increased Blood Pressure and Heart Rate
- 5.4 Psychiatric Adverse Reactions
- 5.5 Priapism
- 5.6 Peripheral Vasculopathy, including Raynaud's Phenomenon
- 5.7 Long-Term Suppression of Growth in Pediatric Patients
- 5.8 Acute Angle Closure Glaucoma
- 5.9 Increased Intraocular Pressure and Glaucoma
- 5.10 Motor and Verbal Tics, and Worsening of Tourette's Syndrome

6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience
- 6.2 Postmarketing Experience

CONTRAINDICATIONS

- Known hypersensitivity to methylphenidate or other components of METADATE CD (4)
- Concurrent treatment with a monoamine oxidase inhibitor (MAOI), or use of an MAOI within the preceding 14 days (4)
- Use in patients with patients with hereditary problems of fructose intolerance, glucose-galactose malabsorption, or sucrose-isomaltase insufficiency (4)

WARNINGS AND PRECAUTIONS

- *Risks to Patients with Serious Cardiac Disease:* Avoid use in patients with known structural cardiac abnormalities, cardiomyopathy, serious cardiac arrhythmias, coronary artery disease, or other serious cardiac disease. (5.2)
- *Increased Blood Pressure and Heart Rate:* Monitor blood pressure and pulse. (5.3)
- *Psychiatric Adverse Reactions:* Prior to initiating METADATE CD, screen patients for risk factors for developing a manic episode. If new psychotic or manic symptoms occur, consider discontinuing METADATE CD. (5.4)
- *Priapism:* If abnormally sustained or frequent and painful erections occur, patients should seek immediate medical attention. (5.5)
- *Peripheral Vasculopathy, including Raynaud's Phenomenon:* Careful observation for digital changes is necessary during METADATE CD treatment. Further clinical evaluation (e.g., rheumatology referral) may be appropriate for patients who develop signs or symptoms of peripheral vasculopathy. (5.6)
- *Long-Term Suppression of Growth in Pediatric Patients:* Closely monitor growth (height and weight) in pediatric patients. Pediatric patients not growing or gaining height or weight as expected may need to have their treatment interrupted. (5.7)
- *Acute Angle Closure Glaucoma:* METADATE CD-treated patients considered at risk for acute angle closure glaucoma (e.g., patients with significant hyperopia) should be evaluated by an ophthalmologist. (5.8)
- *Increased Intraocular Pressure (IOP) and Glaucoma:* Prescribe METADATE CD to patients with open-angle glaucoma or abnormally increased IOP only if the benefit of treatment is considered to outweigh the risk. Closely monitor patients with a history of increased IOP or open angle glaucoma. (5.9)
- *Motor and Verbal Tics, and Worsening of Tourette's Syndrome:* Before initiating METADATE CD, assess the family history and clinically evaluate patients for tics or Tourette's syndrome. Regularly monitor patients for the emergence or worsening of tics or Tourette's syndrome. Discontinue treatment if clinically appropriate. (5.10)

ADVERSE REACTIONS

The most common adverse reactions (≥ 5% and twice the rate of placebo) were anorexia and insomnia (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Aytu BioPharma at 1-855-298-8246 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

- *Antihypertensive Drugs:* Monitor blood pressure. Adjust dosage of antihypertensive drug as needed (7)

See Section 17 for PATIENT COUNSELING INFORMATION and FDA-approved Medication Guide

Revised: 10/2023

7 DRUG INTERACTIONS

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Lactation
- 8.4 Pediatric Use
- 8.5 Geriatric Use

9 DRUG ABUSE AND DEPENDENCE

- 9.1 Controlled Substance
- 9.2 Abuse
- 9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the Full Prescribing Information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: ABUSE, MISUSE, AND ADDICTION

METADATE CD has a high potential for abuse and misuse, which can lead to the development of a substance use disorder, including addiction. Misuse and abuse of CNS stimulants, including METADATE CD, can result in overdose and death [see Overdosage (10)], and this risk is increased with higher doses or unapproved methods of administration, such as snorting or injection.

Before prescribing METADATE CD, assess each patient's risk for abuse, misuse, and addiction. Educate patients and their families about these risks, proper storage of the drug, and proper disposal of any unused drug. Throughout METADATE CD treatment, reassess each patient's risk of abuse, misuse, and addiction and frequently monitor for signs and symptoms of abuse, misuse, and addiction [see Warnings and Precautions (5.1) and Drug Abuse and dependence (9.2)].

1 INDICATIONS AND USAGE

METADATE CD is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in pediatric patients 6 to 15 years of age.

2 DOSAGE AND ADMINISTRATION

2.1 Pretreatment Screening

Prior to treating patients with METADATE CD, 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 (5.10)].
- the family history and clinically evaluate patients for motor or verbal tics or Tourette's syndrome before initiating METADATE CD [see Warnings and Precautions (5.10)].

2.2 Dosage Recommendations

The recommended starting dose of METADATE CD is 20 mg once daily. Dosage may be adjusted in weekly 10 mg to 20 mg increments to the maximum recommended dose of 60 mg per day.

Dosage should be individualized according to the needs and responses of the patient.

2.3 Administration Instructions

Administer METADATE CD orally once daily in the morning, before breakfast.

Swallow the capsule whole with the aid of liquids. Alternatively, open the capsule and sprinkle the contents onto a small amount (teaspoon) of applesauce and administer immediately. Do not store for future use. Drink fluids following the intake of the sprinkled capsule contents with applesauce. The capsules and the capsule contents must not be crushed or chewed.

2.4 Dosage Reduction and Discontinuation

If paradoxical aggravation of symptoms or other adverse reactions occur, reduce dosage or, if necessary, discontinue METADATE CD. If improvement is not observed after appropriate dosage adjustment over a one-month period, discontinue METADATE CD.

3 DOSAGE FORMS AND STRENGTHS

METADATE CD extended-release capsules are available in the following dosage strengths (see Table 1):

Table 1: Strengths and Identifying Characteristics of METADATE CD

| Strength | Capsule Color (cap/body) | Imprinting on Capsule Cap | Imprinting on Capsule Body |
|----------|--------------------------|-----------------------------|----------------------------|
| 10 mg | green/white | "AYTU 579" in white letters | "10 mg" in black letters |
| 20 mg | blue/white | "AYTU 580" in white letters | "20 mg" in black letters |
| 30 mg | reddish-brown/white | "AYTU 581" in white letters | "30 mg" in black letters |
| 40 mg | yellow ivory/white | "AYTU 582" in black letters | "40 mg" in black letters |
| 50 mg | purple/white | "AYTU 583" in white letters | "50 mg" in black letters |
| 60 mg | white/white capsules | "AYTU 584" in black letters | "60 mg" in black letters |

4 CONTRAINDICATIONS

METADATE CD is contraindicated in patients with:

- known hypersensitivity to methylphenidate or other component of METADATE CD. Angioedema has been reported in patients treated with METADATE CD. Anaphylactic reactions have been reported in patients treated with other methylphenidate products [see Adverse Reactions (6)].
- Concomitant treatment with monoamine oxidase inhibitors (MAOIs), or within 14 days following discontinuation of treatment with an MAOI, because of the risk of hypertensive crisis [see Drug Interactions (7)].
- METADATE CD contains sucrose. Therefore, patients with hereditary problems of fructose intolerance, glucose-galactose malabsorption, or sucrase-isomaltase insufficiency should not take this medicine.

5 WARNINGS AND PRECAUTIONS

5.1 Abuse, Misuse, and Addiction

METADATE CD has a high potential for abuse and misuse. The use of METADATE CD exposes individuals to the risks of abuse and misuse, which can lead to the development

of a substance use disorder, including addiction. METADATE CD can be diverted for non-medical use into illicit channels or distribution [see Drug Abuse and Dependence (9.2)]. Misuse and abuse of CNS stimulants, including METADATE CD, can result in overdose and death [see Overdosage (10)], and this risk is increased with higher doses or unapproved methods of administration, such as snorting or injection.

Before prescribing METADATE CD, assess each patient's risk for abuse, misuse, and addiction. Educate patients and their families about these risks and proper disposal of any unused drug. Advise patients to store METADATE CD in a safe place, preferably locked, and instruct patients to not give METADATE CD to anyone else. Throughout METADATE CD treatment, reassess each patient's risk of abuse, misuse, and addiction and frequently monitor for signs and symptoms of abuse, misuse, and addiction.

5.2 Risks to Patients with Serious Cardiac Disease

Sudden death has been reported in patients with structural cardiac abnormalities or other serious cardiac disease who were treated with CNS stimulants at the recommended dosage.

Avoid METADATE CD use in patients with known structural cardiac abnormalities, cardiomyopathy, serious cardiac arrhythmia, coronary artery disease, or other serious cardiac problems.

5.3 Increased Blood Pressure and Heart Rate

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). Some patients may have larger increases.

Monitor all METADATE CD treated 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 METADATE CD 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 the recommended dosages, may cause psychotic or manic symptoms (e.g., hallucinations, delusional thinking, or mania) in patients without a prior history of psychotic illness or mania. 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% of placebo-treated patients. If such symptoms occur, consider discontinuing METADATE CD.

5.5 Priapism

Prolonged and painful erections, sometimes requiring surgical intervention, have been reported with methylphenidate use in both adult and pediatric male patients. Although priapism was not reported with methylphenidate initiation, it developed after some time on methylphenidate, often subsequent to an increase in dosage. Priapism also occurred during methylphenidate withdrawal (drug holidays or during discontinuation).

METADATE CD-treated patients who develop abnormally sustained or frequent and painful erections should seek immediate medical attention.

5.6 Peripheral Vasculopathy, including Raynaud's Phenomenon

CNS stimulants, including METADATE CD, used to treat ADHD are associated with peripheral vasculopathy, including Raynaud's phenomenon. Signs and symptoms are usually intermittent and mild; however, sequelae have included digital ulceration and/or soft tissue breakdown. Effects of peripheral vasculopathy, including Raynaud's phenomenon, were observed in post-marketing reports and at the therapeutic dosages of CNS stimulants in all age groups throughout the course of treatment. Signs and symptoms generally improved after dosage reduction in or discontinuation of the CNS stimulant.

Careful observation for digital changes is necessary during METADATE CD treatment. Further clinical evaluation (e.g., rheumatology referral) may be appropriate for METADATE CD-treated patients who develop signs of symptoms of peripheral vasculopathy.

5.7 Long-Term Suppression of Growth in Pediatric Patients

CNS stimulants have been associated with weight loss and slowing of growth rate in pediatric patients.

Careful follow-up of weight and height in children 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 children over 36 months (to the ages of 10 to 13 years), suggests that pediatric patients who received methylphenidate treatment for 7 days per week throughout the year had 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 development period.

Closely monitor growth (weight and height) in METADATE CD-treated pediatric patients. Pediatric patients who are not growing or gaining height or weight as expected may need to have their treatment interrupted.

5.8 Acute Angle Closure Glaucoma

There have been reports of angle closure glaucoma associated with methylphenidate treatment. Although the mechanism is not clear, METADATE CD-treated patients considered at risk for acute angle closure glaucoma (e.g., patients with significant hyperopia) should be evaluated by an ophthalmologist.

5.9 Increased Intraocular Pressure and Glaucoma

There have been reports of an elevation of intraocular pressure (IOP) associated with methylphenidate treatment [see Adverse Reactions (6.2)].

Prescribe METADATE CD to patients with open-angle glaucoma or abnormally increased IOP only if the benefit of treatment is considered to outweigh the risk. Closely monitor METADATE CD-treated patients with a history of abnormally increased IOP or open angle glaucoma.

5.10 Motor and Verbal Tics, and Worsening of Tourette's Syndrome

CNS stimulants, including methylphenidate, have been associated with the onset or exacerbation of motor and verbal tics. Worsening of Tourette's syndrome has also been reported [see Adverse Reactions (6.2)].

Before initiating METADATE CD, assess the family history and clinically evaluate patients for tics or Tourette's syndrome. Regularly monitor METADATE CD-treated patients for the emergence or worsening of tics or Tourette's syndrome, and discontinue treatment if clinically appropriate.

6 ADVERSE REACTIONS

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

- Abuse, Misuse, and Addiction [see Warnings and Precautions (5.1), Drug Abuse and Dependence (9.2, 9.3)]
- Hypersensitivity to Methylphenidate and Other Component of METADATE CD [see Contraindications (4)]
- Hypertensive Crisis when Used Concomitantly with MAOIs [see Contraindications (4) and Drug Interactions (7)]
- Risks to Patients with Serious Cardiac Disease [see Warnings and Precautions (5.2)]
- Increased Blood Pressure and Heart Rate [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 in Pediatric Patients [see Warnings and Precautions (5.7)]
- Acute Angle Closure Glaucoma [see Warnings and Precautions (5.8)]
- Increased Intraocular Pressure and Glaucoma [see Warnings and Precautions (5.9)]
- Motor and Verbal Tics, and Worsening of Tourette's Syndrome [see Warnings and Precautions (5.10)]

6.1 Clinical Trials 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 practice.

Clinical trials experience with METADATE CD included 188 pediatric patients 6 to 15 years old with ADHD exposed to METADATE CD. Patients received METADATE CD 20 mg, 40 mg, and/or 60 mg per day. The 188 patients were evaluated in the following studies: Study 1, a 3-week placebo-controlled clinical study consisting of a total of 314 pediatric patients (ages 6 to 15 years; METADATE CD n=155); Study 2, a placebo-controlled, crossover clinical study consisting of 25 pediatric patients (ages 7 to 12 years); and Study 3, an uncontrolled clinical study consisting of 8 pediatric patients (ages 6 to 10 years).

Adverse Reactions Leading to Discontinuation of Treatment

In the 3-week placebo-controlled, parallel-group trial, two METADATE CD-treated patients (1%) and no placebo-treated patients discontinued due to an adverse reaction (rash and pruritus; and headache, abdominal pain, and dizziness, respectively).

Most Common Adverse Reactions

The most common adverse reactions that occurred in 5% or more of patients treated with METADATE CD in a pool of Studies 1, 2 and 3 (ages 6 to 15 years) where the incidence in patients treated with METADATE CD was at least twice the incidence in placebo-treated patients were anorexia and insomnia.

Adverse reactions that occurred in ≥5% of patients treated with METADATE CD and greater than placebo in pooled Studies, 1, 2, and 3 are presented in Table 2:

Table 2: Adverse Reactions (≥5% and Greater than Placebo) in Pediatric Patients Ages 6 to 15 Years Receiving METADATE CD in Pooled Three to Four Week Trials

| Body System | Preferred Term | METADATE CD (n=188) % | Placebo (n=190) % |
|------------------|------------------------------|--------------------------|----------------------|
| General | Headache | 12 | 8 |
| | Abdominal Pain (stomachache) | 7 | 4 |
| Digestive System | Anorexia | 9 | 2 |
| Nervous System | Insomnia | 5 | 2 |

6.2 Postmarketing Experience

The following adverse reactions have been identified during postmarketing use of METADATE CD and other methylphenidate HCl 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.

Adverse Reactions with METADATE CD

Blood and the lymphatic system disorders: thrombocytopenia

Cardiac disorders: cardiac arrest, sudden death

Immune system disorders: angioedema

Musculoskeletal and connective tissue disorders: rhabdomyolysis

Psychiatric disorders: abnormal behavior, aggression, anxiety, irritability, obsessive-compulsive disorder, suicidal behavior (including completed suicide), libido changes, serotonin syndrome in combination with serotonergic drugs

Nervous System Disorder: migraine, reversible ischemic neurological deficit, bruxism

Skin and subcutaneous tissue disorders: fixed drug eruption

Vascular disorders: peripheral coldness, Raynaud's phenomenon

Adverse Reactions with Other Methylphenidate HCl Products

Blood and the lymphatic system disorders: leukopenia, anemia, pancytopenia

Cardiac disorders: palpitations; increased blood pressure, tachycardia, angina pectoris, cardiac arrhythmia, myocardial infarction, bradycardia, extrasystole

Eye disorders: blurred vision, difficulties in visual accommodation, diplopia, increased intraocular pressure, mydriasis

Gastrointestinal disorders: nausea, abdominal pain, dry mouth, vomiting, dyspepsia, diarrhea, constipation

General Disorders: fatigue, hyperpyrexia

Hepatobiliary disorders: abnormal liver function, ranging from transaminase elevation to severe hepatic injury

Immune system disorders: hypersensitivity, including anaphylaxis, auricular swelling, bullous conditions, eruptions, exanthemas

Infections and infestations: nasopharyngitis

Metabolism and nutrition disorders: decreased appetite, reduced weight gain and suppression of growth during prolonged use in pediatric patients

Musculoskeletal and connective tissue disorders: arthralgia, muscle cramps, myalgia, muscle twitching

Nervous System Disorder: nervousness, dizziness, headache, dyskinesia, including choreoathetoid movements, drowsiness, tremor, convulsions, cerebrovascular disorders (including vasculitis, cerebral hemorrhages and cerebrovascular accidents), serotonin syndrome in combination with serotonergic drugs, motor and verbal tics

Psychiatric disorders: depressed mood, restlessness, agitation, psychosis (sometimes with visual and tactile hallucinations), affect lability, mania, disorientation

Renal and urinary disorders: hematuria

Reproductive system and breast disorders: gynecomastia

Respiratory, thoracic and mediastinal disorders: pharyngolaryngeal pain, dyspnea, cough

Skin and subcutaneous tissue disorders: scalp hair loss, hyperhidrosis, angioneurotic edema, erythema, exfoliative dermatitis, thrombocytopenic purpura, urticaria, erythema multiforme rash

Urogenital disorders: priapism

Vascular disorders: isolated cases of cerebral arteritis and/or occlusion

7 DRUG INTERACTIONS

Table 3 presents clinically important drug interactions with METADATE CD.

Table 3: Clinically Important Drug Interactions with METADATE CD

| Monoamine Oxidase Inhibitors (MAOI) | |
|-------------------------------------|---|
| <i>Clinical Impact:</i> | Concomitant use of MAOIs and CNS stimulants, including METADATE CD, can cause hypertensive crisis. Potential outcomes include death, stroke, myocardial infarction, aortic dissection, ophthalmological complications, eclampsia, pulmonary edema, and renal failure [see Contraindications (4)]. |
| <i>Intervention:</i> | Concomitant use of METADATE CD with monoamine oxidase inhibitors (MAOIs) or within 14 days after discontinuing MAOI treatment is contraindicated. |
| Antihypertensive Drugs | |
| <i>Clinical Impact:</i> | METADATE CD may decrease the effectiveness of drugs used to treat hypertension [see Warnings and Precautions (5.3)]. |
| <i>Intervention:</i> | Adjust the dosage of the antihypertensive drug as needed. |
| Halogenated Anesthetics | |
| <i>Clinical Impact:</i> | Concomitant use of halogenated anesthetics and METADATE CD may increase the risk of sudden blood pressure and heart rate increase during surgery. |
| <i>Intervention:</i> | Monitor blood pressure and avoid use of METADATE CD in patients being treated with anesthetics on the day of surgery. |
| Risperidone | |
| <i>Clinical Impact:</i> | Combined use of methylphenidate with risperidone when there is a change, whether an increase or decrease, in dosage of either or both medications, may increase the risk of extrapyramidal symptoms (EPS). |
| <i>Intervention:</i> | Monitor for signs of EPS. |

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to ADHD medications, including METADATE CD, during pregnancy. Healthcare providers are encouraged to register patients by calling the National Pregnancy Registry for Psychostimulants at 1-866-961-2388.

Risk Summary

Published studies and postmarketing reports on methylphenidate use during pregnancy have not identified a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. There may be risks to the fetus associated with the use of CNS stimulants use during pregnancy (see Clinical Considerations).

No effects on morphological development were observed in embryo-fetal development studies with oral administration of methylphenidate to pregnant rats and rabbits during organogenesis at doses up to 10 and 15 times, respectively, the maximum recommended human dose (MRHD) of 60 mg/day given to adolescents on a mg/m² basis. However, spina bifida was observed in rabbits at a dose 53 times the MRHD given to adolescents. 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 6 times the MRHD given to adolescents (*see Data*).

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

CNS stimulants, such as METADATE CD, 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.

Animal Data

In embryo-fetal development 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. Malformations (increased incidence of fetal spina bifida) were observed in rabbits at the highest dose, which is approximately 52 times the MRHD of 60 mg/day given to adolescents on a mg/m² basis. The no effect level for embryo-fetal development in rabbits was 60 mg/kg/day (15 times the MRHD given to adolescents on a mg/m² basis). There was no evidence of morphological development effects in rats, although increased incidences of fetal skeletal variations were seen at the highest dose level (10 times the MRHD of 60 mg/day given to adults on a mg/m² basis), which was also maternally toxic. The no effect level for embryo-fetal development in rats was 25 mg/kg/day (3 times the MRHD on a mg/m² 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 (6 times the MRHD of 60 mg/day given to adults on a mg/m² 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 (~2 times the MRHD given to adolescents on a mg/m² basis).

8.2 Lactation

Risk Summary

Limited published literature, based on milk sampling from seven 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. 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 METADATE CD and any potential adverse effects on the breastfed infant from METADATE CD or from the underlying maternal condition.

Clinical Considerations

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

8.4 Pediatric Use

The safety and effectiveness of METADATE CD for the treatment of ADHD have been established in pediatric patients 6 to 15 years of age. The safety and effectiveness of METADATE CD in pediatric patients younger than 6 years of age have not been established. Long-term efficacy of methylphenidate in pediatric patients have not been established.

Long-Term Suppression of Growth

Growth should be monitored during treatment with stimulants, including Metadate CD. Pediatric patients who are not growing or gaining weight as expected may need to have their treatment interrupted [see Warnings and Precautions (5.6)].

Juvenile Animal Toxicity Data

In a 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 to 14), decreased spontaneous locomotor activity was observed in males and females previously treated with 50 mg/kg/day (approximately 6 times the MRHD on a mg/m² basis) or greater, and a deficit in the acquisition of a specific learning task was seen in females exposed to the highest dose (12 times the MRHD on a mg/m² basis). The no effect level for juvenile neurobehavioral development in rats was 5 mg/kg/day (half the MRHD on a mg/m² basis). The clinical significance of the long-term behavioral effects observed in rats is unknown.

8.5 Geriatric Use

METADATE CD has not been studied in patients over the age of 65 years.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

METADATE CD contains methylphenidate hydrochloride, a Schedule II controlled substance.

9.2 Abuse

METADATE CD has a high potential for abuse and misuse which can lead to the development of a substance use disorder, including addiction [*see Warnings and Precautions (5.1)*]. METADATE CD can be diverted for non-medical use into illicit channels or distribution.

Abuse is the intentional non-therapeutic use of a drug, even once, to achieve a desired psychological or physiological effect. Misuse is the intentional use, for therapeutic purposes, of a drug by an individual in a way other than prescribed by a health care provider or for whom it was not prescribed. Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that may include a strong desire to take the

drug, difficulties in controlling drug use (e.g., continuing drug use despite harmful consequences, giving a higher priority to drug use than other activities and obligations), and possible tolerance or physical dependence.

Misuse and abuse of methylphenidate may cause increased heart rate, respiratory rate, or blood pressure; sweating; dilated pupils; hyperactivity; restlessness; insomnia; decreased appetite; loss of coordination; tremors; flushed skin; vomiting; and/or abdominal pain. Anxiety, psychosis, hostility, aggression, and suicidal or homicidal ideation have also been observed with CNS stimulants abuse and/or misuse. Misuse and abuse of CNS stimulants, including METADATE CD, can result in overdose and death [*see Overdosage (10)*], and this risk is increased with higher doses or unapproved methods of administration, such as snorting or injection.

9.3 Dependence

Physical Dependence

METADATE CD may produce physical dependence. Physical dependence is a state that develops as a result of physiological adaptation in response to repeated drug use, manifested by withdrawal signs and symptoms after abrupt discontinuation or a significant dose reduction of a drug.

Withdrawal signs and symptoms after abrupt discontinuation or dose reduction following prolonged use of CNS stimulants including METADATE CD include dysphoric mood; depression; fatigue; vivid; unpleasant dreams; insomnia or hypersomnia; increased appetite; and psychomotor retardation or agitation.

Tolerance

METADATE CD may produce tolerance. Tolerance is a physiological state characterized by a reduced response to a drug after repeated administration (i.e., a higher dose of a drug is required to produce the same effect that was once obtained at a lower dose).

10 OVERDOSAGE

Clinical Effects of Overdose

Overdose of CNS stimulants is characterized by the following sympathomimetic effects:

- Cardiovascular effects including tachyarrhythmias, and hypertension or hypotension. Vasospasm, myocardial infarction, or aortic dissection may precipitate sudden cardiac death. Takotsubo cardiomyopathy may develop.
- CNS effects including psychomotor agitation, confusion, and hallucinations. Serotonin syndrome, seizures, cerebral vascular accidents, and coma may occur.
- Life-threatening hyperthermia (temperatures greater than 104°F) and rhabdomyolysis may develop.

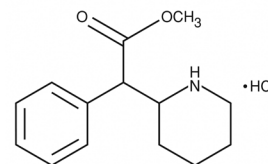
Overdose Management

Consider the possibility of multiple drug ingestion. The pharmacokinetic profile of METADATE CD should be considered when treating patients with overdose. Because methylphenidate has a large volume of distribution and is rapidly metabolized, dialysis is not useful. Consider contacting the Poison Help line (1-800-222-1222) or a medical toxicologist for additional overdose management recommendations.

11 DESCRIPTION

METADATE CD contains methylphenidate hydrochloride, a CNS stimulant. The extended-release capsules comprise both immediate-release (IR) and extended-release (ER) beads such that 30% of the dose is provided by the IR component and 70% of the dose is provided by the ER component. METADATE CD is available in six capsule strengths containing 10 mg (3 mg IR; 7 mg ER), 20 mg (6 mg IR; 14 mg ER), 30 mg (9 mg IR; 21 mg ER), 40 mg (12 mg IR; 28 mg ER), 50 mg (15 mg IR; 35 mg ER), or 60 mg (18 mg IR; 42 mg ER) of methylphenidate hydrochloride for oral administration.

Chemically, methylphenidate HCl is *d,l*-(racemic)-*threo*-methyl α -phenyl-2-piperidineacetate hydrochloride. Its empirical formula is C₁₄H₁₉NO₂•HCl. Its structural formula is:



Methylphenidate HCl USP is a white, odorless, 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.

METADATE CD also contains the following inactive ingredients: Dibutyl sebacate, ethylcellulose aqueous dispersion, gelatin, hydroxypropylmethylcellulose, polyethylene glycol, povidone, sugar spheres, and titanium dioxide.

The individual capsules contain the following color agents:
10 mg capsules: FD&C Blue No. 2, FDA/E172 Yellow Iron Oxide
20 mg capsules: FD&C Blue No. 2
30 mg capsules: FD&C Blue No. 2, FDA/E172 Red Iron Oxide
40 mg capsules: FDA/E172 Yellow Iron Oxide
50 mg capsules: FD&C Blue No. 2, FDA/E172 Red Iron Oxide

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Methylphenidate hydrochloride is a central nervous system (CNS) stimulant. The mode of therapeutic action in ADHD is not known.

12.2 Pharmacodynamics

Methylphenidate is a racemic mixture comprised of the *d*- and *l*-*threo* enantiomers. The *d*-*threo* enantiomer is more pharmacologically active than the *l*-*threo* enantiomer. Methylphenidate blocks the reuptake of norepinephrine and dopamine into the presynaptic neuron and increases the release of these monoamines into the extraneuronal space.

12.3 Pharmacokinetics

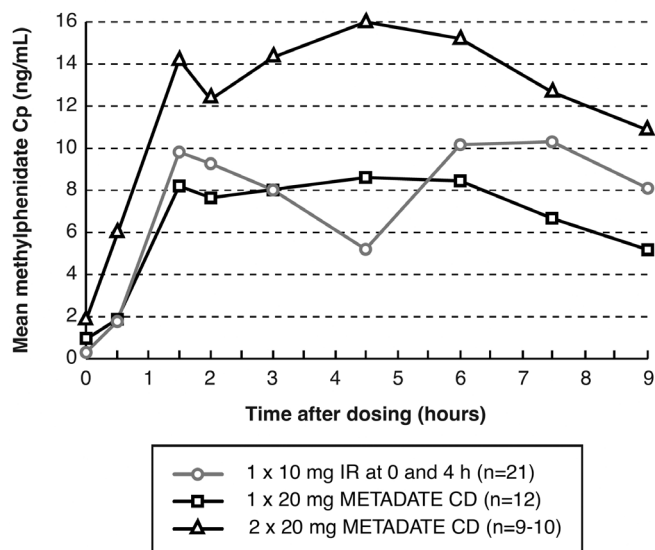
Following one week of once-daily doses of 20 mg or 40 mg METADATE CD to children aged 7 to 12 years old with ADHD, C_{max} and AUC of methylphenidate were approximately proportional to the administered doses.

Absorption

Following administration of METADATE CD in children aged 7 to 12 years old with ADHD, the plasma concentration time profile of methylphenidate showed two phases of drug release with a sharp, initial slope similar to a methylphenidate immediate-release tablet (median T_{max1} about 1.5 hours post dose), and a second rising portion approximately three hours later (median T_{max2} about 4.5 hours post dose)*, followed by a gradual decline (Figure 1). The means for C_{max} and area under the curve (AUC) following a dose of 20 mg were slightly lower than those seen with 10 mg of the immediate-release formulation, dosed at 0 and 4 hours.

*25-30% of the subjects had only one observed peak (C_{max}) concentration of methylphenidate.

Figure 1: Comparison of Immediate Release (IR) and METADATE CD Formulations After Repeated Doses of Methylphenidate HCl in Pediatric Patients 7 to 12 Years of Age with ADHD



Effect of Food

Ingestion of a high-fat meal with METADATE CD increased the mean C_{max} and AUC of methylphenidate by about 30% and 17%, respectively. The presence of food delayed the early peak by approximately 1 hour (range -2 to 5 hours delay). [see Dosage and Administration (2.1)].

The bioavailability (C_{max} and AUC) of methylphenidate was unaffected by sprinkling the METADATE CD capsule contents on applesauce as compared to the intact capsule.

Effect of Alcohol

At an alcohol concentration of 40%, there was an increase in the release rate of methylphenidate in the first hour, resulting in 84% of the methylphenidate being released. The results with the 60 mg capsule are considered to be representative of the other available capsule strengths [see Drug Interactions (7)].

Distribution

Plasma protein binding is 10% to 33%. The volume of distribution was 2.65 ± 1.11 L/kg for d- methylphenidate and 1.80 ± 0.91 L/kg for l- methylphenidate.

Elimination

The mean terminal half-life ($t_{1/2}$) of methylphenidate following administration of METADATE CD ($t_{1/2}$ =6.8 hours) is longer than the mean terminal $t_{1/2}$ following administration of methylphenidate hydrochloride immediate-release tablets ($t_{1/2}$ =2.9 hours) and methylphenidate hydrochloride extended-release tablets ($t_{1/2}$ =3.4 hours) in healthy adult volunteers.

Metabolism

In vitro studies showed that methylphenidate was not metabolized by cytochrome P450 isoenzymes. Methylphenidate is metabolized primarily by deesterification to alpha-phenyl-piperidine acetic acid (ritalinic acid), which has little or no pharmacologic activity.

Excretion

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

Specific Populations

Male and Female Patients

The pharmacokinetics of methylphenidate after a single dose of METADATE CD were similar between adult men and women.

Racial or Ethnic Groups

The influence of race on the pharmacokinetics of methylphenidate after METADATE CD administration has not been studied.

Pediatric Patients

The pharmacokinetics of methylphenidate after METADATE CD administration has not been studied in children less than 6 years of age.

Patients with Renal Impairment

METADATE CD has not been studied in patients with renal insufficiency. Since renal clearance is not an important route of methylphenidate clearance, and the major metabolite (ritalinic acid), has little or no pharmacologic activity, renal insufficiency is expected to have minimal effect on the pharmacokinetics of METADATE CD.

Patients with Hepatic Impairment

METADATE CD has not been studied in patients with hepatic insufficiency. Hepatic impairment is expected to have minimal effect on the pharmacokinetics of methylphenidate since it is metabolized primarily to ritalinic acid by nonmicrosomal hydrolytic esterases that are widely distributed throughout the body

Drug Interaction Studies

In vitro studies showed that methylphenidate did not inhibit cytochrome P450 isoenzymes at clinically observed plasma drug concentrations.

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 per day. This dose is approximately 2 times the maximum recommended human dose (MRHD) of 60 mg/day given to children on a mg/m² 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 increases 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 4 times the MRHD (children) on a mg/m² basis.

In a 24-week carcinogenicity study in the transgenic mouse strain p53+/-, which is sensitive to genotoxic carcinogens, there was no evidence of carcinogenicity. Male and female mice were fed diets containing the same concentration of methylphenidate as in the lifetime carcinogenicity study; the high-dose groups were exposed to 60 to 74 mg/kg per day of methylphenidate.

Mutagenesis

Methylphenidate was not mutagenic in the *in vitro* Ames reverse mutation assay, in the *in vitro* mouse lymphoma cell forward mutation assay, or in the *in vitro* chromosomal aberration assay using human lymphocytes. Sister chromatid exchanges and chromosome aberrations were increased, indicative of a weak clastogenic response, in an *in vitro* assay in cultured Chinese Hamster Ovary cells. Methylphenidate was negative *in vivo* in males and females in the mouse bone marrow micronucleus 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 up to 160 mg/kg per day, approximately 10 times the maximum recommended human dose of 60 mg/day given to adolescents on a mg/m² basis.

14 CLINICAL STUDIES

METADATE CD was evaluated in a double-blind, parallel-group, placebo-controlled trial in which 321 untreated or previously treated pediatric patients with a DSM-IV diagnosis of Attention Deficit Hyperactivity Disorder (ADHD), 6 to 15 years of age, received a single morning dose for up to 3 weeks. Patients were required to have the combined or predominantly hyperactive-impulsive subtype of ADHD; patients with the predominantly inattentive subtype were excluded. Patients randomized to the METADATE CD group received 20 mg daily for the first week. Their dosage could be increased weekly to a maximum of 60 mg by the third week, depending on individual response to treatment.

The patient's regular school teacher completed the teachers' version of the Conners' Global Index Scale (TCGIS), a scale for assessing ADHD symptoms, in the morning and again in the afternoon on three alternate days of each treatment week. The primary efficacy endpoint was determined by the average of the total scores for the 10-item TCGIS completed by the classroom teacher in the morning and again in the afternoon on the three observation days during the last week of double-blind therapy. Patients treated with METADATE CD showed a statistically significant improvement in symptom scores from baseline over patients who received placebo (See Figure 2). Separate analyses of TCGIS scores in the morning and afternoon revealed superiority in improvement with METADATE CD over placebo during both time periods (See Figure 3).

Figure 2: Least Squares Mean Change from Baseline in TCGIS Total Score in Pediatric Patients 6 to 15 years of Age with ADHD

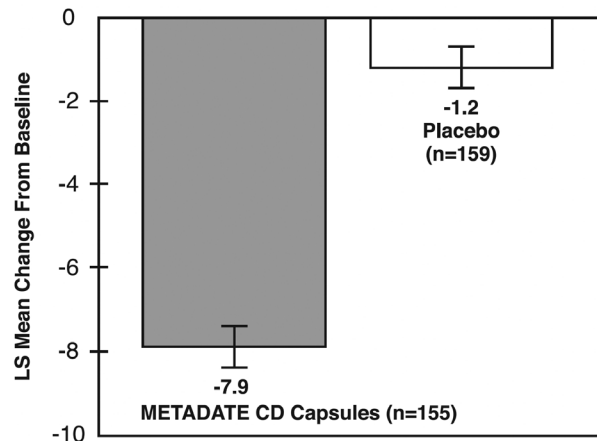
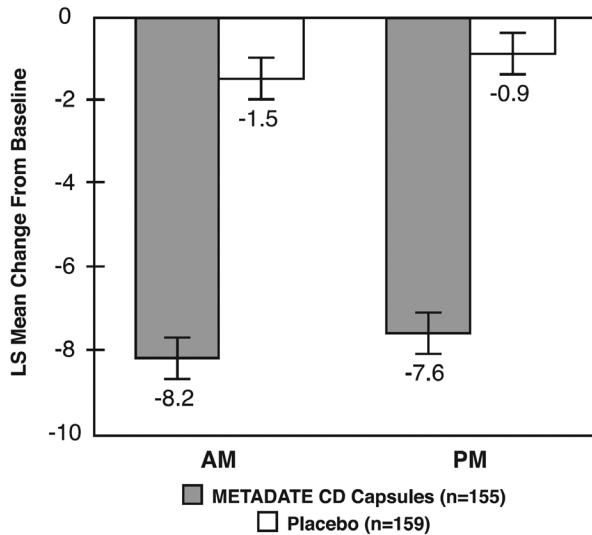


Figure 3: Least Squares Mean Change from Baseline in TCGIS Total Score in Pediatric Patients 6 to 15 years of Age with ADHD: Morning (AM) and Afternoon (PM)



* FIGURES 2 & 3: Last observation carried forward analysis at week 3. Error bars represent the standard error of the mean.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

METADATE CD (methylphenidate HCl, USP) extended-release capsules are available in six strengths (see Table 4):

Table 4: Strengths, Identifying Characteristics, and Packaging Configurations of METADATE CD

| Strength | Capsule Color (cap/body) | Imprinting on Capsule Cap | Imprinting on Capsule Body | Capsules per Bottle | NDC Number |
|----------|--------------------------|-----------------------------|----------------------------|---------------------|------------------|
| 10 mg | green/white | “AYTU 579” in white letters | “10 mg” in black letters | 30 | NDC 69654-579-30 |
| 20 mg | blue/white | “AYTU 580” in white letters | “20 mg” in black letters | 30 | NDC 69654-580-30 |
| 30 mg | reddish-brown/white | “AYTU 581” in white letters | “30 mg” in black letters | 30 | NDC 69654-581-30 |
| 40 mg | yellow ivory/white | “AYTU 582” in black letters | “40 mg” in black letters | 30 | NDC 69654-582-30 |
| 50 mg | purple/white | “AYTU 583” in white letters | “50 mg” in black letters | 30 | NDC 69654-583-30 |
| 60 mg | white/white capsules | “AYTU 584” in black letters | “60 mg” in black letters | 30 | NDC 69654-584-30 |

Storage and Handling

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

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

Abuse, Misuse, and Addiction

Educate patients and their families about the risks of abuse, misuse, and addiction of METADATE CD, which can lead to overdose and death, and proper disposal of any unused drug [see Warnings and Precautions (5.1)], Drug Abuse and Dependence (9.2), Overdosage (10)]. Advise patients to store METADATE CD in a safe place, preferably locked, and instruct patients to not give METADATE CD to anyone else.

Administration Instructions

Instruct patients and their caregivers that the METADATE CD capsules and the capsule contents must not be crushed or chewed. Instruct patients that the capsule may be swallowed whole, or alternatively, the capsule may be opened and the capsule contents sprinkled onto a small amount (tablespoon) of applesauce and given immediately, and not stored for future use [see Dosage and Administration (2.3)].

Risks to Patients with Serious Cardiac Disease

Advise patients that there are potential risks to patients with serious cardiac disease, including sudden death, with METADATE CD 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)].

Increased Blood Pressure and Heart Rate

Instruct patients and their caregivers that METADATE CD can cause elevations of their blood pressure and pulse rate [see Warnings and Precautions (5.3)].

Psychiatric Adverse Reactions

Advise patients and their caregivers that METADATE CD, at recommended doses, can cause psychotic or manic symptoms, even in patients without a prior history of psychotic symptoms or mania [see Warnings and Precautions (5.4)].

Priapism

Advise patients and their caregivers of the possibility of painful or prolonged penile erections (priapism). Instruct the patient 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 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 color 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. Further clinical evaluation (e.g., rheumatology referral) may be appropriate for certain patients [see Warnings and Precautions (5.6)].

Long-Term Suppression of Growth in Pediatric Patients

Advise patients and their caregivers that METADATE CD can cause slowing of growth and weight loss [see Warnings and Precautions (5.7)].

Increased Intraocular Pressure (IOP) and Glaucoma

Advise patients what IOP and glaucoma may occur during treatment with METADATE CD [see Warnings and Precautions (5.9)].

Motor and Verbal Tics, and Worsening of Tourette’s Syndrome

Advise patients that motor and verbal tics and worsening of Tourette’s Syndrome may occur during treatment with METADATE CD. Instruct patients to notify their healthcare provider if emergence of new tics or worsening of tics or Tourette’s syndrome occurs [see Warnings and Precautions (5.10)].

Pregnancy Registry

Inform patients that there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to METADATE CD during pregnancy [see Use in Specific Populations (8.1)].

Alcohol Use

Advise patients to avoid alcohol while taking METADATE CD. Consumption of alcohol while taking METADATE CD may result in a more rapid release of the dose of methylphenidate [see Drug Interactions (7)].

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Aytu BioPharma
Denver, CO 80237

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MEDICATION GUIDE
METADATE CD® (meh-tuh-dayt CD®)
(methylphenidate)
extended-release capsules, CII

What is the most important information I should know about METADATE CD?

METADATE CD may cause serious side effects, including:

- **Abuse, misuse, and addiction.** METADATE CD has a high chance for abuse and misuse and may lead to substance use problems, including addiction. Misuse and abuse of METADATE CD, other methylphenidate containing medicines, and amphetamine containing medicines, can lead to overdose and death. The risk of overdose and death is increased with higher doses of METADATE CD or when it is used in ways that are not approved, such as snorting or injection.
 - Your healthcare provider should check your child's risk for abuse, misuse, and addiction before starting treatment with METADATE CD and will monitor your child during treatment.
 - METADATE CD may lead to physical dependence after prolonged use, even if taken as directed by your healthcare provider.
 - Do not give METADATE CD to anyone else. See **“What is METADATE CD?”** for more information.

Keep METADATE CD in a safe place and properly dispose of any unused medicine. See **“How should I store METADATE CD?”** for more information. Tell your healthcare provider if your child has ever abused or been dependent on alcohol, prescription medicines, or street drugs.

- **Risks for people with serious heart disease.** Sudden death has happened in people who have heart defects or other serious heart disease. Your healthcare provider should check your child carefully for heart problems before starting treatment with METADATE CD. Tell your healthcare provider if your child has any heart problems, heart disease, or heart defects.

Call your healthcare provider or go to the nearest hospital emergency room right away if your child has any signs of heart problems such as chest pain, shortness of breath, or fainting during treatment with METADATE CD.

- **Increased blood pressure and heart rate.**

Your healthcare provider should check your child's blood pressure and heart rate regularly during treatment with METADATE CD.

- **Mental (psychiatric) problems, including:**

- new or worse behavior and thought problems
- new or worse bipolar illness
- new psychotic symptoms (such as hearing voices, or seeing or believing things that are not real) or new manic symptoms

Tell your healthcare provider about any mental problems your child has, or about a family history of, suicide, bipolar illness, or depression.

Call your healthcare provider right away if your child has any new or worsening mental symptoms or problems during treatment with METADATE CD, especially hearing voices, seeing or believing things that are not real, or new manic symptoms.

What is METADATE CD?

METADATE CD is a prescription medicine used for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children 6 to 15 years of age. METADATE CD may help increase attention and decrease impulsiveness and hyperactivity in people with ADHD.

It is not known if METADATE CD is safe and effective for use in children younger than 6 years of age or older than 15 years of age.

METADATE CD is a federally controlled substance (CII) because it contains methylphenidate that can be a target for people who abuse prescription medicines or street drugs. Keep METADATE CD in a safe place to protect it from theft. Never give your METADATE CD to anyone else, because it may cause death or harm them. Selling or giving away METADATE CD may harm others and is against the law.

Who should not take METADATE CD?

Your child should not take METADATE CD if your child:

- is allergic to methylphenidate hydrochloride or any of the ingredients in METADATE CD. See the end of this Medication Guide for a complete list of ingredients in METADATE CD.
- has a rare inherited problem with the breaking down, absorbing, and processing of certain types of sugar in the body. METADATE CD contains a type of sugar called sucrose.
- is taking, or has stopped taking within the past 14 days, a medicine called a monoamine oxidase inhibitor (MAOI).

Before starting METADATE CD tell your healthcare provider about all your child's medical conditions, including: if your child:

- has heart problems, heart disease, heart defects, or high blood pressure
- has mental problems including psychosis, mania, bipolar illness, or depression or has a family history of suicide, bipolar illness, or depression
- has circulation problems in fingers and toes
- have eye problems, including increased pressure in your eye, glaucoma, or problems with your close-up vision (farsightedness)
- have or had repeated movements or sounds (tics) or Tourette's syndrome, or have a family history of tics or Tourette's syndrome
- is pregnant or plan to become pregnant. It is not known if METADATE CD will harm the unborn baby.
 - There is a pregnancy registry for females who are exposed to METADATE CD during pregnancy. The purpose of the registry is to collect information about the health of females exposed to METADATE CD and their baby. If you or your child becomes pregnant during treatment with METADATE CD, talk to your healthcare provider about registering with the National Pregnancy Registry for Psychostimulants at 1-866-961-2388.
- is breastfeeding or plan to breastfeed. METADATE CD passes into breast milk. Talk to your healthcare provider about the best way to feed the baby during treatment with METADATE CD.

Tell your healthcare provider about all the medicines that your child takes, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

METADATE CD and some medicines may interact with each other and cause serious side effects. Sometimes the doses of other medicines will need to be changed during treatment with METADATE CD. Your healthcare provider will decide whether METADATE CD can be taken with other medicines.

Especially tell your healthcare provider if your child takes a medicine used to treat depression called a monoamine oxidase inhibitor (MAOI). Know the medicines that your child takes. Keep a list of the medicines with you to show your healthcare provider and pharmacist. **Your child should not start taking any new medicines during treatment with METADATE CD without talking to your healthcare provider first.**

How should METADATE CD be taken?

- Take METADATE CD exactly as prescribed by your healthcare provider.
- Your healthcare provider may change the dose if needed.
- Take METADATE CD 1 time each day in the morning before breakfast.
- Swallow METADATE CD capsules whole with water or other liquids.
- If METADATE CD capsules cannot be swallowed whole, the capsule may be opened and the contents sprinkled onto a tablespoonful of applesauce.
 - Follow with a drink of water or other liquid.
 - **Do not** chew the applesauce and medicine mixture.
 - Swallow all the applesauce and medicine mixture right away. Do not store the applesauce and medicine mixture.

If your child takes too much METADATE CD, call your healthcare provider or Poison Help line at 1-800-222-1222 or go to the nearest hospital emergency room right away.

What should be avoided during treatment with METADATE CD?

Avoid drinking alcohol during treatment with METADATE CD. This may cause a faster release of the METADATE CD medicine.

What are the possible side effects of METADATE CD?

METADATE CD may cause serious side effects, including:

- See “**What is the most important information I should know about METADATE CD?**”
- **Painful and prolonged erections (priapism).** Priapism has happened in males who take products that contain methylphenidate. **If your child develops priapism, get medical help right away.**
- **Circulation problems in fingers and toes (peripheral vasculopathy, including Raynaud’s phenomenon).** Signs and symptoms may include:
 - fingers or toes may feel numb, cool, painful
 - fingers or toes may change color from pale, to blue, to red

Tell your healthcare provider if your child has numbness, pain, skin color change, or sensitivity to temperature in the fingers or toes.

Call your healthcare provider right away if your child has any signs of unexplained wounds appearing on the fingers or toes during treatment with METADATE CD.

- **Slowing of growth (height and weight) in children.** Children should have their height and weight checked often during treatment with METADATE CD. METADATE CD treatment may be stopped if your child is not growing or gaining weight.
- **Eye problems (increased pressure in the eye and glaucoma).** Call your healthcare provider right away if you or your child develop changes in your vision or eye pain, swelling, or redness.
- **New or worsening tics or worsening Tourette’s syndrome.** Tell your healthcare provider if you or your child get any new or worsening tics or worsening Tourette’s syndrome during treatment with METADATE CD.

The most common side effects of METADATE CD include anorexia and trouble sleeping.

These are not all the possible side effects of METADATE CD.

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 METADATE CD?

- Store METADATE CD at room temperature between 68°F to 77°F (20°C to 25°C).
- Store METADATE CD in a safe place, like a locked cabinet. Protect from light and moisture.
- Dispose of remaining, unused, or expired METADATE CD by a medicine take-back program at a U.S. Drug Enforcement Administration (DEA) authorized collection site. If no take-back program or DEA authorized collector is available, mix METADATE CD with an undesirable, nontoxic substance such as dirt, cat litter, or used coffee grounds to make it less appealing to children and pets. Place the mixture in a container such as a sealed plastic bag and throw away METADATE CD in the household trash. Visit www.fda.gov/drugdisposal for additional information on disposal of unused medicines.

Keep METADATE CD and all medicines out of the reach of children

General information about the safe and effective use of METADATE CD.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use METADATE CD for a condition for which it was not prescribed. Do not give METADATE CD to other people, even if they have the same symptoms. It may harm them and it is against the law. You can ask your healthcare provider or pharmacist for information about METADATE CD that is written for healthcare professionals.

What are the ingredients in METADATE CD?

Active Ingredient: methylphenidate hydrochloride

Inactive Ingredients: sugar spheres, povidone, hydroxypropylmethylcellulose and polyethylene glycol, ethylcellulose aqueous dispersion, dibutyl sebacate, gelatin, and titanium dioxide.

The individual capsules contain the following coloring agents:

10 mg capsules: FD&C Blue No. 2, FDA/E172 Yellow Iron Oxide

20 mg capsules: FD&C Blue No. 2

30 mg capsules: FD&C Blue No. 2, FDA/E172 Red Iron Oxide

40 mg capsules: FDA/E172 Yellow Iron Oxide

50 mg capsules: FD&C Blue No. 2, FDA/E172 Red Iron Oxide

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METADATE CD is a registered trademark of the Lannett Company, Inc.

For more information about METADATE CD call 1-855-298-8246.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

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