

# COTEMPLA XR-ODT- methylphenidate tablet, orally disintegrating

## Neos Therapeutics, LP

-----

### HIGHLIGHTS OF PRESCRIBING INFORMATION

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

COTEMPLA XR-ODT (methylphenidate extended-release orally disintegrating tablets), CII  
Initial U.S. Approval: 1955

#### WARNING: ABUSE AND DEPENDENCE

See full prescribing information for complete boxed warning.

- CNS stimulants, including COTEMPLA XR-ODT, 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

COTEMPLA XR-ODT is a central nervous system (CNS) stimulant indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in pediatric patients 6 to 17 years of age. (1)

#### DOSAGE AND ADMINISTRATION

- Recommended starting dose for pediatric patients 6 to 17 years of age is 17.3 mg given orally once daily in the morning. Dosage may be increased weekly in increments of 8.6 mg to 17.3 mg per day. Daily dosage above 51.8 mg is not recommended. (2.2)
- Patients are advised to take COTEMPLA XR-ODT consistently either with food or without food. (2.2)

#### DOSAGE FORMS AND STRENGTHS

Extended-Release Orally Disintegrating Tablets: 8.6 mg, 17.3 mg and 25.9 mg. (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 Reactions:* Sudden death has been reported in association with CNS stimulants at recommended doses in children and adolescents 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 COTEMPLA XR-ODT 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

Based on accumulated data from other methylphenidate products, the most common (>5% and twice the rate of placebo) adverse reactions are appetite decreased, insomnia, nausea, vomiting, dyspepsia, abdominal pain, weight decreased, anxiety, dizziness, irritability, affect lability, tachycardia, and blood pressure increased. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Neos Therapeutics, Inc. at 1-888-319-1789 or <http://www.COTEMPLAXRODT.com> or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).  
See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

**FULL PRESCRIBING INFORMATION: CONTENTS\***

**WARNING: ABUSE AND DEPENDENCE**

**1 INDICATIONS AND USAGE**

**2 DOSAGE AND ADMINISTRATION**

- 2.1 Pretreatment Screening
- 2.2 General Dosing Information
- 2.3 Dose Reduction and Discontinuation
- 2.4 COTEMPLA XR-ODT Administration

**3 DOSAGE FORMS AND STRENGTHS**

**4 CONTRAINDICATIONS**

**5 WARNINGS AND PRECAUTIONS**

- 5.1 Potential for Abuse and Dependence
- 5.2 Serious Cardiovascular Reactions
- 5.3 Blood Pressure and Heart Rate Increases
- 5.4 Psychiatric Adverse Reactions
- 5.5 Priapism
- 5.6 Peripheral Vasculopathy, including Raynaud's Phenomenon
- 5.7 Long-Term Suppression of Growth

**6 ADVERSE REACTIONS**

- 6.1 Clinical Trial Experience
- 6.2 Postmarketing Experience

**7 DRUG INTERACTIONS**

- 7.1 Clinically Important Interactions with COTEMPLA XR-ODT

**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**

- 10.1 Signs and Symptoms
- 10.2 Management of Overdose

**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**

**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 AND DEPENDENCE

**CNS stimulants, including COTEMPLA XR-ODT, 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 Warnings and Precautions (5.1), Drug Abuse and Dependence (9.2, 9.3)].**

## 1 INDICATIONS AND USAGE

COTEMPLA XR-ODT is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in pediatric patients 6 to 17 years of age [see *Clinical Studies (14)*].

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Pretreatment Screening

Prior to initiating treatment with COTEMPLA XR-ODT, 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, and periodically re-evaluate the need for COTEMPLA XR-ODT use [see *Boxed Warning, Warnings and Precautions (5.1), and Drug Abuse and Dependence (9)*].

### 2.2 General Dosing Information

COTEMPLA XR-ODT is given orally once daily in the morning.

Advise patients to take COTEMPLA XR-ODT consistently either with food or without food [see *Clinical Pharmacology (12.3)*].

The recommended starting dose of COTEMPLA XR-ODT for patients 6 to 17 years of age is 17.3 mg once daily in the morning. The dose may be titrated weekly in increments of 8.6 mg to 17.3 mg. Daily doses above 51.8 mg have not been studied and are not recommended.

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

Pharmacological treatment of ADHD may be needed for extended periods. Periodically re-evaluate the long-term use of COTEMPLA XR-ODT and adjust dosage as needed.

### 2.3 Dose Reduction and Discontinuation

If paradoxical aggravation of symptoms or other adverse effects occur, reduce dosage, or, if necessary, discontinue the drug. COTEMPLA XR-ODT should be periodically discontinued to assess the child's condition. If improvement is not observed after appropriate dosage adjustment over a one-month period, discontinue the drug.

### 2.4 COTEMPLA XR-ODT Administration

Instruct the patient or caregiver on the following administration instructions:

- Do not remove the tablet from the blister pack until just prior to dosing. Take the tablet immediately after opening the blister pack. Do not store the tablet for future use.

- Use dry hands when opening the blister pack.
- Remove the tablet by peeling back the foil on the blister pack. Do not push the tablet through the foil.
- As soon as the blister is opened, remove the tablet and place on the patient's tongue.
- Place the whole tablet on the tongue and allow it to disintegrate without chewing or crushing.
- The tablet will disintegrate in saliva so that it can be swallowed. No liquid is needed to take the tablet.

### 3 DOSAGE FORMS AND STRENGTHS

- 8.6 mg Extended-Release Orally Disintegrating Tablet: round, purple to light purple mottled (debossed "T1" on one side and plain on the other)
- 17.3 mg Extended-Release Orally Disintegrating Tablet: round, purple to light purple mottled (debossed "T2" on one side and plain on the other)
- 25.9 mg Extended-Release Orally Disintegrating Tablet: round, purple to light purple mottled (debossed "T3" on one side and plain on the other)

### 4 CONTRAINDICATIONS

COTEMPLA XR-ODT is contraindicated in patients with:

- Known hypersensitivity to methylphenidate or other components of COTEMPLA XR-ODT. Hypersensitivity reactions such as angioedema and anaphylactic reactions have been reported in patients treated with methylphenidate products [see *Adverse Reactions (6.2)*].
- Concomitant treatment with monoamine oxidase inhibitors (MAOIs), and also within a minimum of 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 COTEMPLA XR-ODT, 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 Reactions

Sudden death, stroke and myocardial infarction have occurred in adults treated with CNS stimulants at recommended doses. Sudden death has occurred in pediatric patients with structural cardiac abnormalities and other serious cardiac problems taking CNS stimulants at recommended doses for ADHD. Avoid use in patients with known structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, and other serious heart problems. Perform further evaluation on patients who develop exertional chest pain, unexplained syncope, or arrhythmias during COTEMPLA XR-ODT treatment.

#### 5.3 Blood Pressure and Heart Rate Increases

CNS stimulants cause an increase in blood pressure (mean increase approximately 2 to 4 mm Hg) 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 COTEMPLA XR-ODT. 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**

CNS stimulants, including COTEMPLA XR-ODT, 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.

Careful follow-up of weight and height in pediatric patients ages 7 to 10 years who were randomized to either methylphenidate or nonmedication-treatment groups over 14 months, as well as in naturalistic subgroups of newly methylphenidate-treated and nonmedication-treated pediatric patients over 36 months (to the ages of 10 to 13 years), suggests that consistently medicated children (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.

Closely monitor growth (weight and height) in pediatric patients treated with CNS stimulants, including COTEMPLA XR-ODT. 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:

- Known hypersensitivity to methylphenidate or other ingredients of Cotempla XR-ODT [*see Contraindications (4)*]

- Hypertensive crisis when used concomitantly with monoamine oxidase inhibitors [see *Contraindications (4) and Drug Interactions (7.1)*]
- Drug dependence [see *Boxed Warning, Warnings and Precautions (5.1), and Drug Abuse and Dependence (9.2, 9.3)*]
- Serious cardiovascular reactions [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 ( $\geq 2\%$  of the methylphenidate group and at least twice the rate of the placebo group) adverse reactions from placebo-controlled trials of methylphenidate products include: appetite decreased, weight decreased, nausea, abdominal pain, dyspepsia, dry mouth, vomiting, insomnia, anxiety, nervousness, restlessness, affect lability, agitation, irritability, dizziness, vertigo, tremor, blurred vision, blood pressure increased, heart rate increased, tachycardia, palpitations, hyperhidrosis, and pyrexia.

### *Clinical Trials Experience with COTEMPLA XR-ODT in Children with ADHD*

There is limited experience with COTEMPLA XR-ODT in controlled trials. Based on this limited experience, the adverse reaction profile of COTEMPLA XR-ODT appears similar to other methylphenidate extended release-products.

## 6.2 Postmarketing 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, Pruritis NEC, Rashes, Eruptions, and Exanthemas NEC

*Investigations:* Alkaline phosphatase increased, Bilirubin increased, Hepatic enzyme increased, Platelet count decreased, White blood cell count abnormal

*Musculoskeletal, Connective Tissue and Bone Disorders:* Arthralgia, Myalgia, Muscle twitching, Rhabdomyolysis

*Nervous System Disorders:* Convulsion, Grand mal convulsion, Dyskinesia, Serotonin syndrome in

combination with serotonergic drugs

*Psychiatric Disorders:* Disorientation, Hallucination, Hallucination auditory, Hallucination visual, Libido changes, Mania

*Urogenital System:* Priapism

*Skin and Subcutaneous Tissue Disorders:* Alopecia, Erythema

*Vascular Disorders:* Raynaud's phenomenon

## 7 DRUG INTERACTIONS

### 7.1 Clinically Important Interactions with COTEMPLA XR-ODT

**Table 1: Drugs Having Clinically Important Interactions with Methylphenidate**

<b>Monoamine Oxidase Inhibitors (MAOI)</b>	
<i>Clinical Impact:</i>	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)].
<i>Intervention:</i>	Do not administer COTEMPLA-XR ODT concomitantly with MAOIs or within 14 days after discontinuing MAOI treatment.
<i>Examples:</i>	selegiline, tranylcypromine, isocarboxazid, phenelzine, linezolid, methylene blue
<b>Gastric pH Modulators</b>	
<i>Clinical Impact:</i>	May change the release profile and alter the pharmacodynamics of COTEMPLA-XR ODT.
<i>Intervention:</i>	Concomitant use of Cotempla XR-ODT with a gastric pH modulator (i.e., a H2-blocker or a proton pump inhibitor) is not recommended.
<i>Examples:</i>	omeprazole, famotidine, sodium bicarbonate

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to COTEMPLA XR-ODT 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 are insufficient to inform a drug-associated risk of adverse pregnancy-related outcomes [see Data]. There are risks to the fetus associated with the use of central nervous system (CNS) stimulants during pregnancy [see Clinical Considerations]. No teratogenic effects were observed in embryo-fetal development studies with oral administration of methylphenidate to pregnant rats and rabbits during organogenesis at doses 4 and 18 times, respectively, the maximum recommended human dose (MRHD) of 51.8 mg (as base). However, spina bifida was observed in rabbits at a dose 60 times the MRHD [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 2-4% and 15-20%, respectively.

### Clinical Considerations

#### *Fetal/Neonatal adverse reactions*

CNS stimulants, such as COTEMPLA XR-ODT, 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

#### *Human Data*

A limited number of pregnancies have been reported in published observational studies and postmarketing reports describing methylphenidate use during pregnancy. Due to the small number of methylphenidate-exposed pregnancies with known outcomes, these data cannot definitely establish or exclude any drug-associated risk during pregnancy. Methodological limitations of these observational studies include small sample size, concomitant use of other medications, lack of detail regarding dose and duration of exposure to methylphenidate and non-generalizability of the enrolled populations.

#### *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 60 times the maximum recommended human dose (MRHD) of 51.8 mg (as base) for adolescents on a mg/m<sup>2</sup> basis. The no effect level for embryo-fetal development in rabbits was 60 mg/kg/day (18 times the MRHD for adolescent on a mg/m<sup>2</sup> 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 (11 times the MRHD on a mg/m<sup>2</sup> basis for adolescent), which was also maternally toxic. The no effect level for embryo-fetal development in rats was 25 mg/kg/day (4 times the MRHD on a mg/m<sup>2</sup> basis for adolescent).

## **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. 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 COTEMPLA XR-ODT and any potential adverse effects on the breastfed child from COTEMPLA XR-ODT 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 COTEMPLA XR-ODT have been established in pediatric patients 6 to 17 years of age in one adequate and well-controlled study in pediatric patients 6 to 12 years, pharmacokinetic data in adolescents, and safety information from other methylphenidate-containing products [see *Clinical Pharmacology (12) and Clinical Studies (14)*].

The long-term efficacy of methylphenidate in pediatric patients has not been established. Safety and



effectiveness of COTEMPLA XR-ODT in pediatric patients below 6 years of age have not been established.

### Long Term Suppression Growth

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

### Juvenile Animal Toxicity 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) of 51.8 mg (as base) for pediatric patients on a mg/m<sup>2</sup> 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 MRHD of 51.8 mg (as base) on a mg/m<sup>2</sup> 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<sup>2</sup> basis). The no effect level for juvenile neurobehavioral development in rats was 5 mg/kg/day (half the MRHD on a mg/m<sup>2</sup> basis). The clinical significance of the long-term behavioral effects observed in rats is unknown.

## **8.5 Geriatric Use**

COTEMPLA XR-ODT has not been studied in patients over the age of 65 years.

## **9 DRUG ABUSE AND DEPENDENCE**

### **9.1 Controlled Substance**

COTEMPLA XR-ODT contains methylphenidate, a Schedule II controlled substance.

### **9.2 Abuse**

CNS stimulants including COTEMPLA XR-ODT, other methylphenidate-containing products, and amphetamines have a high potential for abuse. Abuse is characterized by impaired control over drug use, compulsive use, continued 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 COTEMPLA XR-ODT, 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 [see *How Supplied/Storage and Handling (16)*], monitor for signs of abuse while on therapy, and re-evaluate the need for COTEMPLA XR-ODT 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 COTEMPLA XR-ODT.

### 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 COTEMPLA XR-ODT. Withdrawal symptoms after abrupt cessation following prolonged high-dosage administration of CNS stimulants include dysphoric mood; depression, fatigue; vivid, unpleasant dreams; insomnia or hypersomnia; increased appetite; and psychomotor retardation or agitation.

## **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, hyperflexia, muscle twitching, convulsion (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 overdose with methylphenidate. Provide supportive care, including close medical supervision and monitoring. Treatment should consist of general measures employed in the management of overdose with any drug. Consider the possibility of multiple drug overdose. Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. Use supportive and symptomatic measures.

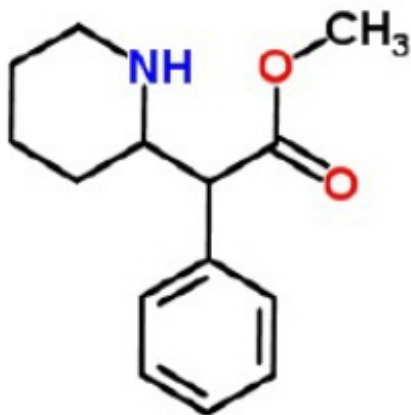
## **11 DESCRIPTION**

COTEMPLA XR-ODT contains methylphenidate, a central nervous system (CNS) stimulant. COTEMPLA XR-ODT is an extended-release orally disintegrating tablet intended for once daily administration. COTEMPLA XR-ODT contains approximately 25% immediate-release and 75% extended-release methylphenidate. Methylphenidate is ionically-bound to the sulfonate of polystyrene sulfonate particles.

COTEMPLA XR-ODT contains 8.6 mg, 17.3 mg or 25.9 mg of methylphenidate which is the same as the amount of methylphenidate (base equivalent) found, respectively, in 10 mg, 20 mg and 30 mg strength methylphenidate hydrochloride products.

The chemical name of methylphenidate is methyl  $\alpha$ -phenyl-2-piperidineacetate, and its structural formula is shown in Figure 1.

### **Figure 1: Methylphenidate Structure**



C<sub>14</sub>H<sub>19</sub>NO<sub>2</sub> Mol. Wt. 233.31

COTEMPLA XR-ODT also contains the following inactive ingredients: Mannitol, Fructose, Microcrystalline Cellulose, Crospovidone, Methacrylic Acid, Polystyrene Sulfonate, Citric Acid, Colloidal Silicon Dioxide, Grape Flavor, Natural Masking Type Powder, Triethyl Citrate, Magnesium Stearate, Ethylcellulose, Sucralose, Lake Blend Purple, and Polyethylene Glycol.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Methylphenidate 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*-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.

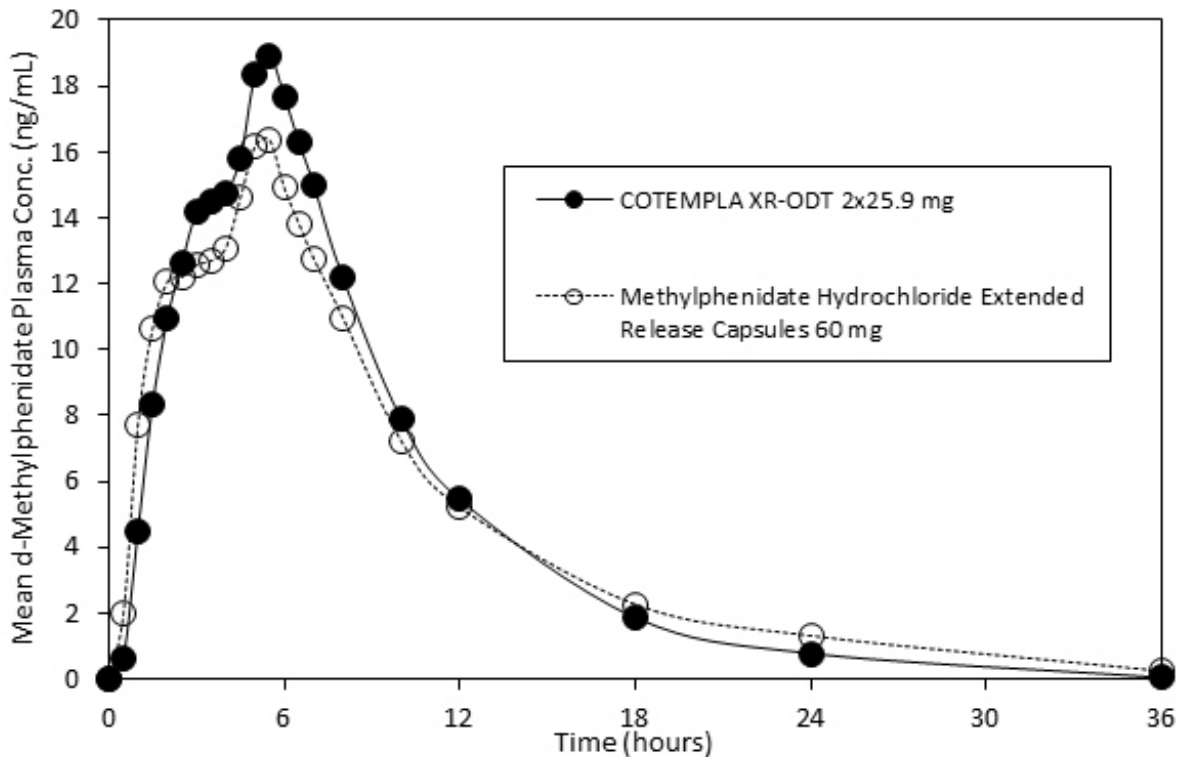
### 12.3 Pharmacokinetics

After oral administration of COTEMPLA XR-ODT, circulation levels of *l*-methylphenidate (MPH) were about 2% of total MPH.

#### Absorption

Following a single dose of 51.8 mg (2×25.9 mg daily) COTEMPLA XR-ODT in healthy adult subjects under fasted conditions, plasma methylphenidate (MPH) reached maximal concentration (C<sub>max</sub>) at a median time of 5 hours after dosing. Compared to an extended release capsule formulation of methylphenidate, methylphenidate mean C<sub>max</sub> and exposure (AUC<sub>inf</sub>) was about 26% and 6% higher, respectively, after COTEMPLA XR-ODT administration (Figure 2).

**Figure 2: Mean *d*-Methylphenidate Plasma Concentration-Time Profiles After Administration of COTEMPLA XR-ODT or Methylphenidate Hydrochloride Extended-Release Capsule in Healthy Volunteers Under Fasted Conditions**



### *Effect of Food*

Administration of 51.8 mg COTEMPLA XR-ODT with food (a high fat meal) decreased the  $C_{max}$  and increased  $AUC_{inf}$  of total MPH by approximately 24% and 16%, respectively. Food shortened the median time to peak concentration ( $T_{max}$ ) by 0.5 hour (fed: 4.5 hours vs. fasted: 5.0 hours).

### *Effect of Alcohol*

There is no in vivo study conducted for the effect of alcohol on drug exposure. An in vitro dissolution study showed alcohol-induced dose dumping potential in the presence of 40% alcohol. Dose dumping was not observed in the presence of lower alcohol concentrations.

### Elimination

Plasma methylphenidate concentrations decline monophasically following oral administration of COTEMPLA XR-ODT. The mean plasma terminal elimination half-life of methylphenidate was about 4 hours in healthy volunteers following a single 51.8 mg dose administration.

### *Metabolism*

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

### *Excretion*

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

### Specific Populations

#### *Male and Female Patients and Ethnic Groups*

There is insufficient experience with the use of COTEMPLA XR-ODT to detect gender or ethnic variations in pharmacokinetics.

#### *Pediatric Patients*

The pharmacokinetics of methylphenidate after COTEMPLA XR-ODT administration were studied in pediatric patients (6-17 years of age) with ADHD under fasted conditions. After a single oral dose of 51.8 mg COTEMPLA XR-ODT, plasma concentrations of methylphenidate in children (6-12 years of age) were approximately twice the concentrations observed in adults. Exposure levels in adolescent patients (13 -17 years of age) were similar to those in adults. Body weight normalized clearance values were similar across the age groups (Table 2).

**Table 2: PK Parameters (Mean ±SD) of d-MPH After 51.8 mg Oral Dosing of COTEMPLA XR-ODT Under Fasted Conditions**

PK Parameter	Children (n=24)	Adolescent (n=8)	Adult (n=38)
T <sub>max</sub> (hr)*	4.6 (2.0-8.0)	5.31 (3.5-8.0)	4.98 (2.5 – 6.5)
T <sub>1/2</sub> (hr)	4.43±1.0	3.93±0.33	4.00±0.73
C <sub>max</sub> (ng/mL)	32.7±9.83	20.2±5.79	20.8±5.22
Cl (L/hr/kg)	6.21±1.48	5.54±1.19	5.48±1.46
AUC <sub>∞</sub> (hr*ng/mL)	328.9±90.21	187.2±62.05	169.1±57.13

\* data presented as median range

#### *Patients with Renal Impairment*

There is no experience with the use of COTEMPLA XR-ODT 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 PPAA. Since renal clearance is not an important route of methylphenidate clearance, renal insufficiency is expected to have little effect on the pharmacokinetics of COTEMPLA XR-ODT.

#### *Patients with Hepatic Impairment*

There is no experience with the use of COTEMPLA XR-ODT 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. For pediatric patients, this dose is approximately 4 times the maximum recommended human dose of 51.8 (as base) on a mg/m<sup>2</sup> 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 dose of 51.8 mg (as base) for pediatric patients on a mg/m<sup>2</sup> basis.

#### Mutagenesis

Methylphenidate was not mutagenic in the *in vitro* Ames reverse mutation assay or 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. Methylphenidate was negative in an *in vivo* 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/day, approximately 12-fold the maximum recommended human dose of 51.8 (as base) for adolescents on a mg/m<sup>2</sup> basis.

## 14 CLINICAL STUDIES

The efficacy of COTEMPLA XR-ODT was evaluated in a laboratory classroom study conducted in 87 pediatric patients (Aged 6 to 12 years) with ADHD. Following washout of previous methylphenidate medication, there was an open-label dose-optimization period (4 weeks) with an initial dose of 17.3 mg of COTEMPLA XR-ODT once daily in the morning. The dose could be titrated on a weekly basis from 17.3 mg, to 25.9 mg, to 34.6 mg, and up to 51.8 mg until an optimal dose or the maximum dose of 51.8 mg/day was reached. At the end of this period, subjects remained on their optimized dose for an additional week. Subjects then entered a 1-week randomized, double-blind, parallel group treatment period with the individually optimized dose of COTEMPLA XR-ODT or placebo. At the end of this week, raters evaluated the attention and behavior of the subjects in a laboratory classroom setting, using the Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP) rating scale SKAMP is a validated 13-item teacher-rated scale that assesses manifestations of ADHD in a classroom setting.

The primary efficacy endpoint was the average of the SKAMP-Combined (Attention and Department) scores over the test day (not including the baseline score), with assessments conducted at baseline, and 1, 3, 5, 7, 10, 12, and 13 hours post-dosing. The key secondary efficacy endpoints were onset and duration of effect, defined as the first point at which active drug separated from placebo on SKAMP-Combined scores and the last time point at which active drug separated from placebo on SKAMP-Combined scores, respectively.

The SKAMP-Combined scores test day average was statistically significantly lower (improved) with COTEMPLA XR-ODT compared to placebo (difference of -11 (95% CI: -13.9, -8.2)) (Table 3).

**Table 3: Efficacy Analysis Results: SKAMP-Combined Scores Averaged Over Classroom Day in Patients with ADHD**

Study Number	Treatment Group	Baseline Score at Randomization* (SD)	Pre-dose Score on Classroom Day† (SD)	LS Mean‡ (SE)	Placebo-subtracted Difference§ (95% CI)
Study 1	Cotempla XR-ODT (17.3-51.8 mg/day)	21.1 (9.56)	26.8 (11.52)	14.3 (1.07)	-11.0 (-13.9, -8.2)
	Placebo	20.4 (9.09)	19.1 (11.04)	25.3 (1.16)	--

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

\* Visit 7 baseline score (Visit 7 occurred prior to the 1-week randomized, double-blind, parallel group treatment period).

† Visit 8 baseline score (Visit 8 occurred at the end of the 1-week randomized, double-blind, parallel group treatment period).

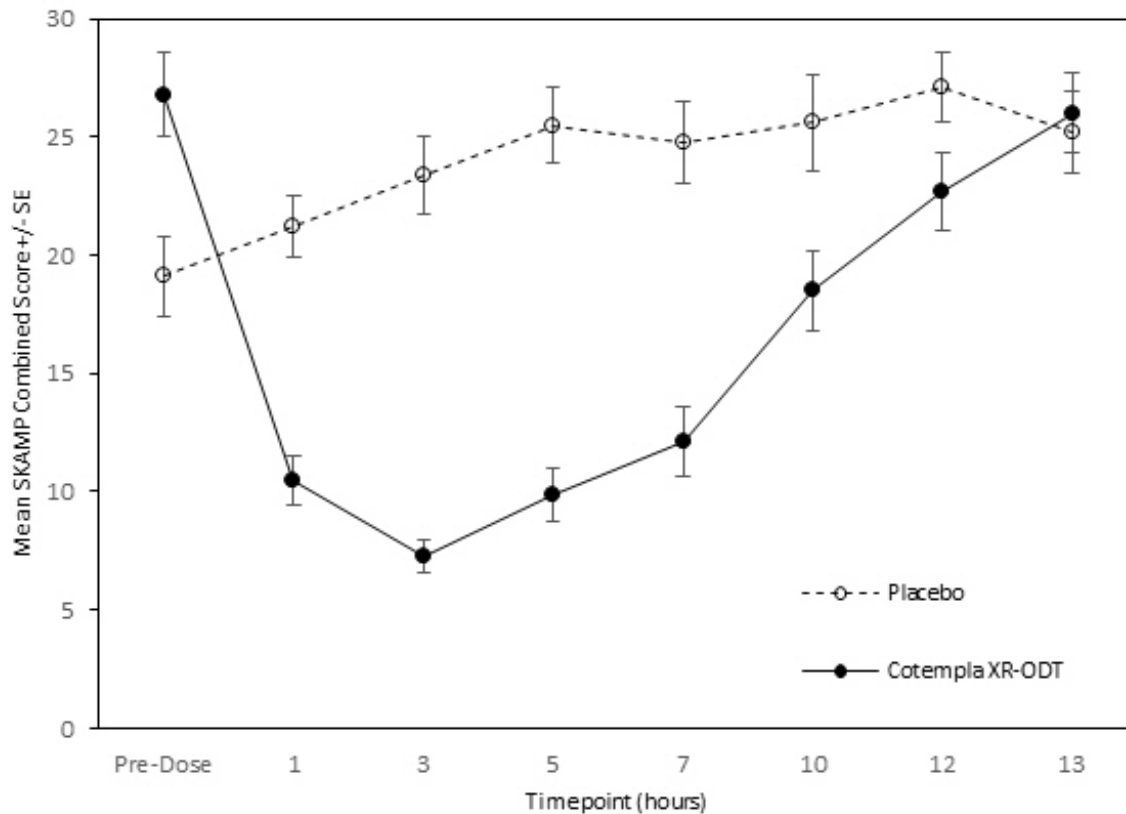
‡ Visit 8 LS mean over hours 1, 3, 5, 7, 10, 12, and 13.

§ Difference (drug minus placebo) in least-squares means.

The SKAMP-Combined scores were also statistically significantly lower (improved) at time points (1, 3, 5, 7, 10, 12 hours) post-dosing with COTEMPLA XR-ODT compared to placebo (Figure 3).

**Figure 3: LS Mean SKAMP Combined Score After Treatment with COTEMPLA XR-ODT or**

## Placebo During Classroom Day in Patients with ADHD



\*SE = Standard Error

The database was not large enough to assess whether there were differences in effects in age, gender, or race subgroups.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

COTEMPLA XR-ODT Extended Release Orally Disintegrating Tablets are available in three strengths:

- 8.6 mg tablets, round, purple to light purple, mottled, and debossed "T1" on one side of the tablet;
- 17.3 mg tablets, round, purple to light purple, mottled, and debossed "T2" on one side of the tablet;
- 25.9 mg tablets, round, purple to light purple, mottled, and debossed "T3" on one side of the tablet.

They are available as follows:

NDC 70165-100-30 8.6 mg tablets: carton containing 5 blister cards of 6 tablets each, for a total of 30 tablets with a reusable travel case.

NDC 70165-200-30 17.3 mg tablets: carton containing 5 blister cards of 6 tablets each, for a total of 30 tablets with a reusable travel case.

NDC 70165-300-30 25.9 mg tablets: carton containing 5 blister cards of 6 tablets each, for a total of 30 tablets with a reusable travel case.

Store at 20°C to 25°C (68°F to 77°F); excursions permitted from 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

Store COTEMPLA XR-ODT blister packages in the reusable travel case after removal from the carton.

## Disposal

Comply with local laws and regulations on drug disposal of CNS stimulants. Dispose of remaining, unused, or expired COTEMPLA XR-ODT by a medicine take-back program or by an authorized collector registered with the Drug Enforcement Administration. If no take-back program or authorized collector is available, mix COTEMPLA XR-ODT with an undesirable, nontoxic substance to make it less appealing to children and pets. Place the mixture in a container such as a sealed plastic bag and discard COTEMPLA XR-ODT in the household trash.

## **17 PATIENT COUNSELING INFORMATION**

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

### Controlled Substance Status/Potential for Abuse and Dependence

Advise patients and their caregivers that COTEMPLA XR-ODT is a federally controlled substance, and it can be abused or lead to dependence [see *Drug Abuse and Dependence (9.1, 9.2, and 9.3)*]. Instruct patients that they should not give COTEMPLA XR-ODT to anyone else. Advise patients to store COTEMPLA XR-ODT in a safe place, preferably locked, to prevent abuse. Advise patients and their caregivers to comply with laws and regulations on drug disposal. Advise patients and their caregivers to dispose of remaining, unused, or expired COTEMPLA XR-ODT through a medicine take-back program if available [see *Warnings and Precautions (5.1), Abuse and Dependence (9.2, 9.3), How Supplied/Storage and Handling (16)*].

### Instructions for Taking COTEMPLA XR-ODT

Instruct patients and their caregivers on the following:

- The tablet should remain in the blister pack until the patient is ready to take it.
- The tablet should be taken immediately after opening the blister pack. It should not be stored for future use.
- The patient or caregiver should use dry hands when opening the blister pack.
- The patient or caregiver should remove the tablet by peeling back the foil on the blister pack. The tablet should not be pushed through the foil.
- As soon as the blister is opened, the tablet should be removed and placed on the patient's tongue.
- The whole tablet should be placed on the tongue and allowed to disintegrate without chewing or crushing.
- The tablet will disintegrate in saliva and can be swallowed. No liquid is needed to take the tablet.

### Serious Cardiovascular Risks

Advise patients, caregivers, and their family members that there is a potential for serious cardiovascular risks including sudden death, myocardial infarction, and stroke with COTEMPLA XR-ODT. 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

Advise patients and their caregivers that COTEMPLA XR-ODT can elevate blood pressure and heart rate [see *Warnings and Precautions (5.3)*].

### Psychiatric Risks

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

### Priapism



Advise patients, caregivers, and family members 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 while taking COTEMPLA XR-ODT.
- Further clinical evaluation (e.g., rheumatology referral) may be appropriate for certain patients [see *Warnings and Precautions (5.6)*].

#### Suppression of Growth

Advise patients, families, and caregivers that COTEMPLA XR-ODT can cause slowing of growth and weight loss [see *Warnings and Precautions (5.7)*].

#### Alcohol effect

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

#### Pregnancy Registry

Advise patients that there is a pregnancy exposure registry that monitors pregnancy outcomes in females exposed to COTEMPLA XR-ODT during pregnancy [see *Use in Specific Populations (8.1)*].

Manufactured for Neos Therapeutics Brands, LLC. Grand Prairie, TX 75050. Made in USA.

For more information, call 1-(888)-319-1789

COTEMPLA XR-ODT is a registered trademark of Neos Therapeutics, Inc.

Copyright© 2014, Neos Therapeutics, Inc.

Item # PIN010299

Rev. 06/2017

<b>Medication Guide</b> <b>COTEMPLA XR-ODT (koh-TEM-pluh - oh dee tee)</b> <b>(methylphenidate)</b> <b>extended-release orally disintegrating tablets, CII</b>
---

#### **What is the most important information I should know about COTEMPLA XR-ODT?**

COTEMPLA XR-ODT can cause serious side effects, including:

- **Abuse and dependence.** COTEMPLA XR-ODT, other methylphenidate containing medicines, and amphetamines have a high chance for abuse and can cause physical and psychological dependence. Your healthcare provider should check your child for signs of abuse and dependence before and during treatment with COTEMPLA XR-ODT.
  - Tell your healthcare provider if your child has ever abused or been dependent on alcohol, prescription medicines, or street drugs.
  - Your healthcare provider can tell you more about the differences between physical and psychological dependence and drug addiction.
- **Heart-related problems, including:**
  - sudden death in children who have heart problems or heart defects

- increased blood pressure and heart rate

Your healthcare provider should check your child carefully for heart problems before starting COTEMPLA XR-ODT. Tell your healthcare provider if your child has any heart problems, heart defects, high blood pressure, or a family history of these problems.

Your healthcare provider should check your child's blood pressure and heart rate regularly during treatment with COTEMPLA XR-ODT.

**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 COTEMPLA XR-ODT.**

- **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 COTEMPLA XR-ODT, especially hearing voices, seeing or believing things that are not real, or new manic symptoms.**

### **What is COTEMPLA XR-ODT?**

COTEMPLA XR-ODT is a central nervous system (CNS) stimulant prescription medicine used for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children 6 to 17 years of age. COTEMPLA XR-ODT may help increase attention and decrease impulsiveness and hyperactivity in children 6 to 17 years of age with ADHD.

It is not known if COTEMPLA XR-ODT is safe and effective in children under 6 years of age.

**COTEMPLA XR-ODT 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 COTEMPLA XR-ODT in a safe place to protect it from theft. Never give your COTEMPLA XR-ODT to anyone else, because it may cause death or harm them. Selling or giving away COTEMPLA XR-ODT may harm others and is against the law.

Do not give COTEMPLA XR-ODT to your child if they are:

- allergic to methylphenidate or any of the ingredients in COTEMPLA XR-ODT. See the end of this Medication Guide for a complete list of ingredients in COTEMPLA XR-ODT.
- taking, or has taken within the past 14 days, a medicine used to treat depression called a monoamine oxidase inhibitor (MAOI).

### **Before taking COTEMPLA XR-ODT tell your child's healthcare provider about all medical conditions, including if your child:**

- has heart problems, heart defects, or high blood pressure
- has mental problems including psychosis, mania, bipolar illness, or depression
- has circulation problems in fingers and toes
- is pregnant or plans to become pregnant. It is not known if COTEMPLA XR-ODT will harm the unborn baby.
  - There is a pregnancy registry for females who are exposed to COTEMPLA XR-ODT during pregnancy. The purpose of the registry is to collect information about the health of females exposed to COTEMPLA XR-ODT and their baby. If your child becomes pregnant during treatment with COTEMPLA XR-ODT, talk to your healthcare provider about registering with the National Pregnancy Registry for Psychostimulants. You can register by calling 1-866-961-2388.
- is breastfeeding or plans to breastfeed. COTEMPLA XR-ODT passes into breast milk. You and your healthcare provider should decide if your child will take COTEMPLA XR-ODT or

breastfeed.

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

COTEMPLA XR-ODT and some medicines may interact with each other and cause serious side effects. Sometimes the doses of other medicines will need to be adjusted during treatment with COTEMPLA XR-ODT.

Your healthcare provider will decide whether COTEMPLA XR-ODT can be taken with other medicines. **Especially tell your healthcare provider if your child takes:**

- anti-depression medicines including MAOIs

Know the medicines that your child takes. Keep a list of the medicines with you to show your healthcare provider and pharmacist. **Do not start any new medicine during treatment with COTEMPLA XR-ODT without talking to your healthcare provider first.**

#### **How should COTEMPLA XR-ODT be taken?**

- Take COTEMPLA XR-ODT exactly as prescribed by your healthcare provider.
- Your healthcare provider may change the dose if needed.
- Take COTEMPLA XR-ODT 1 time each day in the morning.
- COTEMPLA XR-ODT can be taken with or without food but take it the same way each time.

#### **Take COTEMPLA XR-ODT as follows:**

- Keep COTEMPLA XR-ODT in the blister pack until your child is ready to take it. Take COTEMPLA XR-ODT right after opening the blister pack. Do not store the tablet for future use.
- Use dry hands when opening the blister pack.
- Remove the tablet by peeling back the foil on the blister pack. **Do not push the tablet through the foil.**
- As soon as the blister is opened, remove the tablet and place it on the tongue. **Do not chew or crush the tablet.**
- The tablet will dissolve and can be swallowed with saliva. No liquid is needed to take the tablet.
- Your healthcare provider may sometimes stop your child's COTEMPLA XR-ODT treatment for a while to check ADHD symptoms.
- If your child takes too much COTEMPLA XR-ODT, call your healthcare provider or go to the nearest hospital emergency room right away.

#### **What should I avoid during treatment with COTEMPLA XR-ODT?**

You should avoid drinking alcohol during treatment with COTEMPLA XR-ODT.

#### **What are possible side effects of COTEMPLA XR-ODT?**

COTEMPLA XR-ODT can cause serious side effects, including:

- See "**What is the most important information I should know about COTEMPLA XR-ODT?**"
- **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 their fingers or toes.

**Call your healthcare provider right away if your child has any signs of unexplained wounds appearing on fingers or toes during treatment with COTEMPLA XR-ODT.**

- **Slowing of growth (height and weight) in children.** Children should have their height and weight checked often during treatment with COTEMPLA XR-ODT. COTEMPLA XR-ODT treatment may be stopped if your child is not gaining weight or height.

**The most common side effects of methylphenidate products include:**

- decreased appetite
- trouble sleeping
- nausea
- vomiting
- indigestion
- stomach pain
- weight loss
- anxiety
- dizziness
- irritability
- mood swings
- increased heart rate
- increased blood pressure

These are not all the possible side effects of COTEMPLA XR-ODT.

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 COTEMPLA XR-ODT?**

- Store COTEMPLA XR-ODT at room temperature between 68°F to 77°F (20°C to 25°C).
- Store COTEMPLA XR-ODT in a safe place, like a locked cabinet.
- Store COTEMPLA XR-ODT in the blister packaging until it is ready to be taken.
- Dispose of remaining, unused, or expired COTEMPLA XR-ODT by a medicine take-back program at authorized collection sites such as retail pharmacies, hospital or clinic pharmacies, and law enforcement locations. If no take-back program or authorized collector is available, mix COTEMPLA XR-ODT 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 COTEMPLA XR-ODT in the household trash.

**Keep COTEMPLA XR-ODT and all medicines out of the reach of children.**

**General information about the safe and effective use of COTEMPLA XR-ODT**

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

**What are the ingredients in COTEMPLA XR-ODT?**

**Active Ingredient:** Methylphenidate

**Inactive Ingredients:** Mannitol, Fructose, Microcrystalline Cellulose, Crospovidone, Methacrylic Acid, Polystyrene Sulfonate, Citric Acid, Colloidal Silicon Dioxide, Grape Flavor, Natural Masking Type Powder, Triethyl Citrate, Magnesium Stearate, Ethylcellulose, Sucralose, Lake Blend Purple, and Polyethylene Glycol

Manufactured for Neos Therapeutics Brands, LLC, Grand Prairie, TX 75050

For more information go to <http://www.COTEMPLAXRODT.com> or call 1-888-319-1789

COTEMPLA XR-ODT is registered in the US Patent and Trademark Office © 2014 Neos Therapeutics, Inc.

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

Revised  
June/2017

**PRINCIPAL DISPLAY PANEL - 8.6 mg Tablet Blister Pack Carton**

**Contains:**

**NDC 70165-100-30**

30 Tablets (5 x 6-count blister cards)  
Travel Case

Rx Only

**Cotempla XR-ODT™CII**  
Methylphenidate Extended-Release  
Orally Disintegrating Tablets

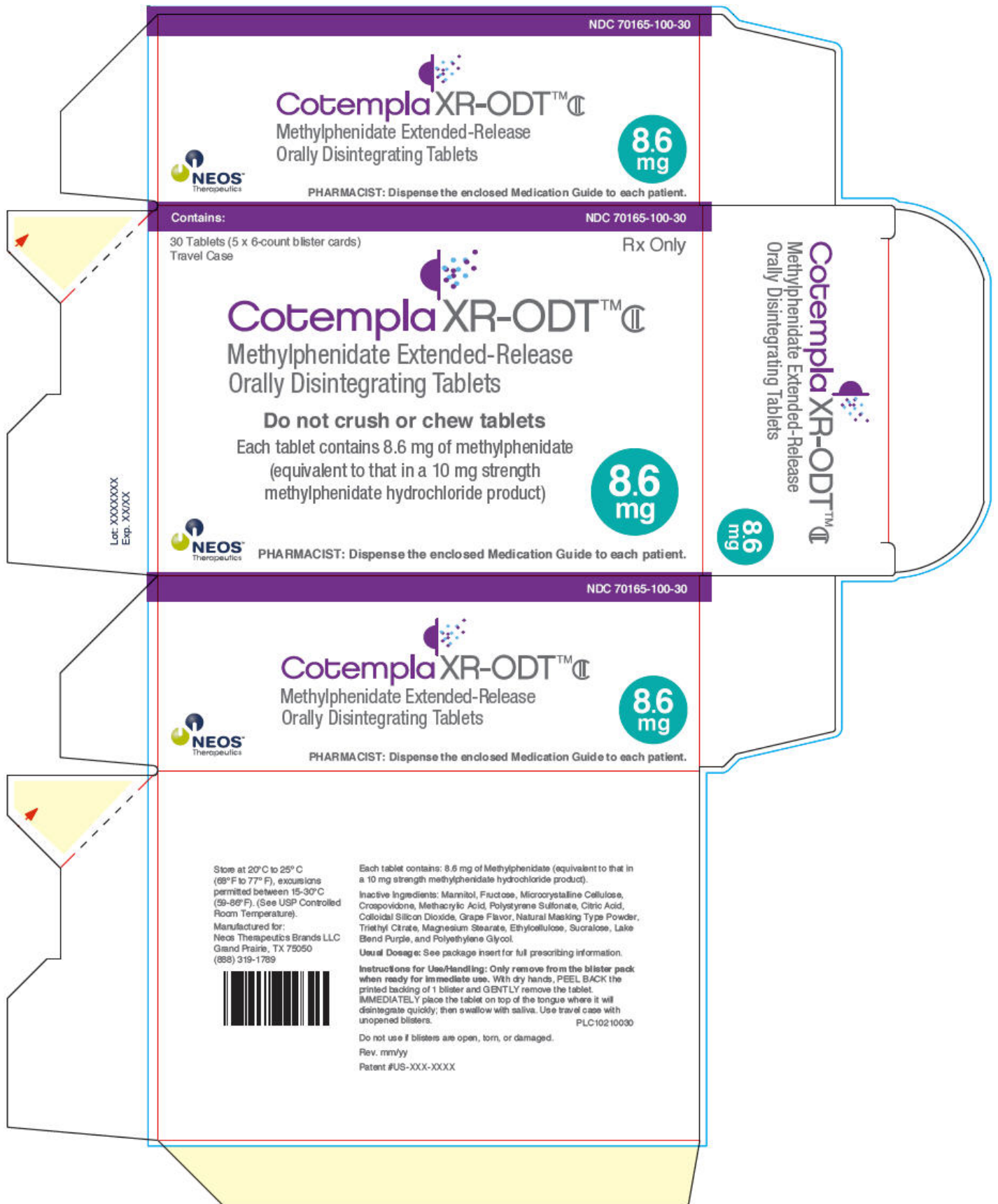
**Do not crush or chew tablets**

Each tablet contains 8.6 mg of methylphenidate  
(equivalent to that in a 10 mg strength  
methylphenidate hydrochloride product)

**8.6  
mg**

**NEOS™**  
Therapeutics

**PHARMACIST: Dispense the enclosed Medication Guide to each patient.**



**PRINCIPAL DISPLAY PANEL - 17.3 mg Tablet Blister Pack Carton**

**Contains:**

**NDC 70165-200-30**

30 Tablets (5 x 6-count blister cards)

Travel Case

Rx Only

**Cotempla XR-ODT™CII**

Methylphenidate Extended-Release

Orally Disintegrating Tablets

**Do not crush or chew tablets**

Each tablet contains 17.3 mg of methylphenidate  
(equivalent to that in a 20 mg strength  
methylphenidate hydrochloride product)

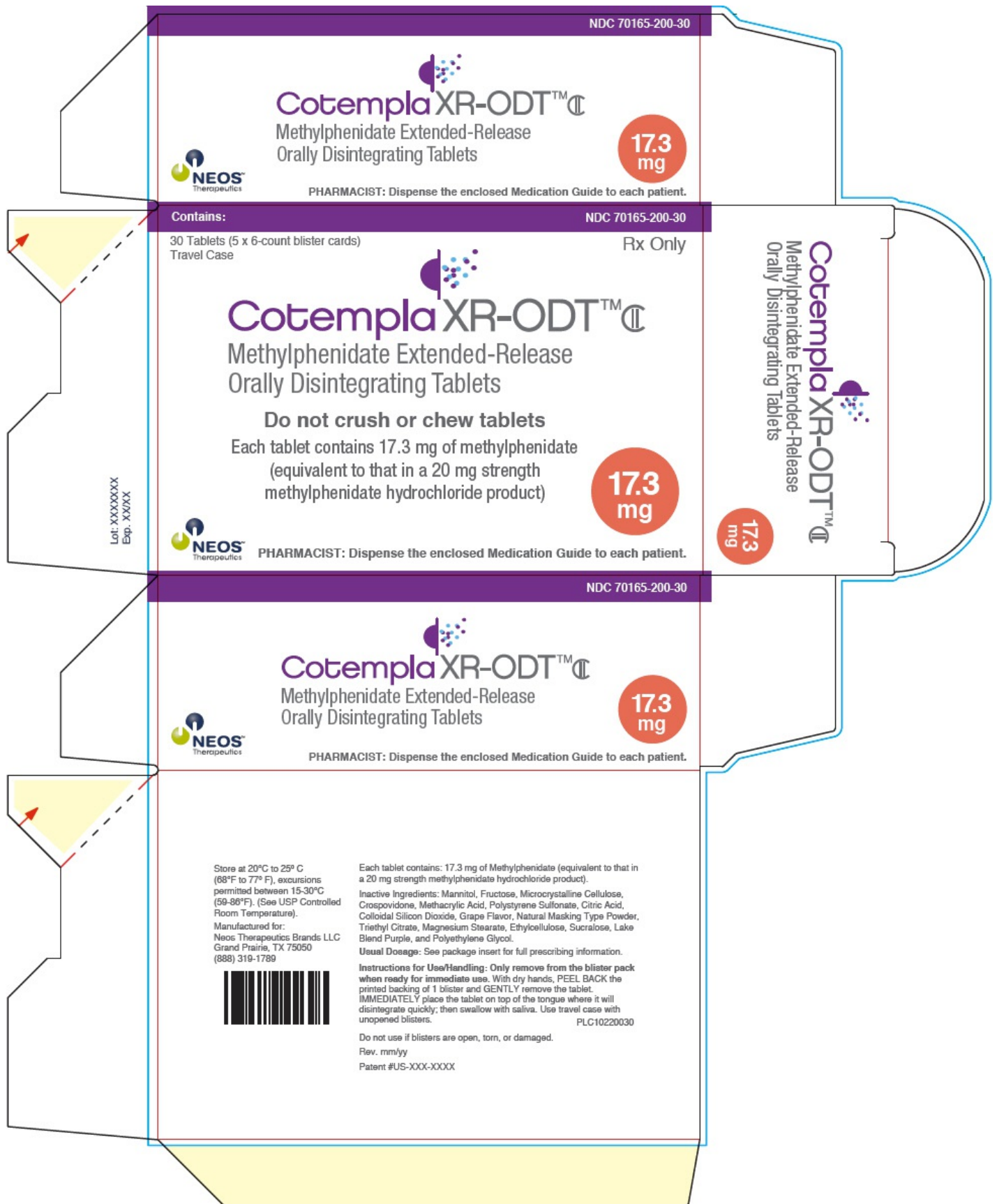
**17.3**

**mg**

**NEOS™**

Therapeutics

**PHARMACIST: Dispense the enclosed Medication Guide to each patient.**



**PRINCIPAL DISPLAY PANEL - 25.9 mg Tablet Blister Pack Carton**

**Contains:**

**NDC 70165-300-30**

30 Tablets (5 x 6-count blister cards)



Travel Case

Rx Only

**Cotempla XR-ODT™CII**

Methylphenidate Extended-Release

Orally Disintegrating Tablets

**Do not crush or chew tablets**

Each tablet contains 25.9 mg of methylphenidate  
(equivalent to that in a 30 mg strength  
methylphenidate hydrochloride product)

**25.9**

**mg**

**NEOS™**

Therapeutics

**PHARMACIST: Dispense the enclosed Medication Guide to each patient.**

NDC 70165-300-30

**Cotempla XR-ODT™**  
Methylphenidate Extended-Release  
Orally Disintegrating Tablets



**25.9 mg**

PHARMACIST: Dispense the enclosed Medication Guide to each patient.

Contains:

NDC 70165-300-30

30 Tablets (5 x 6-count blister cards)  
Travel Case

Rx Only

**Cotempla XR-ODT™**  
Methylphenidate Extended-Release  
Orally Disintegrating Tablets

**Do not crush or chew tablets**

Each tablet contains 25.9 mg of methylphenidate  
(equivalent to that in a 30 mg strength  
methylphenidate hydrochloride product)

**25.9 mg**



PHARMACIST: Dispense the enclosed Medication Guide to each patient.

Lot: XXXXXX  
Exp. XXXX

**Cotempla XR-ODT™**  
Methylphenidate Extended-Release  
Orally Disintegrating Tablets

**25.9 mg**

NDC 70165-300-30

**Cotempla XR-ODT™**  
Methylphenidate Extended-Release  
Orally Disintegrating Tablets



**25.9 mg**

PHARMACIST: Dispense the enclosed Medication Guide to each patient.

Store at 20°C to 25°C  
(68°F to 77°F), excursions  
permitted between 15-30°C  
(59-86°F). (See USP Controlled  
Room Temperature).

Manufactured for:  
Neos Therapeutics Brands LLC  
Grand Prairie, TX 75050  
(888) 319-1789



Each tablet contains: 25.9 mg of Methylphenidate (equivalent to that in a 30 mg strength methylphenidate hydrochloride product).

Inactive Ingredients: Mannitol, Fructose, Microcrystalline Cellulose, Croscopolidone, Methacrylic Acid, Polystyrene Sulfonate, Citric Acid, Colloidal Silicon Dioxide, Grape Flavor, Natural Masking Type Powder, Triethyl Citrate, Magnesium Stearate, Ethylcellulose, Sucralose, Lake Blend Purple, and Polyethylene Glycol.

Usual Dosage: See package insert for full prescribing information.

Instructions for Use/Handling: Only remove from the blister pack when ready for immediate use. With dry hands, PEEL BACK the printed backing of 1 blister and GENTLY remove the tablet. IMMEDIATELY place the tablet on top of the tongue where it will disintegrate quickly; then swallow with saliva. Use travel case with unopened blisters. PLC10230030

Do not use if blisters are open, torn, or damaged.

Rev. mm/yy

Patent #US-XXX-XXXX

## COTEMPLA XR-ODT

methylphenidate tablet, orally disintegrating

### Product Information

<b>Product Type</b>	HUMAN PRESCRIPTION DRUG	<b>Item Code (Source)</b>	NDC:70 165-100
<b>Route of Administration</b>	ORAL	<b>DEA Schedule</b>	CII

### Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
Methylphenidate (UNII: 207ZZ9QZ49) (Methylphenidate - UNII:207ZZ9QZ49)	Methylphenidate	8.6 mg

### Inactive Ingredients

Ingredient Name	Strength
Mannitol (UNII: 3OWL53L36A)	
Fructose (UNII: 6YSS42VSEV)	
Microcrystalline Cellulose (UNII: OP1R32D61U)	
Crospovidone, Unspecified (UNII: 2S7830E561)	
Methacrylic Acid (UNII: 1CS02G8656)	
Polystyrene Sulfonic Acid (UNII: 70KO0R01RY)	
Citric Acid Monohydrate (UNII: 2968PHW8QP)	
Silicon Dioxide (UNII: ETJ7Z6XBU4)	
Triethyl Citrate (UNII: 8Z96QXD6UM)	
Magnesium Stearate (UNII: 70097M6I30)	
Ethylcellulose, Unspecified (UNII: 7Z8S9VYZ4B)	
Sucralose (UNII: 96K6UQ3ZD4)	
Polyethylene Glycol, Unspecified (UNII: 3WJQ0SDW1A)	

### Product Characteristics

<b>Color</b>	PURPLE (purple to light purple, mottled)	<b>Score</b>	no score
<b>Shape</b>	ROUND	<b>Size</b>	8mm
<b>Flavor</b>	GRAPE	<b>Imprint Code</b>	T1
<b>Contains</b>			

### Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:70 165-100-30	5 in 1 CARTON	06/20/2016	
1		6 in 1 BLISTER PACK; Type 0: Not a Combination Product		

### Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA205489	06/20/2016	

## COTEMPLA XR-ODT

methylphenidate tablet, orally disintegrating

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:70 165-200
Route of Administration	ORAL	DEA Schedule	CII

Active Ingredient/Active Moiety		
Ingredient Name	Basis of Strength	Strength
Methylphenidate (UNII: 207ZZ9QZ49) (Methylphenidate - UNII:207ZZ9QZ49)	Methylphenidate	17.3 mg

Inactive Ingredients	
Ingredient Name	Strength
Mannitol (UNII: 3OWL53L36A)	
Fructose (UNII: 6YSS42VSEV)	
Microcrystalline Cellulose (UNII: OP1R32D61U)	
Crospovidone, Unspecified (UNII: 2S7830E561)	
Methacrylic Acid (UNII: 1CS02G8656)	
Polystyrene Sulfonic Acid (UNII: 70KO0R01RY)	
Citric Acid Monohydrate (UNII: 2968PHW8QP)	
Silicon Dioxide (UNII: ETJ7Z6XBU4)	
Triethyl Citrate (UNII: 8Z96QXD6UM)	
Magnesium Stearate (UNII: 70097M6I30)	
Ethylcellulose, Unspecified (UNII: 7Z8S9VYZ4B)	
Sucralose (UNII: 96K6UQ3ZD4)	
Polyethylene Glycol, Unspecified (UNII: 3WJQ0SDW1A)	

Product Characteristics			
Color	PURPLE (purple to light purple, mottled)	Score	no score
Shape	ROUND	Size	10mm
Flavor	GRAPE	Imprint Code	T2
Contains			

Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:70 165-200-30	5 in 1 CARTON	06/20/2016	
1		6 in 1 BLISTER PACK; Type 0: Not a Combination Product		

Marketing Information			
Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA205489	06/20/2016	

**COTEMPLA XR-ODT**

methylphenidate tablet, orally disintegrating

### Product Information

<b>Product Type</b>	HUMAN PRESCRIPTION DRUG	<b>Item Code (Source)</b>	NDC:70 165-300
<b>Route of Administration</b>	ORAL	<b>DEA Schedule</b>	CII

### Active Ingredient/Active Moiety

<b>Ingredient Name</b>	<b>Basis of Strength</b>	<b>Strength</b>
Methylphenidate (UNII: 207ZZ9QZ49) (Methylphenidate - UNII:207ZZ9QZ49)	Methylphenidate	25.9 mg

### Inactive Ingredients

<b>Ingredient Name</b>	<b>Strength</b>
Mannitol (UNII: 3OWL53L36A)	
Fructose (UNII: 6YSS42VSEV)	
Microcrystalline Cellulose (UNII: OP1R32D61U)	
Crospovidone, Unspecified (UNII: 2S7830E561)	
Methacrylic Acid (UNII: 1CS02G8656)	
Polystyrene Sulfonic Acid (UNII: 70KO0R01RY)	
Citric Acid Monohydrate (UNII: 2968PHW8QP)	
Silicon Dioxide (UNII: ETJ7Z6XBU4)	
Triethyl Citrate (UNII: 8Z96QXD6UM)	
Magnesium Stearate (UNII: 70097M6I30)	
Ethylcellulose, Unspecified (UNII: 7Z8S9VYZ4B)	
Sucralose (UNII: 96K6UQ3ZD4)	
Polyethylene Glycol, Unspecified (UNII: 3WJQ0SDW1A)	

### Product Characteristics

<b>Color</b>	PURPLE (purple to light purple, mottled)	<b>Score</b>	no score
<b>Shape</b>	ROUND	<b>Size</b>	12mm
<b>Flavor</b>	GRAPE	<b>Imprint Code</b>	T3
<b>Contains</b>			

### Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:70 165-300-30	5 in 1 CARTON	06/20/2016	
1		6 in 1 BLISTER PACK; Type 0: Not a Combination Product		

### Marketing Information

<b>Marketing Category</b>	<b>Application Number or Monograph Citation</b>	<b>Marketing Start Date</b>	<b>Marketing End Date</b>
NDA	NDA205489	06/20/2016	

**Labeler** - Neos Therapeutics, LP (836126052)

**Establishment**

Name	Address	ID/FEI	Business Operations
Neos Therapeutics, LP		836126052	MANUFACTURE(70165-100, 70165-200, 70165-300), PACK(70165-100, 70165-200, 70165-300), LABEL(70165-100, 70165-200, 70165-300), ANALYSIS(70165-100, 70165-200, 70165-300)

Revised: 6/2017

Neos Therapeutics, LP