DEXMETHYLPHENIDATE HYDROCHLORIDE- dexmethylphenidate hydrochloride capsule, extended release
Bryant Ranch Prepack

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use DEXMETHYLPHENIDATE HYDROCHLORIDE EXTENDED-RELEASE CAPSULES safely and effectively. See full prescribing information for DEXMETHYLPHENIDATE HYDROCHLORIDE EXTENDED-RELEASE CAPSULES.

DEXMETHYLPHENIDATE HYDROCHLORIDE Extended-Release Capsules, for Oral Use CII
Initial U.S. Approval: 2001

See full prescribing information for complete boxed warning.

- CNS stimulants, including dexmethylphenidate hydrochloride extended-release, 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

Dexmethylphenidate hydrochloride extended-release is a central nervous system (CNS) stimulant indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) (1)

DOSAGE AND ADMINISTRATION

- Patients new to methylphenidate: Recommended starting dose is 5 mg once daily for pediatric patients and 10 mg once daily for adults with or without food in the morning (2.2).
- Patients currently on methylphenidate: Dexmethylphenidate hydrochloride extended-release dosage is half (1/2) the current total daily dosage of methylphenidate (2.2).
- Patients currently on dexmethylphenidate immediate-release tablets: Give the same daily dose of dexmethylphenidate hydrochloride extended-release (2.2).
- Titrate weekly in increments of 5 mg in pediatric patients and 10 mg in adult patients (2.2).
- Maximum recommended daily dose: 30 mg in pediatric patients and 40 mg in adults (2.2).
- Capsules may be swallowed whole or opened and the entire contents sprinkled on applesauce (2.3).

DOSAGE FORMS AND STRENGTHS

Extended-Release Capsules: 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg, and 40 mg of dexmethylphenidate hydrochloride (3)

CONTRAINDICATIONS

- Known hypersensitivity to methylphenidate or other components of dexmethylphenidate hydrochloride extended-release (4).
- Concurrent treatment with a monoamine oxidase inhibitor (MAOI), or use of an MAOI within the preceding 14 days (4).

WARNINGS AND PRECAUTIONS

- *Serious Cardiovascular Events:*Sudden death has been reported in association with CNS stimulant treatment at usual doses in pediatric patients with structural cardiac abnormalities or other serious heart problems. In adults, sudden death, stroke, and myocardial infarction have been reported. Avoid use in patients with known structural cardiac abnormalities, cardiomyopathy, serious heart rhythm arrhythmias, or coronary artery disease (5.2).
- *Blood Pressure and Heart Rate Increases:* Monitor blood pressure and pulse. Consider the benefits and risk 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 preexisting psychiatric illness. Evaluate for existing psychotic or bipolar disorder prior to dexmethylphenidate hydrochloride extended-release use (5.4).
- *Priapism:*Cases of painful and prolonged penile erections and priapism have been reported with methylphenidate products. Immediate medical attention should be sought if signs or symptoms of prolonged penile erections or priapism are observed (5.5).
- *Peripheral Vasculopathy, including Raynaud's Phenomenon:*Stimulants used to treat ADHD are associated with peripheral vasculopathy, including Raynaud's phenomenon. Careful observation for digital changes is necessary during treatment with ADHD stimulants. (5.6)
- *Long-Term Suppression of Growth:*Monitor height and weight at appropriate intervals in pediatric patients (5.7).

ADVERSE REACTIONS

The most common adverse reactions (greater than or equal to 5% and twice the rate of placebo):

- Pediatric patients 6 to 17 years: dyspepsia, decreased appetite, headache, and anxiety (6.1).
- Adults: dry mouth, dyspepsia, headache, pharyngolaryngeal pain, and anxiety (6.1).

- **To report SUSPECTED ADVERSE REACTIONS, contact Par Pharmaceutical at 1-800-828-9393 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**

DRUG INTERACTIONS

- *Antihypertensive Drugs*: Monitor blood pressure. Adjust dosage of antihypertensive drugs as needed (7.1).

- *Halogenated Anesthetics*: Avoid use of dexmethylphenidate hydrochloride extended-release on the day of surgery if halogenated anesthetics will be used (7.1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised 07/2021

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 3/2023

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FULL PRESCRIBING INFORMATION

WARNING: ABUSE AND DEPENDENCE

CNS stimulants, including dexmethylphenidate hydrochloride extended-release, 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

Dexmethylphenidate hydrochloride extended-release is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) *[see Clinical Studies (14)].*

2 DOSAGE AND ADMINISTRATION

2.1 Pre-treatment Screening

Prior to treating pediatric patients and adults with central nervous system (CNS) stimulants including dexmethylphenidate hydrochloride extended-release, assess for the presence of cardiac disease (i.e., perform a careful history including family history of sudden death or ventricular arrhythmia, and physical examination) *[see Warnings and Precautions 5.2].*

Assess the risk of abuse prior to prescribing, and monitor for signs of abuse and dependence while on therapy. Maintain careful prescription records, educate patients about abuse, monitor for signs of abuse and overdose, and periodically re-evaluate the need for dexmethylphenidate hydrochloride extended-release use *[see Boxed Warning, Warnings and Precautions (5.1), Drug Abuse and Dependence (9.2, 9.3)].*

2.2 Treatment of Attention Deficit Hyperactivity Disorder

Patients New to Methylphenidate

The recommended starting dosage of dexmethylphenidate hydrochloride extended-release for patients who are not currently taking dexmethylphenidate or racemic methylphenidate, or for patients who are on stimulants other than methylphenidate are:

- Pediatric patients: Start with 5 mg orally once daily in the morning with or without food.
- Adult patients: Start with 10 mg orally once daily in the morning with or without food.

  Patients Currently on Methylphenidate

  The recommended starting dose of dexmethylphenidate hydrochloride extended-

release for patients currently using methylphenidate is half (1/2) the total daily dose of racemic methylphenidate.
Patients currently using dexmethylphenidate immediate-release tablets may be given the same daily dose of dexmethylphenidate hydrochloride extended-release.
Titration Schedule
The dose may be titrated weekly in increments of 5 mg in pediatric patients and 10 mg in adult patients. The dose should be individualized according to the needs and response of the patient. Daily doses above 30 mg in pediatrics and 40 mg in adults have not been studied and are not recommended.
Maintenance/Extended Treatment
Pharmacological treatment of ADHD may be needed for extended periods. Periodically re-evaluate the long-term use of dexmethylphenidate hydrochloride extended-release and adjust dosage as needed.

2.3 Administration Instructions

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

2.4 Dose Reduction and Discontinuation

If paradoxical aggravation of symptoms or other adverse reactions occur, reduce the dosage, or if necessary,discontinue dexmethylphenidate hydrochloride extended-release. If improvement is not observed after appropriate dosage adjustment over a one-month period, the drug should be discontinued.

3 DOSAGE FORMS AND STRENGTHS

5 mg, extended-release capsule, light blue opaque body and light blue opaque capsule, imprinted in black ink “par” on capsule and 048 on body.

10 mg, extended-release capsule, beige opaque body and beige opaque capsule, imprinted in black ink “par” on capsule and 049 on body.

15 mg, extended-release capsule, spring green opaque body and spring green opaque capsule, imprinted in black ink “par” on capsule and 090 on body.

20 mg, extended-release capsule, white opaque body and white opaque capsule, imprinted in black ink “par” on capsule and 248 on body.

25 mg, extended-release capsule, white opaque body and yellow transparent capsule, imprinted in black ink “par” on capsule and 333 on body.

30 mg, extended-release capsule, white opaque body and yellow transparent capsule, imprinted in black ink “par” on capsule and 539 on body.

35 mg, extended-release capsule, white opaque body and yellow transparent capsule, imprinted in black ink “par” on capsule and 339 on body.

40 mg, extended-release capsule, white opaque body and yellow transparent capsule, imprinted in black ink “par” on capsule and 546 on body.

4 CONTRAINDICATIONS

- Hypersensitivity to methylphenidate or other components of dexmethylphenidate hydrochloride extended-release. Hypersensitivity reactions such as angioedema and

anaphylactic reactions have been reported in patients treated with methylphenidate *[see Adverse Reactions (6.1)].*
- Concomitant treatment with monoamine oxidase inhibitors (MAOIs) or within 14 days following discontinuation of treatment with an MAOI, because of the risk of hypertensive crises *[see Drug Interactions (7.1)].*

5 WARNINGS AND PRECAUTIONS

5.1 Potential for Abuse and Dependence

CNS stimulants, including dexmethylphenidate hydrochloride extended-release, 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, Drug Abuse and Dependence (9.2, 9.3)].*

5.2 Serious Cardiovascular Reactions

Sudden death, stroke and myocardial infarction have been reported in adults with CNS stimulant treatment at recommended doses. Sudden death has been reported in pediatric patients with structural cardiac abnormalities and other serious heart problems taking CNS stimulants at recommended doses for ADHD. Avoid use in patients with known serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, and other serious heart problems. Further evaluate patients who develop exertional chest pain, unexplained syncope, or arrhythmias during dexmethylphenidate hydrochloride extended-release treatment.

5.3 Blood Pressure and Heart Rate Increases

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

5.4 Psychiatric Adverse Reactions

Exacerbation of Preexisting Psychosis

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

Induction of a Manic Episode in Patients with Bipolar Disorder

CNS stimulants may induce a manic or mixed mood episode in patients. Prior to initiating treatment, screen patients for risk factors for developing 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 dexmethylphenidate hydrochloride extended-release. 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 dexmethylphenidate hydrochloride extended-release, 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 postmarketing 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 treating 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.

In a 7-week, double-blind, placebo-controlled study of dexmethylphenidate hydrochloride extended-release, the mean weight gain was greater for pediatric patients (ages 6 to 17 years) receiving placebo (+0.4 kg) than for patients receiving dexmethylphenidate hydrochloride extended-release (-0.5 kg).

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

Closely monitor growth (weight and height) in pediatric patients treated with CNS stimulants, including dexmethylphenidate hydrochloride extended-release, and patients who are not growing or gaining height or weight as expected may need to have their treatment interrupted.

6 ADVERSE REACTIONS

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

- Abuse and Dependence *[see Boxed Warning, Warnings and Precautions (5.1), Drug Abuse and Dependence (9.2, 9.3)]*
- Known hypersensitivity to methylphenidate or other ingredients of dexmethylphenidate hydrochloride extended-release *[see Contraindications (4)]*
- Hypertensive Crisis with Concomitant Use of Monoamine Oxidase Inhibitors *[see Contraindications (4), Drug Interactions (7.1)]*
- 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 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 clinical practice.

Clinical Trials Experience withDexmethylphenidate Hydrochloride Extended-Release in Pediatric Patients with ADHD

The safety data in this section is based on data from a 7-week controlled clinical study of dexmethylphenidate hydrochloride extended-release in 100 (103 randomized) pediatric patients with ADHD ages 6 to 17 years (ages 6 to 12, n = 86; ages 13 to 17, n = 17).

This study was a randomized, double-blind, placebo-controlled, parallel-group study to evaluate the time of onset, duration of efficacy, tolerability, safety of dexmethylphenidate hydrochloride extended-release5 mg to 30 mg/day who met The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for ADHD *[see Clinical Studies (14.1)]* .

Most Common Adverse Reactions(incidence of greater than or equal to 5% and at least twice placebo): dyspepsia, decreased appetite, headache and anxiety.

Adverse Reactions Leading to Discontinuation*:*50 of 684 (7.3%) pediatric patients treated with dexmethylphenidate immediate-release tablets experienced an adverse reaction that resulted in discontinuation. The most common reasons for discontinuation were twitching (described as motor or vocal tics), anorexia, insomnia, and tachycardia (approximately 1% each).

Table 1enumerates adverse reactions for the placebo-controlled, parallel-group study in children and adolescents with ADHD at flexible dexmethylphenidate hydrochloride extended-release doses of 5 to 30 mg/day. The table includes only those events that occurred in 5% or more of patients treated with dexmethylphenidate hydrochloride extended-release and for which the incidence in patients treated with dexmethylphenidate hydrochloride extended-release was at least twice the incidence in placebo-treated patients.

Table 1: Common Adverse Reactions in Pediatric Patients (6 to 17 years of age) with ADHD

System Organ Class Adverse Reaction	**Dexmethylphenidate Hydrochloride Extended-Release N=53**	**Placebo N=47**
Gastrointestinal Disorders	38%	19%
Dyspepsia	8%	4%
Metabolism and Nutrition Disorders	34%	11%
Decreased Appetite	30%	9%
Nervous System Disorders	30%	13%
Headache	25%	11%
Psychiatric Disorders	26%	15%
Anxiety	6%	0%

Abbreviation: ADHD, attention deficit hyperactivity disorder.

Table 2below enumerates the incidence of dose-related adverse reactions that occurred during a fixed-dose, double-blind, placebo-controlled trial in pediatric patients with ADHD taking dexmethylphenidate hydrochloride extended-release up to 30 mg daily versus placebo. The table includes only those reactions that occurred in patients treated with dexmethylphenidate hydrochloride extended-release for which the incidence was at least 5% and greater than the incidence among placebo-treated patients.

Table 2: Dose-Related Adverse Reactions in Pediatric Patients (6 to 17 years of age) with ADHD

System Organ Class Adverse Reaction	**Dexmethylphenidate Hydrochloride Extended-Release 10 mg/day N = 64**	**Dexmethylphenidate Hydrochloride Extended-Release 20 mg/day N = 60**	**Dexmethylphenidate Hydrochloride Extended-Release 30 mg/day N = 58**	**Placebo N = 63**
Gastrointestinal Disorders	22%	23%	29%	24%
Vomiting	2%	8%	9%	0%
Metabolism and Nutritional Disorders	16%	17%	22%	5%
Anorexia	5%	5%	7%	0%
Psychiatric Disorders	19%	20%	38%	8%
Insomnia	5%	8%	17%	3%
Depression	0%	0%	3%	0%
Mood Swings	0%	0%	3%	2%
Other Adverse Reactions				
Irritability	0%	2%	5%	0%
Nasal Congestion	0%	0%	5%	0%
Pruritus	0%	0%	3%	0%

Abbreviation: ADHD, attention deficit hyperactivity disorder.

Clinical Trials Experience with Dexmethylphenidate Hydrochloride Extended-Release in Adult Patients with ADHD

The safety data in this section is based on data from a 5-week controlled clinical study of dexmethylphenidate hydrochloride extended-release in 218 adult patients (221 randomized) with ADHD ages 18 to 60 years. In this study, 101 adult patients were treated for at least 6 months.

This study was a randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy, safety, and tolerability of dexmethylphenidate hydrochloride extended-release 20 mg, 30 mg, or 40 mg daily who met DSM-IV criteria for ADHD *[see Clinical Studies (14.2)]* .

Most Common Adverse Reactions(incidence of greater than or equal to 5% and at least twice placebo): dry mouth, dyspepsia, headache, anxiety, and pharyngolaryngeal pain.

*Adverse Reactions Leading to Discontinuation:*During the double-blind phase of the study, 10.7% of the dexmethylphenidate hydrochloride extended-release - treated patients and 7.5% of the placebo-treated patients discontinued due to adverse reactions. Three patients (1.8%) in the dexmethylphenidate hydrochloride extended-release discontinued due to insomnia and jittery, respectively and two patients (1.2%) in the dexmethylphenidate hydrochloride extended-release discontinued due to anorexia and anxiety, respectively.

Table 3enumerates adverse reactions for the placebo-controlled, parallel-group study in adults with ADHD at fixed dexmethylphenidate hydrochloride extended-release doses of

20, 30, and 40 mg/day. The table includes only those events that occurred in 5% or more of patients in a dexmethylphenidate hydrochloride extended-release dose group and for which the incidences in patients treated with dexmethylphenidate hydrochloride extended-release appeared to increase with dose.

Table 3: Dose-Related Adverse Reactions in Adult Patients (18 to 60 years of age) with ADHD

System Organ Class Adverse Reaction	**Dexmethylphenidate Hydrochloride Extended-Release 20 mg N = 57**	**Dexmethylphenidate Hydrochloride Extended-Release 30 mg N = 54**	**Dexmethylphenidate Hydrochloride Extended-Release 40 mg N = 54**	**Placebo N = 53**
Gastrointestinal Disorders	28%	32%	44%	19%
Dry Mouth	7%	20%	20%	4%
Dyspepsia	5%	9%	9%	2%
Nervous System Disorders	37%	39%	50%	28%
Headache	26%	30%	39%	19%
Psychiatric Disorders	40%	43%	46%	30%
Anxiety	5%	11%	11%	2%
Respiratory, Thoracic and Mediastinal Disorders	16%	9%	15%	8%
Pharyngolaryngeal Pain	4%	4%	7%	2%

Two other adverse reactions occurring in clinical trials with dexmethylphenidate hydrochloride extended-release at a frequency greater than placebo, but which were not dose related were: feeling jittery (12% and 2%, respectively) and dizziness (6% and 2%, respectively).

Table 4summarizes changes in vital signs and weight that were recorded in the adult study (N=218) of dexmethylphenidate hydrochloride extended-release in the treatment of ADHD.

Table 4: Changes (Mean ± SD) in Vital Signs and Weight by Randomized Dose During Double-Blind Treatment-Adults

	Dexmethylphenidate Hydrochloride ER 20 mg (N=57)	**Dexmethylphenidate Hydrochloride ER 30 mg (N=54)**	**Dexmethylphenidate Hydrochloride ER 40 mg (N=54)**	**Placebo (N=53)**
Pulse (bpm)	3.1 ± 11.1	4.3 ± 11.7	6.0 ± 10.1	-1.4 ± 9.3
Diastolic BP (mmHg)	-0.2 ± 8.2	1.2 ± 8.9	2.1 ± 8.0	0.3 ± 7.8
Weight (kg)	-1.4 ± 2.0	-1.2 ± 1.9	-1.7 ± 2.3	-0.1 ± 3.9

6.2 Postmarketing Experience

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

*Musculoskeletal:*rhabdomyolysis

*Immune System Disorders:*hypersensitivity reactions, including angioedema and anaphylaxis

Adverse Reactions Reported with All Ritalin and Dexmethylphenidate Hydrochloride Extended-Release Formulations

The following adverse reactions associated with the use of all Ritalin and dexmethylphenidate hydrochloride extended-release formulations were identified in clinical trials, spontaneous reports, and literature. Because these reactions were reported voluntarily from a population of uncertain size, it is not always possible to estimate their frequency reliably or to establish a causal relationship to drug exposure.

*Infections and Infestations:*nasopharyngitis

*Blood and the Lymphatic System Disorders:*leukopenia, thrombocytopenia, anemia

*Immune System Disorders:*hypersensitivity reactions, including angioedema and anaphylaxis

*Metabolism and Nutrition Disorders:*decreased appetite, reduced weight gain, and suppression of growth during prolonged use in pediatric patients

*Psychiatric Disorders:*insomnia, anxiety, restlessness, agitation, psychosis (sometimes with visual and tactile hallucinations), depressed mood

*Nervous system disorders:*headache, dizziness, tremor, dyskinesia including choreoathetoid movements, drowsiness, convulsions, cerebrovascular disorders (including vasculitis, cerebral hemorrhages and cerebrovascular accidents), serotonin syndrome in combination with serotonergic drugs

*Eye Disorders:*blurred vision, difficulties in visual accommodation

*Cardiac Disorders:*tachycardia, palpitations, increased blood pressure, arrhythmias, angina pectoris

*Respiratory, Thoracic and Mediastinal Disorders:*cough

*Gastrointestinal Disorders:*dry mouth, nausea, vomiting, abdominal pain, dyspepsia

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

*Skin and Subcutaneous Tissue Disorders:*hyperhidrosis, pruritus, urticaria, exfoliative dermatitis, scalp hair loss, erythema multiforme rash, thrombocytopenic purpura

*Musculoskeletal and Connective Tissue Disorders:*arthralgia, muscle cramps, rhabdomyolysis

*Investigations:*weight loss (adult ADHD patients)

Additional Adverse Reactions Reported with Other Methylphenidate Products

The list below shows adverse reactions not listed with Ritalin and Dexmethylphenidate Hydrochloride Extended-Release formulations that have been reported with other methylphenidate products based on clinical trials data and postmarketing spontaneous reports.

*Blood and Lymphatic Disorders:*pancytopenia

*Immune System Disorders:*hypersensitivity reactions such as auricular swelling, bullous

conditions, eruptions, exanthemas

*Psychiatric Disorders:*affect lability, mania, disorientation, libido changes

*Nervous System Disorders:*migraine

*Eye Disorders:*diplopia, mydriasis

*Cardiac Disorders:*sudden cardiac death, myocardial infarction, bradycardia, extrasystole, supraventricular tachycardia, ventricular extrasystole

*Vascular Disorders:*peripheral coldness, Raynaud's phenomenon

*Respiratory, Thoracic and Mediastinal Disorders:*pharyngolaryngeal pain, dyspnea

*Gastrointestinal Disorders:*diarrhea, constipation

*Skin and Subcutaneous Tissue Disorders:*angioneurotic edema, erythema, fixed drug eruption

*Musculoskeletal, Connective Tissue and Bone Disorders:*myalgia, muscle twitching

*Renal and Urinary Disorders:*hematuria

*Reproductive System and Breast Disorders:*gynecomastia

*General Disorders:*fatigue, hyperpyrexia

*Urogenital Disorders:*priapism

7 DRUG INTERACTIONS

7.1 Clinically Important Drug Interactions with Dexmetyhlphenidate Hydrochloride Extended-Release

Table 5presents clinically important drug interactions with dexmethylphenidate hydrochloride extended-release.

Table 5: Clinically Important Drug Interactions with Dexmethylphenidate Hydrochloride Extended-Release

Monoamine Oxidase Inhibitors (MAOI)	
Clinical Impact	Concomitant use of MAOIs and CNS stimulants, including dexmethylphenidate hydrochloride extended-release, can cause hypertensive crisis. Potential outcomes include death, stroke, myocardial infarction, aortic dissection, ophthalmological complications, eclampsia, pulmonary edema, and renal failure *[see Contraindications (4)]*.
Intervention	Concomitant use of dexmethylphenidate hydrochloride extended-release with MAOIs or within 14 days after discontinuing MAOI treatment is contraindicated.
Examples	selegiline, tranylcypromine, isocarboxazid, phenelzine, linezolid, methylene blue
Antihypertensive Drugs	
	Dexmethylphenidate hydrochloride

Clinical Impact	extended-release may decrease the effectiveness of drugs used to treat hypertension *[see Warnings and Precautions (5.3)]*.
Intervention	Monitor blood pressure and adjust the dosage of the antihypertensive drug as needed.
Examples	Potassium-sparing and thiazide diuretics, calcium channel blockers, angiotensin-converting-enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), beta blockers, centrally acting alpha-2 receptor agonists
Halogenated Anesthetics	
Clinical Impact	Concomitant use of halogenated anesthetics and dexmethylphenidate hydrochloride extended-release may increase the risk of sudden blood pressure and heart rate increase during surgery.
Intervention	Avoid use of dexmethylphenidate hydrochloride extended-release in patients being treated with anesthetics on the day of surgery.
Examples	halothane, isoflurane, enflurane, desflurane, sevoflurane
Risperidone	
Clinical Impact	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)
Intervention	Monitor for signs of EPS

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 ADHD medications, including dexmethylphenidate hydrochloride extended-release, during pregnancy. Healthcare providers are encouraged to register patients by calling the National Pregnancy registry for ADHD medications at 1-866-961-2388 or visit https://womensmentalhealth.org/adhdmedications/.

Risk Summary

Dexmethylphenidate is the d-threo enantiomer of racemic methylphenidate. 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*). Embryo-fetal development studies in rats showed delayed fetal skeletal ossification at doses up to 5 times the maximum recommended human dose (MRHD) of 20 mg/day given to adults based on plasma levels. A decrease in pup weight in males was observed in a pre- and

post-natal development study with oral administration of methylphenidate to rats throughout pregnancy and lactation at doses 5 times the MRHD of 20 mg/day given to adults based on plasma levels (*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 dexmethylphenidate hydrochloride extended-release, can cause vasoconstriction and thereby decrease placental perfusion. No fetal and/or neonatal adverse reactions have been reported with the use of therapeutic doses of methylphenidate during pregnancy; however, premature delivery and low birth weight infants have been reported in amphetamine-dependent mothers.

Data

Animal Data

In embryo-fetal development studies conducted in rats and rabbits, dexmethylphenidate was administered orally at doses of up to 20 and 100 mg/kg/day, respectively, during the period of organogenesis. No evidence of malformations was found in either the rat or rabbit study; however, delayed fetal skeletal ossification was observed at the highest dose level in rats. When dexmethylphenidate was administered to rats throughout pregnancy and lactation at doses of up to 20 mg/kg/day, post-weaning body weight gain was decreased in male offspring at the highest dose, but no other effects on postnatal development were observed. At the highest doses tested, plasma levels [area under the curve (AUCs)] of dexmethylphenidate in pregnant rats and rabbits were approximately 5 and 1 times, respectively, those in adults dosed with 20 mg/day. Plasma levels in adults were comparatively similar to plasma levels in adolescents.

Racemic methylphenidate has been shown to cause malformations (increased incidence of fetal spina bifida) in rabbits when given in doses of 200 mg/kg/day throughout organogenesis.

8.2 Lactation

Risk Summary

Dexmethylphenidate is the *d-threo*enantiomer of racemic methylphenidate. 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 dexmethylphenidate hydrochloride extended-release and any potential adverse effects on the breastfed infant from dexmethylphenidate hydrochloride extended-release 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 dexmethylphenidate hydrochloride extended-release in pediatric patients less than 6 years have not been established.

The safety and effectiveness of dexmethylphenidate hydrochloride extended-release for the treatment of ADHD have been established in pediatric patients ages 6 to 17 years in two adequate and well-controlled clinical trials *[see Clinical Studies (14.2)]* . The long-term efficacy of dexmethylphenidate hydrochloride extended-release in pediatric patients has not been established.

Long Term Suppression of Growth

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

Juvenile Animal Toxicity Data

Rats treated with racemic 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 MRHD of 60 mg/day given to children on a mg/m ^{2}basis.

In a study conducted in young rats, racemic 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 4 times the MRHD of 60 mg/day of racemic methylphenidate given to children on a mg/m ^{2}basis) or greater, and a deficit in the acquisition of a specific learning task was seen in females exposed to the highest dose (8 times the MRHD given to children on a mg/m ^{2}basis). The no effect level for juvenile neurobehavioral development in rats was 5 mg/kg/day (approximately 0.5 times the MRHD given to children on a mg/m ^{2}basis). The clinical significance of the long-term behavioral effects observed in rats is unknown.

8.5 Geriatric Use

Dexmethylphenidate hydrochloride extended-release has not been studied in the geriatric population.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Dexmethylphenidate hydrochloride extended-release contains dexmethylphenidate hydrochloride, a Schedule II controlled substance.

9.2 Abuse

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

Signs and symptoms of CNS stimulant abuse include increased heart rate, respiratory rate, blood pressure, and/or sweating, dilated pupils, hyperactivity, restlessness, insomnia, decreased appetite, loss of coordination, tremors, flushed skin, vomiting, and/or abdominal pain. Anxiety, psychosis, hostility, aggression, suicidal or homicidal ideation have also been observed. Abusers of CNS stimulants may chew, snort, inject, or

use other unapproved routes of administration which may result in overdose and death *[see Overdosage (10)]* .

To reduce the abuse of CNS stimulants including dexmethylphenidate hydrochloride extended-release, 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 dexmethylphenidate hydrochloride extended-release 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 dexmethylphenidate hydrochloride extended-release.

Dependence

Physical dependence (which is manifested by a withdrawal syndrome produced by abrupt cessation, rapid dose reduction, or administration of an antagonist) may occur in patients treated with CNS stimulants including dexmethylphenidate hydrochloride extended-release. Withdrawal symptoms after abrupt cessation following prolonged high-dosage administration of CNS stimulants include dysphoric mood; fatigue; vivid, unpleasant dreams; insomnia or hypersomnia; increased appetite; and psychomotor retardation or agitation.

10 OVERDOSAGE

Human Experience

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

Overdose Management

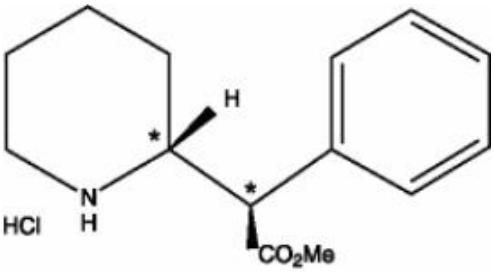
Consult with a Certified Poison Control Center (1-800-222-1222) for the latest recommendations

11 DESCRIPTION

Dexmethylphenidate hydrochloride extended-release contains dexmethylphenidate hydrochloride, a CNS stimulant. Dexmethylphenidate hydrochloride is the *d-threo*enantiomer of racemic methylphenidate hydrochloride. Dexmethylphenidate hydrochloride extended-release is an extended-release formulation of dexmethylphenidate with a bi-modal release profile. Each bead-filled dexmethylphenidate hydrochloride extended-release capsule contains half the dose as immediate-release beads and half as enteric-coated, delayed-release beads, thus providing an immediate release of dexmethylphenidate and a delayed release of dexmethylphenidate. Dexmethylphenidate hydrochloride extended-release is intended for oral administration and is is available as 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg and 40 mg extended-release capsules.

Chemically, dexmethylphenidate hydrochloride is methyl α-phenyl-2-piperidineacetate

hydrochloride, (R,R')-(+)-. Its molecular formula is $C_{14}H_{19}NO_2$•HCl. Its structural formula is:



Note* = asymmetric carbon center

Dexmethylphenidate hydrochloride is a white to off white 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 g/mol.

Inactive ingredientsmethacrylic acid copolymer, amino methacrylate copolymer, triethyl citrate, talc, sugar spheres, polyethylene glycol, gelatin, titanium dioxide and black ink. The black ink contains shellac glaze, iron oxide black, n-butyl alcohol, propylene glycol, FD&C blue #1, FD&C Blue #2, FD&C Red # 40 and D&C Yellow #10. The 5 mg also contains FD& C Blue #1 and FD&C Red #3. The 10 mg contains FD&C Yellow #6. The 15 mg contains FD&C Blue #1and FD&C Yellow #6. The 25 mg, 30 mg, 35 mg and 40 mg contains yellow iron oxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Dexmethylphenidate hydrochloride is a (CNS) stimulant. The mode of therapeutic action in ADHD is not known.

12.2 Pharmacodynamics

Dexmethylphenidate is the more pharmacologically active *d*-enantiomer of racemic methylphenidate. Methylphenidate blocks the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space.

Cardiac Electrophysiology

At the recommended maximum total daily dosage of 40 mg, dexmethylphenidate hydrochloride extended-release does not prolong the QTc interval to any clinically relevant extent.

12.3 Pharmacokinetics

Absorption

Dexmethylphenidate hydrochloride extended-release produces a bi-modal plasma concentration-time profile (i.e., 2 distinct peaks approximately 4 hours apart) when orally administered to healthy adults. The initial rate of absorption for dexmethylphenidate hydrochloride extended-release is similar to that of dexmethylphenidate tablets as shown by the similar rate parameters between the 2 formulations, i.e., first peak concentration (C_{max1}), and time to the first peak (t_{max1}), which is reached in 1.5 hours (typical range 1-4 hours). The mean time to the interpeak minimum (t_{minip})is slightly shorter, and time to the second peak (tmax2) is slightly longer for dexmethylphenidate

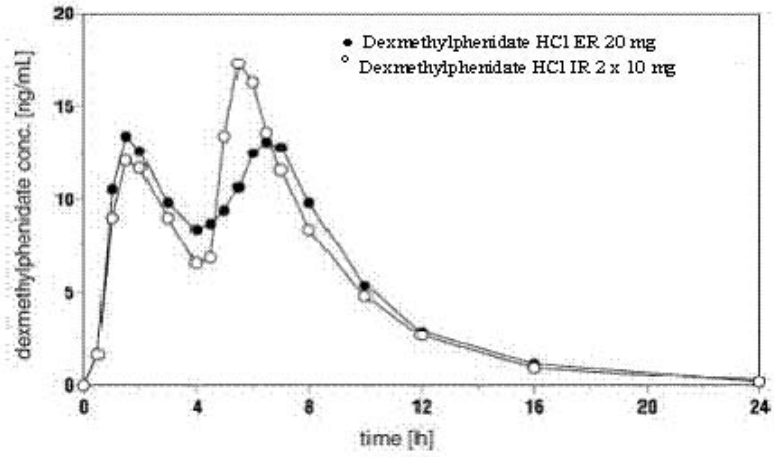
hydrochloride extended-release given once daily (about 6.5 hours, range 4.5-7 hours) compared to dexmethylphenidate hydrochloride tablets given in 2 doses 4 hours apart (see **Figure 1)**, although the ranges observed are greater for dexmethylphenidate hydrochloride extended-release.

Dexmethylphenidate hydrochloride extended-release given once daily exhibits a lower second peak concentration (C_{max2}), higher interpeak minimum concentrations (C_{minip}), and fewer peak and trough fluctuations than dexmethylphenidate hydrochloride tablets given in 2 doses given 4 hours apart. This is due to an earlier onset and more prolonged absorption from the delayed-release beads (see **Figure 1**).

The ratio of geometric mean of $AUC_{(0\text{-}inf)}$and C_{max}after administration of dexmethylphenidate hydrochloride extended-release given once daily are 1.02 and 0.86 respectively, to the same total dose of dexmethylphenidate hydrochloride tablets given in 2 doses 4 hours apart. The variability in C_{max}, C_{min}, and AUC is similar between dexmethylphenidate hydrochloride extended-release and dexmethylphenidate immediate-release tablets with approximately a 3-fold range in each.

Approximately 90% of the dose is absorbed after oral administration of radiolabeled racemic methylphenidate. However, due to first pass metabolism the mean absolute bioavailability of dexmethylphenidate when administered in various formulations was 22% to 25%.

Figure 1 Mean Dexmethylphenidate Plasma Concentration-Time Profiles After Administration of 1 x 20 mg Dexmethylphenidate Hydrochloride Extended-Release(n=24) Capsules and 2 x 10 mg Dexmethylphenidate Hydrochloride Immediate-Release Tablets (n=25)



After single dose administration, dexmethylphenidate hydrochloride extended-release demonstrated dose proportional pharmacokinetics (PK) in the range of 5 mg to 40 mg.

For patients unable to swallow the capsule, the contents may be sprinkled on applesauce and administered *[see Dosage and Administration (2)]* .

Distribution

The plasma protein binding of dexmethylphenidate is not known; racemic methylphenidate is bound to plasma proteins by 12% to 15%, independent of concentration. Dexmethylphenidate shows a volume of distribution of 2.65 ± 1.11 L/kg.

Elimination

Plasma dexmethylphenidate concentrations decline monophasically following oral administration of dexmethylphenidate hydrochloride extended-release. The mean

terminal elimination half-life of dexmethylphenidate was about 3 hours in healthy adults. Pediatric patients tend to have slightly shorter half-lives with means of 2 to 3 hours. Dexmethylphenidate was eliminated with a mean clearance of 0.40 ± 0.12 L/hr/kg after intravenous administration.

Metabolism

In humans, dexmethylphenidate is metabolized primarily via de-esterification to *d*-α-phenyl-piperidine acetic acid (also known as *d*-ritalinic acid). This metabolite has little or no pharmacological activity. There is no *in vivo*interconversion to the *l-threo*-enantiomer.

Excretion

After oral dosing of radiolabeled racemic methylphenidate in humans, about 90% of the radioactivity was recovered in urine. The main urinary metabolite of racemic *dl*-methylphenidate was *dl*-ritalinic acid, accountable for approximately 80% of the dose. Urinary excretion of parent compound accounted for 0.5% of an intravenous dose.

Studies in Specific Populations

Male and Female Patients

After administration of dexmethylphenidate hydrochloride extended-release, the first peak, (C_{max1}) was on average 45% higher in women. The interpeak minimum and the second peak also tended to be slightly higher in women although the difference was not statistically significant, and these patterns remained even after weight normalization.

Racial or Ethnic Groups

There is insufficient experience with the use of dexmethylphenidate hydrochloride extended-release to detect ethnic variations in pharmacokinetics.

Pediatric Patients

The pharmacokinetics of dexmethylphenidate after dexmethylphenidate hydrochloride extended-release administration have not been studied in pediatrics less than 18 years of age. When a similar formulation of racemic methylphenidate was examined in 15 patients between 10 and 12 years of age and 3 patients with ADHD between 7 and 9 years of age, the time to the first peak was similar, although the time until the between peak minimum, and the time until the second peak were delayed and more variable in pediatric patients compared to adults. After administration of the same dose to pediatric patients and adults, concentrations in pediatric patients were approximately twice the concentrations observed in adults. This higher exposure is almost completely due to smaller body size as no relevant age-related differences in dexmethylphenidate pharmacokinetic parameters (i.e., clearance and volume of distribution) are observed after normalization to dose and weight.

Patients with Renal Impairment

There is no experience with the use of dexmethylphenidate hydrochloride extended-release in patients with renal impairment. Since renal clearance is not an important route of methylphenidate elimination, renal impairment is expected to have little effect on the pharmacokinetics of dexmethylphenidate hydrochloride extended-release.

Patients with Hepatic Impairment

There is no experience with the use of dexmethylphenidate hydrochloride extended-release in patients with hepatic impairment.

Drug Interaction Studies

Methylphenidate is not metabolized by cytochrome P450 (CYP) isoenzymes to a clinically relevant extent. Inducers or inhibitors of CYPs are not expected to have any relevant impact on methylphenidate pharmacokinetics. Conversely, the *d*- and *l*-enantiomers of methylphenidate did not relevantly inhibit CYP1A2, 2C8, 2C9, 2C19, 2D6, 2E1 or 3A.

Clinically, methylphenidate coadministration did not increase plasma concentrations of the CYP2D6 substrate desipramine.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis and Mutagenesis and Impairment of Fertility

Carcinogenesis

Lifetime carcinogenicity studies have not been carried out with dexmethylphenidate. In a lifetime carcinogenicity study carried out in B6C3F1 mice, racemic methylphenidate caused an increase in hepatocellular adenomas, and in males only, an increase in hepatoblastomas was seen at a daily dose of approximately 60 mg/kg/day. This dose is approximately 2 times the MRHD of 60 mg/day of racemic methylphenidate given to children on a mg/m ^{2}basis. Hepatoblastoma is a relatively rare rodent malignant tumor type. There was no increase in total malignant hepatic tumors. The mouse strain used is sensitive to the development of hepatic tumors, and the significance of these results to humans is unknown.

Racemic 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 4 times the MRHD (children) of 60mg/day racemic methylphenidate in children on a mg/m ^{2}basis.

In a 24-week carcinogenicity study with racemic methylphenidate 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 concentrations as in the lifetime carcinogenicity study; the high-dose group was exposed to 60 to 74 mg/kg/day of racemic methylphenidate.

Mutagenesis

Dexmethylphenidate 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 vivo* mouse bone marrow micronucleus test. In an *in vitro* assay using cultured Chinese Hamster Ovary cells treated with racemic methylphenidate, sister chromatid exchanges and chromosome aberrations were increased, indicative of a weak clastogenic response.

Impairment of Fertility

No human data on the effect of methylphenidate on fertility are available.

Fertility studies have not been conducted with dexmethylphenidate. Racemic methylphenidate did not impair fertility in male or female mice that were fed diets containing the drug in an 18-week continuous breeding study. The study was conducted at doses of up to 160 mg/kg/day, approximately 10 times the MRHD of 60 mg/day of racemic methylphenidate given to adolescents on a mg/m ^{2}basis.

14 CLINICAL STUDIES

14.1 Pediatric Patients

A randomized, double-blind, placebo-controlled, parallel-group study (Study 1) was conducted in 103 pediatric patients (ages 6 to 12, n = 86; ages 13 to 17, n = 17) who met DSM-IV criteria for ADHD inattentive, hyperactive-impulsive or combined inattentive/hyperactive-impulsive subtypes (Study 1).

Patients were randomized to receive either a flexible-dose of dexmethylphenidate hydrochloride extended-release (5 to 30 mg/day) or placebo once daily for 7 weeks. During the first 5 weeks of treatment patients were titrated to their optimal dose and

remained on this optimal dose for the last 2 weeks of the study without dose changes or interruption.

Signs and symptoms of ADHD were evaluated by comparing the mean change from baseline to endpoint for dexmethylphenidate hydrochloride extended-release and placebo-treated patients using an intent-to-treat analysis of the primary efficacy outcome measure, the DSM-IV total subscale score of the Conners ADHD/DSM-IV Scales for teachers (CADS-T). The CADS-T includes the ADHD Index (12 items) and the DSM-IV total subscale (18 items, total score range: 0 to 54); the latter is divided into inattentive (9 items) and hyperactive-impulsive (9 items) subscales. Teachers assessed behavior observed during the school day by completing the CADS-T weekly. A decrease in the CADS-T DSM-IV total subscale score from baseline indicates improvement.

The CADS-T total scores showed a statistically significant treatment effect in favor of dexmethylphenidate hydrochloride extended-release than placebo (**Table 6**). There were insufficient adolescents enrolled in this study to assess the efficacy for dexmethylphenidate hydrochloride extended-release in the adolescent population. However, pharmacokinetic considerations and evidence of effectiveness of immediate-release dexmethylphenidate hydrochloride in adolescents support the effectiveness of dexmethylphenidate hydrochloride extended-release in this population.

Table 6: Summary of Efficacy Results from ADHD Study in Pediatric Patients (6 to 17 years) (Study 1)

Study Number	**Treatment Group**	**Primary Efficacy Measure: CADS-T Total Score**		
		Mean Baseline Score (SD)	**LS Mean Change from Baseline (SE)**	**Placebo-subtracted Difference [a] (95% CI)**
Study 1	Dexmethylphenidate Hydrochloride Extended-Release 5 to 30 mg/day (n = 52)	33.3 (9.18)	16.41 (1.8)	10.64 (5.38, 15.91)
	Placebo (n = 45)	34.9 (10.03)	5.77 (1.93)	--

Abbreviations: ADHD, attention deficit hyperactivity disorder; SD, standard deviation; SE, standard error; LS Mean, least-squares mean; CI, confidence interval, not adjusted for multiple comparisons.

[a]Difference (drug minus placebo) in least-squares mean change from baseline.

In 2 additional cross-over studies (Studies 2 and 3) in pediatric patients aged 6 to 12 years who received 20 mg dexmethylphenidate hydrochloride extended-release or placebo, dexmethylphenidate hydrochloride extended-release was found to have a statistically significant treatment effect versus placebo on the Swanson, Kotkin, Agler, M-Flynn & Pelham (SKAMP) rating scale total scores at all-time points after dosing in each study (0.5, 1, 3, 4, 5, 7, 9, 10, 11 and 12 hours in Study 2 and 1, 2, 4, 6, 8, 9, 10, 11 and 12 hours in the Study 3). SKAMP is a validated 13-item teacher-rated scale that assesses manifestations of ADHD in a classroom setting. A treatment effect was also observed 0.5 hours after administration of dexmethylphenidate hydrochloride extended-release 20 mg in an additional study of ADHD patients aged 6 to 12 years.

14.2 Adult Patients

A randomized, double-blind, placebo-controlled, parallel-group (Study 4) was conducted in 221 adult patients (ages 18 to 60) years who met DSM-IV criteria for ADHD inattentive, hyperactive-impulsive or combined inattentive/hyperactive-impulsive subtypes (Study 4).

Patients were randomized to receive either a fixed dose of dexmethylphenidate hydrochloride extended-release (20, 30, or 40 mg/day) or placebo once daily for 5 weeks. Patients randomized to dexmethylphenidate hydrochloride extended-release were initiated on a 10 mg/day starting dose and titrated in increments of 10 mg/week to the randomly assigned fixed dose. Patients were maintained on their fixed dose (20, 30 or 40 mg/day) for a minimum of 2 weeks.

Signs and symptoms of ADHD were evaluated by comparing the mean change from baseline to endpoint for dexmethylphenidate hydrochloride extended-release and placebo-treated patients using an intent-to-treat analysis of the primary efficacy outcome measure, the investigator-administered DSM-IV Attention-Deficit/Hyperactivity Disorder Rating Scale (DSM-IV ADHD RS).

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

All 3 dexmethylphenidate hydrochloride extended-release doses (20, 30 or 40 mg/day) showed a statistically significant reatment effect compared to placebo. There was no obvious increase in effectiveness with increasing the dose.

Table 7: Summary of Efficacy Results from ADHD Study in Adults (Study 4)

Study Number	**Treatment Group**	**Primary Efficacy Measure: ADHD-RS Total Score**		
		Mean Baseline Score (SD)	**LS Mean Change from Baseline (SE)**	**Placebo-subtracted Difference[a] (95% CI)**
Study 4	Dexmethylphenidate Hydrochloride Extended-Release 20 mg/day (n = 57)	36.8 (7.2)	13.27 (1.44)	5.71 (1.64, 9.78)
	Dexmethylphenidate Hydrochloride Extended-Release 30 mg/day (n = 54)	36.9 (8.07)	12.86 (1.48)	5.31 (1.18, 9.44)
	Dexmethylphenidate Hydrochloride Extended-Release 40 mg/day (n = 54)	36.9 (8.25)	16.51 (1.48)	8.96 (4.83, 13.08)
	Placebo (n = 53)	37.5 (7.82)	7.55 (1.49)	--

Abbreviations: ADHD, attention deficit hyperactivity disorder; SD, standard deviation; SE, standard error; LS Mean, least-squares mean; CI, confidence interval, not adjusted for multiple comparisons.

[a]Difference (drug minus placebo) in least-squares mean change from baseline.

16 HOW SUPPLIED

Dexmethylphenidate hydrochloride extended-release capsules are available as follows:

40 mg Extended-Release Capsules (NDC 72162-1507-1) white opaque body with a yellow transparent cap printed with “par” on capsule and 546 on body in black ink supplied in bottles of 100.

Store dexmethylphenidate hydrochloride extended-release capsules at 20°C to 25°C (68°F to 77°F); excursions permitted to 15° C to 30°C (59°F to 86°F)[See USP Controlled Room Temperature.]

Dispense in tight container (USP).

Disposal

Comply with local laws and regulations on drug disposal of CNS stimulants. Dispose of remaining, unused, or expired dexmethylphenidate hydrochloride extended-release 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 dexmethylphenidate hydrochloride extended-release with an undesirable, non-toxic substance to make it less appealing to children and pets. Place the mixture in a container such as a sealed plastic bag and discard dexmethylphenidate hydrochloride extended-release in the household trash.

17 PATIENT COUNSELING INFORMATION

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

Controlled Substance Status/High Potential for Abuse and Dependence

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

Serious Cardiovascular Risks

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

Blood Pressure and Heart Rate Increases

Instruct patients that dexmethylphenidate hydrochloride extended-release can cause elevations of their blood pressure and pulse rate *[see Warnings and Precautions (5.3)]* .

Psychiatric Risks

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

Priapism

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

Circulation Problems in Fingers and Toes (Peripheral Vasculopathy, including Raynaud's Phenomenon)

Instruct patients beginning treatment with dexmethylphenidate hydrochloride extended-release 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 dexmethylphenidate hydrochloride extended-release. Further clinical evaluation (e.g., rheumatology referral) may be appropriate for certain patients *[see Warnings and Precautions (5.6)]* .

Suppression of Growth

Advise patients that dexmethylphenidate hydrochloride extended-release may cause slowing of growth and weight loss *[see Warnings and Precautions (5.7)].*

Pregnancy Registry

Advise patients that there is a pregnancy exposure registry that monitors pregnancy outcomes in patients exposed to ADHD medications, including dexmethylphenidate hydrochloride extended-release, during pregnancy [*see Use in Specific Populations (8.1)]* .

MEDICATION GUIDE

MEDICATION GUIDE
Dexmethylphenidate Hydrochloride Extended-Release Capsules CII
(Dex-meth-ill-FEN-ĭ-date Hī-dro-KLOR-īd)

What is the most important information I should know about dexmethylphenidate hydrochloride extended-releasecapsules?
Dexmethylphenidate hydrochloride extended-release is a federal controlled substance (CII) because it can be abused or lead to dependence. Keep dexmethylphenidate hydrochloride extended-release in a safe place to prevent misuse and abuse. Selling or giving away dexmethylphenidate hydrochloride extended-release may harm others, and is against the law.
Tell your doctor if you or your child have abused or been dependent on alcohol, prescription medicines or street drugs.
The following have been reported with use of methylphenidate hydrochloride and other stimulant medicines:
1. **Heart-related problems**:
   - **sudden death in patients who have heart problems or heart defects**
   - **stroke and heart attack in adults**
   - **increased blood pressure and heart rate**

Tell your doctor if you or your child have any heart problems, heart defects, high blood pressure, or a family history of these problems.

Your doctor should check you or your child carefully for heart problems before starting dexmethylphenidate hydrochloride extended-release.

Your doctor should check you or your child's blood pressure and heart rate regularly during treatment with dexmethylphenidate hydrochloride extended-release.

Call your doctor right away if you or your child has any signs of heart problems such as chest pain, shortness of breath, or fainting while taking dexmethylphenidate hydrochloride extended-releasecapsules.

2. **Mental (Psychiatric) problems**:

All Patients

- · **new or worse behavior and thought problems**
- · **new or worse bipolar illness**
- · **new or worse aggressive behavior or hostility**
- · **new psychotic symptoms (such as hearing voices, believing things that are not true, are suspicious) or new manic symptoms**

Tell your doctor about any mental problems you or your child have, or about a family history of suicide, bipolar illness, or depression.

Call your doctor right away if you or your child have any new or worsening mental symptoms or problems while taking dexmethylphenidate hydrochloride extended-releasecapsules, especially seeing or hearing things that are not real, believing things that are not real, or are suspicious.

What is dexmethylphenidate hydrochloride extended-release?

- Dexmethylphenidate hydrochloride extended-release is a central nervous system stimulant (CNS) prescription medicine. **It is used for the treatment of Attention-Deficit Hyperactivity Disorder (ADHD).**Dexmethylphenidate hydrochloride extended-release may help increase attention and decrease impulsiveness and hyperactivity in patients with ADHD.
- Dexmethylphenidate hydrochloride extended-release should be used as a part of a total treatment program for ADHD that may include counseling or other therapies.

Who should not takedexmethylphenidate hydrochloride extended-releasecapsules?

Dexmethylphenidate hydrochloride extended-releasecapsules should not be taken if you or your child:

- are allergic to methylphenidate hydrochloride, or any of the ingredients in dexmethylphenidate hydrochloride extended-release. See the end of this Medication Guide for a complete list of ingredients in dexmethylphenidate hydrochloride extended-release.

- are taking or have taken within the past 14 days an anti-depression medicine called a monoamine oxidase inhibitor (MAOI).

Dexmethylphenidate hydrochloride extended-releasecapsulesmay not be right for you or your child. Before starting dexmethylphenidate hydrochloride extended-releasecapsulestell your or your child's doctor about all health conditions (or a family history of) including:

- heart problems, heart defects, high blood pressure
- mental problems including psychosis, mania, bipolar illness, or depression
- circulation problems in fingers or toes
- if you are pregnant or plan to become pregnant. It is not known if dexmethylphenidate hydrochloride extended-release will harm your unborn baby.

- There is a pregnancy registry for females who are exposed to ADHD medications, including dexmethylphenidate hydrochloride extended-release, during pregnancy. The purpose of the registry is to collect information about the health of females exposed to dexmethylphenidate hydrochloride extended-release and their baby. If you or your child becomes pregnant during treatment with dexmethylphenidate hydrochloride extended-release, talk to your healthcare provider about registering with the National Pregnancy Registry of ADHD medications at 1-866-961-2388 or visit online at https://womensmentalhealth.org/adhd-medications/.

- if you are breastfeeding or plan to breastfeed. Dexmethylphenidate hydrochloride extended-release passes into your breast milk. Talk to your healthcare provider about the best way to feed the baby during treatment with dexmethylphenidate hydrochloride extended-release.

Tell your doctor about all of the medicines that you or your child takes, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Dexmethylphenidate hydrochloride extended-release and some medicines may interact with each other and cause serious side effects. Sometimes the doses of other medicines will need to be adjusted while taking dexmethylphenidate hydrochloride extended-release. Your doctor will decide whether dexmethylphenidate hydrochloride extended-release can be taken with other medicines.

Especially tell your doctor if you or your child takes:

- anti-depression medicines including MAOIs
- blood pressure medicines (anti-hypertensive)
  Know the medicines that you or your child takes. Keep a list of your medicines with you to show your doctor and pharmacist.
- You should not take dexmethylphenidate hydrochloride extended-release on the day of your operation if a certain

type of anesthetic is used. This is because there is a chance of a sudden rise in blood pressure and heart rate during the operation.

Do not start any new medicine while taking dexmethylphenidate hydrochloride extended-releasecapsuleswithout talking to your doctor first.

How shoulddexmethylphenidate hydrochloride extended-releasecapsulesbe taken?

- Take dexmethylphenidate hydrochloride extended-release exactly as prescribed. Your doctor may adjust the dose until it is right for you or your child.
- Take dexmethylphenidate hydrochloride extended-release once each day in the morning. Dexmethylphenidate hydrochloride extended-release is an extended-release capsule.
- Dexmethylphenidate hydrochloride extended-release can be taken with or without food. Taking dexmethylphenidate hydrochloride extended-release with food may slow the time it takes for the medicine to start working.
- Swallow dexmethylphenidate hydrochloride extended-release capsules whole with water or other liquids. **Do not chew, crush, or divide the capsules or the beads in the capsule.**If you or your child cannot swallow the capsule, open it and sprinkle the small beads of medicine over a spoonful of applesauce and swallow it right away without chewing.
- From time to time, your doctor may stop dexmethylphenidate hydrochloride extended-release treatment for a while to check ADHD symptoms.
- Your doctor may do regular checks of the blood, heart, and blood pressure while taking dexmethylphenidate hydrochloride extended-release.
- Children should have their height and weight checked often while taking dexmethylphenidate hydrochloride extended-release. Dexmethylphenidate hydrochloride extended-release treatment may be stopped if a problem is found during these check-ups.
- **In case of poisoning call your poison control center at 1-800-222-1222 right away, or go to the nearest hospital emergency room.**

What are the possible side effects of dexmethylphenidate hydrochloride extended-releasecapsules? Dexmethylphenidate hydrochloride extended-release capsules may cause serious side effects, including:

- See **“What is the most important information I should know about dexmethylphenidate hydrochloride extended-release?”**for information on reported heart and mental problems.
- **painful and prolonged erections (priapism)**have occurred with methylphenidate. If you or your child develops priapism, seek medical help right away. Because of the potential for lasting damage, priapism should be evaluated by a doctor immediately.
- **circulation problems in fingers and toes**(Peripheral

vasculopathy, including Raynaud's phenomenon):
  - fingers or toes may feel numb, cool, painful
  - fingers or toes may change color from pale, to blue, to red

  Tell your doctor if you or your child have, numbness, pain, skin color change, or sensitivity to temperature in the fingers or toes.
- **Call your doctor right away if you have or your child has any signs of unexplained wounds appearing on fingers or toes while taking dexmethylphenidate hydrochloride extended-release.**
- **Slowing of growth (height and weight) in children**

Common side effects include:
Children (6 to 17 years)
- dyspepsia ●decreased appetite ●headache●anxiety

Adults
- dry mouth ● dyspepsia●headache●anxiety●pharyngolaryngeal pain

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 dexmethylphenidate hydrochloride extended-release?
- Store dexmethylphenidate hydrochloride extended-release capsules in a safe place and in a tightly closed container at 20°C to 25°C (68°F to 77°F).
- Dispose of remaining, unused, or expired dexmethylphenidate hydrochloride extended-release 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 dexmethylphenidate hydrochloride extended-release 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 (discard) dexmethylphenidate hydrochloride extended-release in the household trash.
- **Keep dexmethylphenidate hydrochloride extended-release and all medicines out of the reach of children.**

General information about the safe and effective use of dexmethylphenidate hydrochloride extended-release capsules.
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. You can ask your pharmacist or doctor for information about dexmethylphenidate hydrochloride extended-release that is written for healthcare professionals. Do not use dexmethylphenidate hydrochloride extended-release for a condition for which it was not prescribed. Do not give dexmethylphenidate hydrochloride extended-release to other people, even if they have the same symptoms that you have.

It may harm them and it is against the law.

What are the ingredients indexmethylphenidate hydrochloride extended-releasecapsules?
Active Ingredient:dexmethylphenidate hydrochloride
Inactive Ingredients:methacrylic acid copolymer, amino methacrylate copolymer, triethyl citrate, talc, sugar spheres, polyethylene glycol, gelatin, titanium dioxide and black ink. The black ink contains shellac glaze, iron oxide black, n-butyl alcohol, propylene glycol, FD&C Blue #1, FD&C Blue #2, FD&C Red #40 and D&C Yellow #10. The 5 mg also contains FD& C Blue #1 and FD&C Red #3. The 10 mg contains FD&C Yellow #6. The 15 mg contains FD&C Blue #1and FD&C Yellow #6. The 25 mg, 30 mg, 35 mg and 40 mg contains yellow iron oxide.
This Medication Guide has been approved by the U.S. Food and Drug Administration.

For Medication Guide, please visit www.parpharm.com.

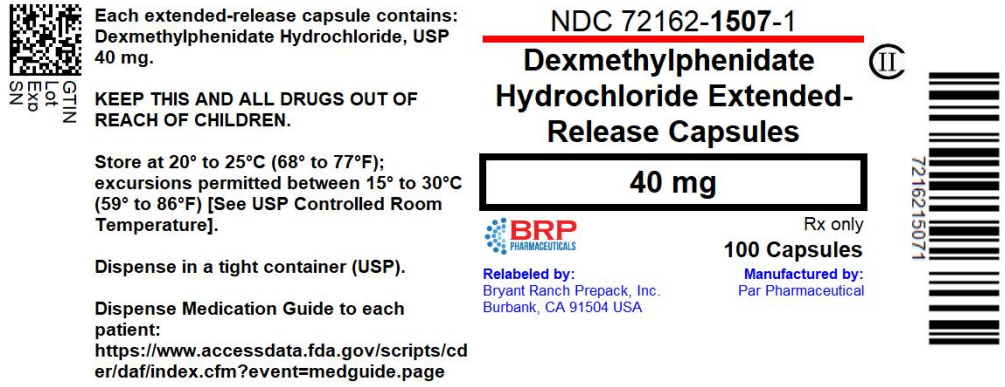
Manufactured by:

Par Pharmaceutical

Chestnut Ridge, NY 10977

R07/2021

Dexmethylphenidate Hcl ER 40 mg Capsule, #100



DEXMETHYLPHENIDATE HYDROCHLORIDE

dexmethylphenidate hydrochloride capsule, extended release

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:72162-1507(NDC:49884-546)
Route of Administration	ORAL	**DEA Schedule**	CII

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
DEXMETHYLPHENIDATE HYDROCHLORIDE (UNII: 1678OK0E08)	DEXMETHYLPHENIDATE	

DEXMETHYLPHENIDATE HYDROCHLORIDE (UNII: 1678OK0E08) (DEXMETHYLPHENIDATE - UNII:M32RH9MFGP)	DEXMETHYLPHENIDATE HYDROCHLORIDE	40 mg

Inactive Ingredients

Ingredient Name	Strength
POLYETHYLENE GLYCOL 4000 (UNII: 4R4HFI6D95)	
WATER (UNII: 059QF0KO0R)	
METHACRYLIC ACID - ETHYL ACRYLATE COPOLYMER (1:1) TYPE A (UNII: NX76LV5T8J)	
METHACRYLIC ACID - METHYL METHACRYLATE COPOLYMER (1:1) (UNII: 74G4R6TH13)	
TRIETHYL CITRATE (UNII: 8Z96QXD6UM)	
TALC (UNII: 7SEV7J4R1U)	
ISOPROPYL ALCOHOL (UNII: ND2M416302)	
FERRIC OXIDE YELLOW (UNII: EX438O2MRT)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
GELATIN, UNSPECIFIED (UNII: 2G86QN327L)	
SHELLAC (UNII: 46N107B71O)	
FERROSOFERRIC OXIDE (UNII: XM0M87F357)	
BUTYL ALCOHOL (UNII: 8PJ61P6TS3)	
1-PROPOXY-2-PROPANOL (UNII: 152BY1743W)	
FD&C BLUE NO. 1 (UNII: H3R47K3TBD)	
FD&C BLUE NO. 2 (UNII: L06K8R7DQK)	
FD&C RED NO. 40 (UNII: WZB9127XOA)	
D&C YELLOW NO. 10 (UNII: 35SW5USQ3G)	

Product Characteristics

Color	white (yellow)	**Score**	no score
Shape	CAPSULE	**Size**	23mm
Flavor		**Imprint Code**	par;546
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:72162-1507-1	100 in 1 BOTTLE; Type 0: Not a Combination Product	03/30/2023	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA202842	01/05/2017	

Labeler - Bryant Ranch Prepack (171714327)

Registrant - Bryant Ranch Prepack (171714327)

Establishment

Name	Address	ID/FEI	Business Operations
Bryant Ranch Prepack		171714327	repack(72162-1507) , relabel(72162-1507)